CLAIMS

WHAT IS CLAIMED IS:

1. A method for treating congenital adrenal hyperplasia (CAH) in a human, comprising:

administering to said human a therapeutically-effective amount of a CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof,

wherein said human has received or has been previously determined to receive a first dose of a glucocorticoid, and

administering to said human a second dose of a glucocorticoid, wherein said second dose of a glucocorticoid is reduced compared to said first dose of a glucocorticoid,

wherein an androstenedione (A4) level in said subject is reduced from baseline, or

wherein an adrenocorticotropic hormone (ACTH) level in said subject is reduced from baseline, or

wherein a 17-hydroxyprogesterone (17-OHP) level in said subject is reduced from baseline.

2. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 5% from baseline.

3. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 10% from baseline.

4. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 15% from baseline.

5. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 20% from baseline.

6. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 25% from baseline.

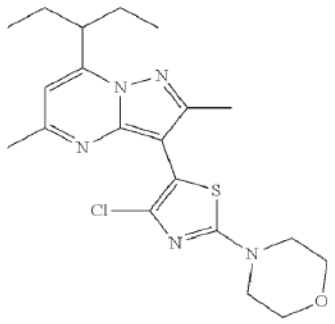
7. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 24 hours.

8. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 4 weeks.

9. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 6 weeks.

10. The method of claim 1, wherein said administering of said first dose of said glucocorticoid is concurrently or sequentially within 2 hours of said administering of said therapeutically-effective amount of a CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof.

11. The method of claim 1, wherein said CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof is Compound 1:



or a pharmaceutically acceptable salt thereof.

12. The method of claim 1, wherein said glucocorticoid is selected from beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone.

13. The method of claim 1, wherein said glucocorticoid is hydrocortisone.

14. The method of claim 1, wherein said first dose of said glucocorticoid comprises a supraphysiologic amount of said glucocorticoid.

15. The method of claim 1, wherein said second dose of said glucocorticoid comprises a physiologic amount of said glucocorticoid.

16. The method of claim 1, wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day.

17. The method of claim 1, wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is orally administered.

18. The method of claim 17, wherein said oral administration is once a day.

19. The method of claim 17, wherein said oral administration is twice a day.

20. The method of claim 1, wherein said first dose is a first daily dose and said second dose is a second daily dose.

21. The method of claim 1, wherein said second dose of said glucocorticoid is at least about 5%, at least about 10%, or at least about 20% lower than said first dose of said glucocorticoid.

PATENT APPLICATION

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

Inventor(s): Alexis HOWERTON
Citizen of USA, Residing at
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

Hal GERBER
Citizen of USA, Residing at
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

Michael HUANG
Citizen of USA, Residing at
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

Assignee: Spruce Biosciences, Inc.
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

a Delaware Corporation

Entity: Large business concern

WILSON
SONSINI

650 Page Mill Road
Palo Alto, CA 94304
(650) 493-9300 (Main)
(650) 493-6811 (Facsimile)

Filed Electronically on: April 26, 2023

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

CROSS-REFERENCE

[0001] This patent application is a continuation of U.S. Patent Application No. 18/078,649, filed December 9, 2022; which is a continuation of U.S. Patent Application No. 17/586,228, filed January 27, 2022; which is a divisional of U.S. Patent Application No. 17/359,411, filed on June 25, 2021, now U.S. Patent No. 11,351,177; which is a continuation of U.S. Patent Application No. 17/063,592, filed on October 5, 2020, now U.S. Patent No. 11,344,557; which is a continuation of U.S. Patent Application No. 16/388,620, filed on April 18, 2019, now U.S. Patent No. 10,849,908; which is a continuation of PCT Application No. PCT/US2018/046760, filed on August 14, 2018; which claims the benefit of U.S. Provisional Patent Application No. 62/545,406, filed August 14, 2017; all of which are incorporated herein by reference in their entirety.

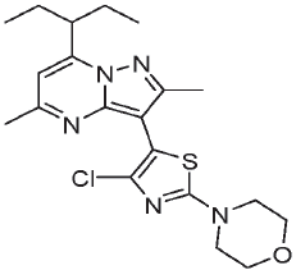
BACKGROUND OF THE INVENTION

[0002] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

SUMMARY OF THE INVENTION

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

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



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

[0005] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

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

[0007] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0008] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0009] In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more

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

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

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

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

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

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

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

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

[0016] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are

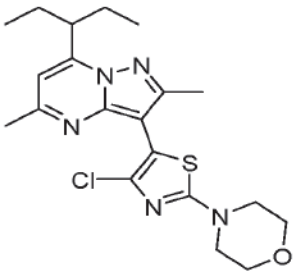
administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid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

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

[0018] In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 mins before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night. In some embodiments, the pharmaceutical composition is administered at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the pharmaceutical composition is administered about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

[0019] In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

[0020] In one aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering Compound 1:



or a pharmaceutically acceptable salt or solvate thereof; and

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

[0021] In some embodiments, the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione. In some embodiments,

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

[0022] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

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

In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 50 mg /day.

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

[0025] In some embodiments, Compound 1 is formulated in a pharmaceutical composition in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0026] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

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

embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0028] In some embodiments the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments,the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, he pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

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

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

[0031] In some embodiments, the method further comprises administering a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or

solvate thereof. In some embodiments, the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount. In some embodiments, the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.

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

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

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

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

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

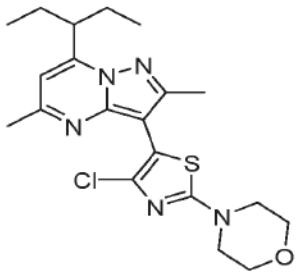
solvate thereof, is administered in the evening. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at 10 pm at night.

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

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

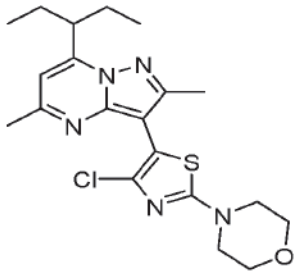
[0039] In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

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



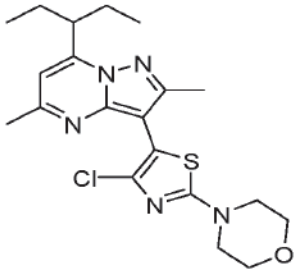
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0041] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

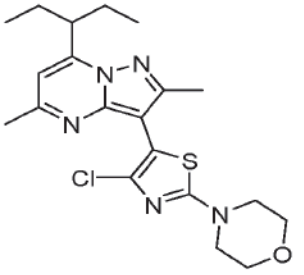


; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

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

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

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

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

INCORPORATION BY REFERENCE

[0044] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

[0050] CRF has been implicated in psychiatric disorders and neurological diseases including depression and anxiety, as well as the following: Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and associated withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia (CAH), Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulceration, premenstrual syndrome, sexual dysfunction, premature labor, inflammatory disorders, allergies, multiple sclerosis, visceral pain, sleep disorders, pituitary tumors or ectopic pituitary derived tumors, chronic fatigue syndrome, and fibromyalgia.

[0051] CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors. A more discrete septallhypothalmic distribution and the availability of alternative endogenous ligands suggest a different functional role for the CRF2 receptor. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF 1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism. In other cases, CRF2 agonism produces similar effects to those reported for CRF 1 antagonists or CRF 1 gene deletion. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well.

[0052] Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous Cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which Cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment

include Cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

[0053] The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient Cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of Addisonian syndrome due to under-treatment. Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione, testosterone, renin activity, and electrolytes.

[0054] Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance. A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes. Treatment of CAH includes efforts to normalize the Cortisol deficiency with glucocorticoids (usually hydrocortisone in children but often more potent agents with narrow therapeutic indices, such as dexamethasone, in adults) and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for Cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients.

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

[0056] 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.

[0057] The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21 -hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-hydroxyprogesterone (17-OHP). Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21 -hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically Cortisol and aldosterone. Cortisol is a critical negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

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

Certain Definitions

[0059] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[0060] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

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

[0062] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or."

[0063] The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[0064] "Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. "Administering" a pharmaceutical composition may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

[0065] By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

[0066] The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as Compound 1, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

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

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

[0069] A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or

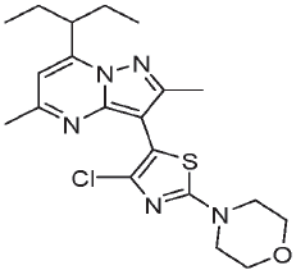
displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

[0070] The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

[0071] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Compound

[0072] Disclosed herein is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine (or alternatively 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine), a pharmaceutically acceptable salt, and/or a solvate thereof:



. In some embodiments, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine is referred to as Compound 1. In some embodiments, 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine is referred to as Compound 1.

Pharmaceutical Compositions

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

Dosage Form

[0074] In some embodiments, the pharmaceutical compositions described herein are provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of Compound 1 that is suitable for administration to an animal, preferably mammal, subject in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

[0075] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0076] In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more

additional pharmaceutically acceptable excipients. *See, e.g., Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

Capsule

[0077] In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

[0078] In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents, flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or delayed release coatings, sustained release coatings, barrier coatings, seal coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary according to the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

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

[0080] In some embodiments, a capsule is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if

solubility is less than 0.002 mg/mL in water. In some embodiments, the capsule has a dose strength of up to 200 mg. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus II.

Tablet

[0081] Poorly soluble drugs may be difficult to formulate using standard technologies such as high shear wet granulation. Optimum delivery of poorly soluble drugs may require complex technologies such as solid solutions amorphous dispersions (hot melt extrusion or spray drying), nano-formulations or lipid-based formulations. Hydrophobic drug substances may be considered poorly soluble according to USP criteria and may be known to be difficult to granulate with water and other excipients. This is likely due to most known excipients for immediate release formulations being water soluble or water-swellable. Making a tablet of a high dose drug substance that is poorly soluble may require a high concentration of the drug substance. However, as the drug concentration is increased above a certain level, formation of granules may become more and more difficult. Furthermore, at a certain drug load, it may become impossible.

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

[0083] In some embodiments, the tablet is made by compression, molding, or extrusion, optionally with one or more pharmaceutically acceptable excipient. In some embodiments, compressed tablets are prepared by compressing Compound 1 in a free-flowing form, optionally mixed with pharmaceutically acceptable excipients. In some embodiments, molded tablets are made by molding a mixture of the powdered Compound 1 moistened with an inert liquid diluent. In some embodiments, the tablet is prepared by hot-melt extrusion. In some embodiments, extruded tablets are made by forcing a mixture comprising Compound 1 through an orifice or die under controlled conditions. In some embodiments, the tablet is coated or scored. In some embodiments, the tablet is formulated so as to provide slow or controlled release of Compound 1. In some embodiments, a tablet is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the tablet has a dose strength of up to 200 mg. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus II.

[0084] In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg,

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

[0085] 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.

[0086] In some embodiments, the tablet is produced at a commercial scale.

[0087] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[0088] In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of Compound 1. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone, polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

Pharmaceutically Acceptable Excipients

[0089] 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.

[0090] 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

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

acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 1 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0092] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the

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

[0093] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0094] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0095] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or

solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0096] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

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

mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0098] In some embodiments, the pharmaceutical composition comprises about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

Particle size

[0099] In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises Compound 1, or a pharmaceutically acceptable salt or solvate thereof, in the form of microparticles. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 100 μm. In some embodiments, microparticles of Compound 1

have an average size from about 1 μm to about 50 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 30 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 20 μm. In some embodiments, microparticles of Compound 1 have an average size from about 5 μm to about 15 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 3 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 4 μm to about 9 μm.

[0100] In some embodiments, microparticles of Compound 1 have an average size less than about 100 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 80 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 60 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 50 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 40 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 30 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 20 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 10 μm.

Pharmacokinetics

[0101] In some embodiments, Compound 1 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, Compound 1 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, Compound 1 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, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

[0102] In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

Stability

[0103] The pharmaceutical compositions described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to pharmaceutical compositions having about 95% or greater of the initial Compound 1 amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of Compound 1. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable pharmaceutical compositions have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable pharmaceutical compositions have about 5% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 4% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 3% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 2% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 1% w/w total impurities or related substances.

[0104] At refrigerated condition, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±5 °C. In some embodiments, refrigerated condition is about 0 °C, about 0.1 °C, about 0.2 °C, about 0.3 °C, about 0.4 °C, about 0.5 °C, about 0.6 °C, about 0.7 °C, about 0.8 °C, about 0.9 °C, about 1 °C, about 1.1 °C, about 1.2 °C, about 1.3 °C, about 1.4 °C, about 1.5 °C, about 1.6 °C, about 1.7 °C, about 1.8 °C, about 1.9 °C, about 2 °C, about 2.1 °C, about 2.2 °C, about 2.3 °C, about 2.4 °C, about 2.5 °C, about 2.6 °C, about 2.7 °C, about 2.8 °C, about 2.9 °C, about 3 °C, about 3.1 °C, about 3.2 °C, about 3.3 °C, about 3.4 °C, about 3.5 °C, about 3.6 °C, about 3.7 °C, about 3.8 °C, about 3.9 °C, about 4 °C, about 4.1 °C, about 4.2 °C, about 4.3 °C, about 4.4 °C, about 4.5 °C, about 4.6 °C, about 4.7 °C, about 4.8 °C, about 4.9 °C, about 5 °C, about 5.1 °C, about 5.2 °C, about 5.3 °C, about 5.4 °C, about 5.5 °C, about 5.6 °C, about 5.7 °C, about 5.8 °C, about 5.9 °C, about 6 °C, about 6.1 °C, about 6.2 °C, about 6.3 °C, about 6.4 °C, about 6.5 °C, about 6.6 °C, about 6.7 °C, about 6.8 °C, about 6.9 °C, about 7 °C, about 7.1 °C, about 7.2 °C, about 7.3 °C, about 7.4 °C, about 7.5 °C, about 7.6 °C, about 7.7 °C, about 7.8 °C, about 7.9 °C, about 8 °C, about 8.1 °C, about 8.2 °C, about 8.3 °C, about 8.4 °C, about 8.5 °C, about 8.6 °C, about 8.7 °C, about 8.8 °C, about 8.9 °C, about 9 °C, about 9.1 °C, about 9.2 °C, about 9.3 °C, about 9.4 °C,

about 9.5 ºC, about 9.6 ºC, about 9.7 ºC, about 9.8 ºC, about 9.9 ºC, or about 10 ºC. At accelerated conditions, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, or at least 24 month. Accelerated conditions for the pharmaceutical compositions described herein include temperatures that are at or above ambient levels (e.g. 25±5 °C). In some instances, an accelerated condition is at about 40±2 °C. In some instances, an accelerated condition is at about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C, or about 60 °C. Accelerated conditions for the pharmaceutical compositions described herein also include relative humidity (RH) that are at or above ambient levels (55±10% RH). In other instances, an accelerated condition is above about 65% RH, about 70% RH, about 75% RH, or about 80% RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40±2 °C at 75±5% RH humidity.

[0105] In some embodiments, the pharmaceutical compositions are stable at about 5±5 ºC to about 25±5 ºC for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 ºC for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 ºC for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 ºC for at least 24 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 ºC for at least 24 months.

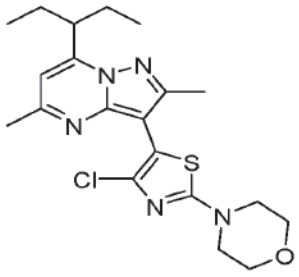
Methods of Use

[0106] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.In some embodiments, the methods described herein result in the reduction of a hormone level. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17α-hydroxy progesterone (17-OHP), dehydroepiandrosterone, androstenediol, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein result in the reduction of 17α-hydroxy progesterone (17-OHP). In some embodiments, the methods described herein result in the reduction of adrenocorticotropic hormone (ACTH), also known as corticotropin.

[0107] Also disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising:

(i) measuring a hormone level in the subject in need thereof;

(ii) administering Compound 1:



or a pharmaceutically acceptable salt or solvate thereof;

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

[0108] In some embodiment, the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione.

[0109] In some embodiment, the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL. In some embodiment, the hormone is 17-OHP, and the pre-determined range is less than about 400 ng/dL, less than about 350 ng/dL, less than about 300 ng/dL, less than about 250 ng/dL, or less than about 200 ng/dL.

[0110] In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL. In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL, below about 90 pg/mL, or below about 80 pg/mL.

[0111] In some embodiment, the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL. In some embodiment, the hormone is testosterone and the pre-determined range is less than about 76 ng/dL, less than about 70 ng/dL, less than about 65 ng/dL, less than about 60 ng/dL, less than about 55 ng/dL, less than about 50 ng/dL, less than about 45 ng/dL, less than about 40 ng/dL, less than about 35 ng/dL, less than about 30 ng/dL, less than about 25 ng/dL, less than about 20 ng/dL, or less than about 15 ng/dL.

[0112] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 200 ng/dL in males. In some embodiment, the hormone is androstenedione and the pre-determined range is less than about 200 ng/dL, less than about 150 ng/dL, less than about 100 ng/dL, less than about 50 ng/dL, or less than about 30 ng/dL in males.

[0113] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 150 ng/dL in females. In some embodiment, the hormone is

androstenedione and the pre-determined range is less about 150 ng/dL, less about 100 ng/dL, less about 50 ng/dL, or less about 40 ng/dL in females.

[0114] In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a month, twice a month, three times a month, once a week, twice a week, three times a week, once every two days, once a day, twice a day, three times a day, or four times a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof twice a day.

[0115] In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1500 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1400 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1300 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1100 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 900 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 60 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 70 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 80 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 90 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 700 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 150 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200

mg/day and about 500 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 400 mg/day.

[0116] 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.

[0117] In some embodiments, about 100 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

[0118] In some embodiments, less than about 2000 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered

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

[0119] 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.

[0120] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

[0121] 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.

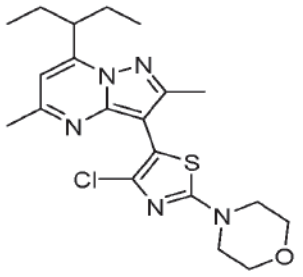
[0122] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

[0123] 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.

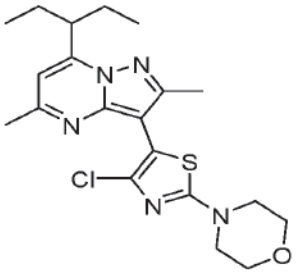
[0124] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

[0125] In one aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



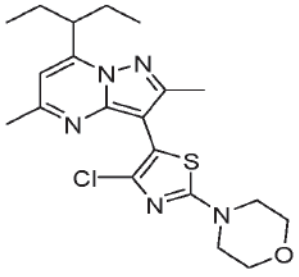
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0126] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

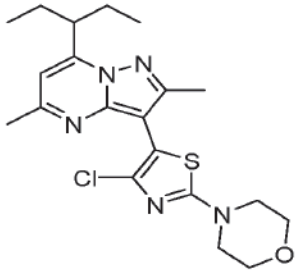


; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

[0127] In one aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition

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

[0128] In one aspect, the present disclosure provides a method of improving quality of life in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

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

Combination Therapy

[0129] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; and a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0130] In some embodiments, the methods described herein reduce the amount of a glucocorticoid administered from a supraphysiologic amount to a physiologic amount.

[0131] In some embodiments, the methods described herein reduce the symptoms associated with high-dose glucocorticoid therapy. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.

[0132] In some embodiments, the amount of glucocorticoid administered is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about

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

[0133] In some embodiments, the amount of glucocorticoid administered is reduced by about 1% to about 90%, about 1% to about 60%, about 1% to about 30%, about 1% to about 10%, about 10% to about 50%, about 10% to about 40%, about 10% to about 30%, about 15% to about 25%, about 20% to about 30%, about 5% to about 25%, about 20% to about 50%, about 30% to about 60%, or about 40% to about 70% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0134] In some embodiments, the glucocorticoid is administered at a dose between about 0.1 mg/day and about 25 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 20 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 15 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 12 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 9 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 8 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 7 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 6 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 5 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 4 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 3 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 2 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 3 mg/day and about 13 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 8 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 9 mg/day and about 12 mg/day. In some embodiments, the

glucocorticoid is administered at a dose between about 9 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 10 mg/day.

[0135] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered in one pharmaceutical composition. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently in separate pharmaceutical compositions.

[0136] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 12 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 8 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 6 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 4 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 2 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 1 hour. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 30 minutes. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 10 minutes.

[0137] In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

[0138] In some embodiments, the glucocorticoid is hydrocortisone and the dose administered is less than the recommended dose of 15-25 mg/day.

[0139] In some embodiments, the glucocorticoid is prednisone and the dose administered is less than the recommended dose of 5-7.5 mg/day.

[0140] In some embodiments, the glucocorticoid is prednisolone and the dose administered is less than the recommended dose of 4-6 mg/day.

[0141] In some embodiments, the glucocorticoid is dexamethasone and the dose administered is less than the recommended dose of 0.25-0.5 mg/day.

[0142] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; a glucocorticoid; and optionally a mineralcorticoid. In some embodiments, the mineralocorticoid is fludrocortisone and the dose is less than the recommended dose of 0.05-0.2 mg/day.

EXAMPLES

[0143] 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.

[0144] All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

Example 1: Pharmaceutical Composition

[0145] The pharmaceutical composition is manufactured as size 1 white hard gelatin capsules containing 200 mg of Compound 1 micronized to and average size of 10 microns or less. The pharmaceutical composition contains no additional excipients.

Example 2: Stability of the Pharmaceutical Composition

Stability Data Summary

[0146] A summary of the pharmaceutical composition stability studies is provided in Table 1. The pharmaceutical composition is a Compound 1 neat-filled into size 0 capsules with no added excipients, in 3 strength configurations: 1-mg, 5-mg, and 50-mg. The capsules were blister packaged in a polyvinyl chloride (PVC)-based film.

[0147] Under long term and accelerated conditions, no significant trend was observed in the three lots for any of the attributes evaluated throughout the course of the stability study.

Table 1. Summary of Stability

Lot Number	Strength	CCS	Stability Conditions	Available Data
#1	1-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#2	5-mg	PVC-based	25 °C/60% RH	6 months

		blister pack	40 °C/75% RH	6 months
#3	50-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#4	200-mg	75 mL HDPE bottle	25 °C/60% RH	1 month
			40 °C/75% RH	9 months
#5	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#6	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months

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

Stability Protocols

[0148] The stability protocol for various pharmaceutical compositions is provided in Table 2, 3, and 4.

Table 2. Stability Protocol

Test	**Acceptance Criteria**	**Time (months)**			
		T_0	1	**3**	**6**
Appearance	Size 0 blue capsule containing yellow powder, blister pack and foil backing intact	X	A,B	A,B	A,B
Assay	Report (% Label Claim)	X	A,B	A,B	A,B
Related Substances	Report RRT and % each individual species and total	X	A,B	A,B	A,B
Disintegration	Report	X	A,B	A,B	A,B

RRT = relative retention time
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

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

Test	**Acceptance Criteria**	**Time (months)**			
		T_0	1	3	6
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	A,B	A,B	A,B

Assay (%LC)	90.0 – 110.0	X	A,B	A,B	A,B
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	A,B	A,B	A,B
Disintegration (min)	NMT 15	X	A,B	A,B	A,B
Water Activity	Report result	X	A,B	A,B	A,B

LC = label claim; NMT = not more than
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

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

Test	**Acceptance Criteria**	**Time (months)**					
		T_0	**1**	**3**	**6**	**9**	**12**
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	B	A,B	A,B	A	A
Assay (%LC)	90.0 – 110.0	X	B	A,B	A,B	A	A
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	B	A,B	A,B	A	A
Disintegration (min)	NMT 15	X	B	A,B	A,B	A	A
Water Activity	Report result	X	n/a	n/a	n/a	A	A
Microbial Enumeration Total Aerobic Microbial Count (CFU/g) Total Combined Yeast and Mold (CFU/g) Count	 NMT 2000 CFU/g NMT 200 CFU/g	X	n/a	n/a	n/a	A	A

Test	Acceptance Criteria	Time (months)					
		T_0	1	3	6	9	12
Test for Specified Microorganisms *E. coli* (/g)	Absent	X	n/a	n/a	n/a	A	A

CFU = colony forming units; LC = label claim; n/a = not applicable; NMT = not more than
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

[0149] The supportive data demonstrate that the pharmaceutical composition is stable for a minimum of 6 months (end of study). No adverse trends were observed under long term and accelerated conditions. The assay results were consistent through the entire study and no new related substances species were observed during the stability study. The reported stability results for lots stored in a blister packaging configuration are considered supportive for the updated packaging configuration of a 30-mL HDPE bottle, induction seal, and a child resistant cap. There are no excipients in either configuration and both configurations provide protection from light.

Example 3: Phase 1 Clinical Studies

[0150] Compound 1 has been investigated in 2 Phase 1 studies in healthy adult volunteers.

[0151] Study 1 was the first-in-human study that investigated the safety, tolerability, and PK of single-escalating doses of Compound 1, given orally, to healthy adult subjects. Safety and tolerability assessments were made over a wide range of single oral doses, and dose escalation did not proceed until safety data from the preceding doses had been reviewed. The data from this study were used for the selection of doses for Study 2.

[0152] The 2-part multiple-dose study, Study 2, determined the safety and tolerability of repeated daily doses of Compound 1 and investigated the effects on biomarkers of relevance for the treatment of alcohol dependence. Part B investigated the interaction of Compound 1 with midazolam (a cytochrome P450 3A4 [CYP3A4] substrate), determining whether Compound 1 significantly inhibited the metabolism of drugs that are metabolized by CYP3A4.

[0153] In Study 1, Compound 1 was administered to healthy adult subjects as a single PO dose of 2, 10, 50, 150, 400, or 800 mg in the fed state and 150 mg in the fasted state. Absorption occurred moderately late, achieving peak C_{max} between 4 to 6 hours following dosing in the fed state.

[0154] Table 5 provides a summary of the PK parameters at each dose level. When Compound 1 was given in the fed state, median time to reach maximum plasma concentration (T_{max}) occurred between 4 and 6 hours. The median T_{max} was 10.05 hours when Compound 1 was given in the fasted state at 150 mg and ranged between 6 and 12 hours, suggesting possible

delayed absorption in the fasted state. Mean half-life ($t_{1/2}$) after a single PO dose (fed and fasted state) was between 31 and 44 hours, ranging from 11 to 101 hours. Apparent volume of distribution (V_z/F) was large and appeared highly variable with greatest variability observed at the 2 highest dose levels of 400 mg and 800 mg.

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

PK Parameters	Geometric Mean (CV%) Analyte = Plasma Compound 1					
	2 mg	**10 mg**	**50 mg**	**150 mg**	**400 mg**	**800 mg**
N	6	6	6	6	6	6
C_{max} (ng/mL)	0.867 (53)	3.01 (87)	19.5 (39)	93.4 (22)	207 (92)	382 (110)
T_{max}[a] (h)	6.00 (4.00-6.00)	4.00 (2.00 -6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	6.00 (4.00 - 6.00)
$t_{1/2}$[b] (h)	NC (NC)	NC (NC)	31 (10.8-53.4)	29.2 (20.0 - 41.5)	44.2 (20.2 - 101)	41.9 (24.1 - 67.8)
$AUC_{0\text{-}tlast}$ (ng•h/mL)	NC (NC)	NC (NC)	152 (60)	891 (26)	2300 (103)	4390 (100)
$AUC_{0\text{-}\infty}$ (ng•h/mL)	NC (NC)	NC (NC)	165 (64)	956 (25)	2580 (93)	4850 (95)
CL/F (L/h)	NC (NC)	NC (NC)	302 (64)	157 (25)	155 (93)	165 (95)
V_z/F (L)	NC (NC)	NC (NC)	13500 (45)	6620 (38)	9890 (212)	9970 (144)
V_{ss}/F (L)	NC (NC)	NC (NC)	8080 (36)	4600 (33)	6580 (152)	6820 (120)

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

a Median (range)

b Geometric mean (range)

[0155] As part of this single-dose escalation study, a food effect PK investigation was performed to examine Compound 1 exposures in both the fed and fasted states at the 150-mg dose level. A total of 6 subjects were administered 150 mg Compound 1 in each of these 2 dosing groups. Of these 6 subjects, 4 subjects received Compound 1 at the same dose in both fed and fasted states. The administration of Compound 1 in the fasted state resulted in a much flatter mean concentration-time (i.e., with significantly lower absorption) profile when compared against the mean profile at the same dose, given within 5 minutes after a standardized breakfast meal. The mean $AUC_{0\text{-}\infty}$, and C_{max} values for a 150-mg dose in the fed state was approximately 3- and 11-fold greater than that of the fasted state, respectively. Table 6 provides a summary of the PK parameters at the 150-mg dose level under both fed and fasted state conditions.

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

Pharmacokinetic Parameters	Geometric Mean (CV %)	
	Analyte = Plasma Compound 1	
	150 mg Fed	150 mg Fasted
N	6	6
C_{max} (ng/mL)	93.4 (22)	8.22 (83)
T_{max}[a] (h)	4.00 (3.00 – 6.00)	10.05 (6.00 – 12.00)
$t_{1/2}$[b] (h)	29.2 (20.0 – 41.5)	38.4 (24.2 – 88.5)
$AUC_{0\text{-tlast}}$ (ng•h/mL)	891 (26)	288 (48)
$AUC_{0\text{-}\infty}$ (ng•h/mL)	956 (25)	331 (44)
CL/F (L/h)	157 (25)	454 (44)
Vz/F (L)	6620 (38)	25100 (81)
Vss/F (L)	4600 (33)	25200 (68)

AUC = area under the plasma concentration-time curve; CL/F = apparent total body clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; N = number of subjects; NC = not calculable; PK = pharmacokinetic; T_{max} = time to reach maximum plasma concentration; t1/2 = elimination half-life; $V_{ss}F$ = apparent volume of distribution at steady state during the terminal phase after extravascular administration; V_z/F = apparent volume of distribution during the terminal phase after extravascular administration.

a Median (range)

b Geometric mean (range)

[0156] PK parameters $AUC_{0\text{-}\infty}$ and C_{max} were analyzed separately for dose proportionality for Compound 1 from 50 to 800 mg when administered in the fed state. The analysis results suggested that for every doubling of dose, $AUC_{0\text{-}\infty}$ can be expected to increase 1.74 times more than what would be expected under dose proportionality. C_{max} appeared more than dose proportional but the formal test was inconclusive as the 90% confidence interval were partially within the 0.8 – 1.25 interval. Dose proportionality across administered doses in the fed state could not be concluded on the basis of $AUC_{0\text{-}\infty}$ or C_{max}.

[0157] PK were also evaluated in the multiple-dose, dose-escalation study, Study 2. In Part A of the study, subjects were divided into 3 cohorts and received 50, 150, or 200 mg Compound 1 or placebo for 14 consecutive days (at least 6 subjects received Compound 1 and 2 subjects received placebo in each cohort). Blood concentrations of Compound 1 were close to steady-state levels after 2 weeks of dosing and the accumulation ratio was between 2.51 to 3.65. Part B investigated the interaction of Compound 1 with midazolam (a CYP3A4 substrate), thereby determining whether this compound significantly inhibited the metabolism of drugs that are metabolized by CYP3A4 serial blood samples were collected to determine plasma concentrations of study drug after a single dose of Compound 1 had been administered and at steady state. All dosing occurred in the fed state. An assessment of diurnal cortisol levels, plus when under conditions of glucose clamp, were also carried out both prior to and during the dosing period.

[0158] Overall concentration time profiles of Compound 1 showed that absorption was moderately delayed with C_{max} achieved at a median of 5 hours following oral dosing. Consistent with the single-dose study (Study 1), concentrations appeared to decline in a bi-exponential manner, characterized by a rapid decrease within the first 24 hours. Following multiple daily dosing for 2 weeks, the $t_{1/2}$ of Compound 1 exceeded 100 hours; therefore, an accumulation ratio of Compound 1 was between 2.51 to 3.65 (see Table 7). The T_{max} appeared to be consistent across doses. Overall half-lives, weight normalized CL/F and V/F were consistent for 150 and 200 mg. However, the values for these latter 2 parameters were almost doubled at the 50-mg dose level. Variability (CV%) for apparent clearance and volume of distribution were large and not reduced with weight-normalization.

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

	Geometric Mean (CV%)					
	50 mg Day 1	**150 mg Day 1**	**200 mg Day 1**	**50 mg Day 14**	**150 mg Day 14**	**200 mg Day 14**
N	**8**	**9**	**7**	**8**	**9**	**6**
C_{max} (ng/mL)	22.7 (59)	127 (52)	143 (62)	50.3 (56)	222 (58)	314 (93)
T_{max} [a] (hr)	4.52 (3.00 – 10.00)	5.00 (5.00 - 6.00)	5.00 (2.00 - 5.00)	5.00 (3.00 - 5.00)	5.00 (3.00 - 5.03)	5.00 (3.00 - 5.00)
Effective $t_{1/2}$ [b] (hr)	NC NC	NC NC	NC NC	37.7 (27.4)	32.7 (29.7)	52.0

$AUC_{0-\infty}$ (ng•hr/mL)	NC NC	NC NC	NC NC	980 (53.8)	4680 (104)	5660 (122)
AUC_{0-24h} (ng•hr/mL)	97.6 (58)	590 (56)	559 (55[c])	273 (56)	1480 (66)	2040 (98)
C_{avg} (ng/mL)	NC NC	NC NC	NC NC	11.4 (56)	61.7 (66)	85.0 (98)
CL_{aa}/F (L/hr)	NC NC	NC NC	NC NC	183 (56)	101 (66)	98 (98)
WT-norm						
Cl_{aa}/F (L/hr/kg)	NC NC	NC NC	NC NC	2.88 (46.9)	1.42 (72.9)	1.50 (89.9)
Vz/F (L)	NC NC	NC NC	NC NC	33500 (90)	17600 (59)	16300 (76)
Vss/F (L)	NC NC	NC NC	NC NC	12900 (91)	6170 (40)	5080 (78)
WT-norm						
Vss/F (L/kg)	NC NC NC	NC NC NC	NC NC NC	204 (71.3) 2.80	86.5 (41.0) 2.51	77.4 (68.6) 3.65
R_A	NC	NC	NC	(27.4)	(29.7)	(34.4)

AUC = area under the plasma concentration-time curve; CL/F = apparent clearance; C_{max} = maximum plasma concentration; RA = accumulation ratio calculated as Day 14 AUC_{0-24}/Day 1 AUC_{0-24}; t1/2 = terminal half-life; effective t1/2 = half-life calculated by accumulation ratio; Tmax = time to maximum plasma concentration; Vss/F = volume of distribution at steady state; Vz/F = volume of distribution at terminal phase; WT-norm = weight normalized

[a] Median (range).

[b] Geometric mean (range).

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

[0159] Table 8 presents the results of the dose proportionality assessment for the AUC_{0-24} and C_{max} over the tested dose range. For AUC_{0-24} and C_{max}, the adjusted mean slope at Day 1 and Day 14 were all above the value of 1, suggesting a slightly more than proportional increase of AUC_{0-24} and C_{max} values with increasing doses.

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

Parameter	Day	Mean Slope	Standard Error	90% CI for Slope	CV%
AUC_{0-24} (ng hr/mL)	1	1.40	0.194	(1.069, 1.737)	59.3
	14	1.48	0.221	(1.104, 1.864)	69.1
C_{max} (ng/mL)	1	1.41	0.185	(1.092, 1.728)	57.5

	14	1.33	0.210	(0.972, 1.693)	64.8

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

Safety

[0160] The safety of Compound 1 was evaluated in 2 Phase 1 studies in healthy adult volunteers (Study 1 and Study 2). In both studies, adverse events (AEs), clinical laboratory tests, vital signs (supine blood pressure and pulse rate), and electrocardiograms (ECGs) were evaluated. Overall, in Study 1, Compound 1 was well-tolerated.

[0161] Compound 1, when administered as multiple doses up to 200 mg, was generally well tolerated in the healthy subject population studied. In Study 1, the effects upon biomarkers of relevance for the treatment of alcohol dependence were investigated. Five clusters of an Addiction Research Center Inventory Questionnaire (ARCI-49) were used to compare the effect of Compound 1 vs. placebo: Morphine-Benzedrine Group Scale measuring euphoria; Lysergic-Acid-Diethylamide Group Scale estimating dysphoric and somatic changes; Pentobarbital-Chlorpromazine-Alcohol Group Scale measuring sedation; Benzedrine Group (BG) Scale measuring intellectual efficiency and energy; Amphetamine Group Scale measuring effects of d-amphetamine, respectively. No systematic pattern or dose-response for the change from baseline or for the difference over placebo in each cluster was observed.

[0162] In summary, single, oral doses up to 800 mg and multiple doses up to 200 mg of Compound 1 were well-tolerated by healthy male and female subjects.

Example 4: Phase 2 Clinical Studies

[0163] Cohort A of the Phase 2 Study includes a 6-week, multiple-dose, dose escalation study of Compound 1 for the treatment of adults with classic CAH. After screening, eligible patients will be enrolled into a 6-week treatment period followed by a 4-week washout/safety follow-up period.

[0164] This cohort will be conducted in approximately 9 patients, who will receive Compound 1 daily for up to 6 weeks. Compound 1 will be administered as an oral daily dose. Patients will undergo titration of Compound 1 through three escalating dosage strengths at 2-week intervals. Patients will have overnight PK/PD assessments performed at baseline, which include an pre-dose overnight assessment and a post-dose overnight assessment for PK/PD following administration of the first dose. At the end of each 2-week dosing period, patients will return for single overnight visits for steady-state PK/PD assessments. A follow-up outpatient visit will occur 30 days after their last dose. Upon completion of the initial cohort (Cohort A), the study will proceed to a multiple ascending dose (MAD) design with up to 3 sequential cohorts (Cohorts B, C, and D) to further evaluate the safety, PK, and PD of various SPR001 dosing regimens and to identify an optimal dose regimen. Each cohort will undergo a 2-week run-in

period, a 2-week treatment period, and a 30-day washout and safety follow-up period. During the run-in period, which will occur during screening, subjects will document in a paper diary each dose of glucocorticoid medication taken, the time of each meal, and the time they went to bed and woke up each day, to ensure compliance with background glucocorticoid regimens and the stability of their daily routine.

[0165] Patients in Cohort B will receive study drug at 200 mg BID, with a dose in the morning and a dose in the evening, either with a meal or consumption of a standardized snack. For Cohorts C and D, the dose level and the frequency and timing of dosing will be determined based on interim data from the previous cohorts. However, the dose level of each successive cohort will be capped at twice the daily dose level of the previous cohort.

Study Design

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

Arms and Interventions

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

Outcome Measures

Primary Outcome Measure:

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

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

Secondary Outcome Measure:

3. To explore the dose(s) of Compound 1 that cause pharmacodynamics changes in plasma concentrations of ACTH, androstenedione, and testosterone, as measured by the absolute and percent change from baseline by dose.

4. To determine pharmacokinetics of Compound 1 in subjects with CAH.

5. To explore potential relationships between pharmacodynamics and pharmacokinetics.

Exploratory

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

Eligibility

- Minimum Age: 18 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Results:

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

[0166] With respect to patient-level response to Compound 1, 80% showed reduced ACTH (see FIG. 2). Generally, attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of patient subjects demonstrated reduction in ACTH. 70% of subject demonstrated more than 25% reduction in ACTH. 40% of subjects were in the normal range after treatment.

[0167] A reduction of 17-OHP demonstrates "control" of the disease based on Standard guidelines. This allows for steroid taper. 80% of subjects demonstrated reduction in 17-OHP (see FIG. 3). 50% of subjects demonstrated more than 25% reduction in 17-OHP. 50% of subjects were within the guideline range (1200 ng/dL) after treatment.

[0168] Compound 1 attenuates morning rise in A4 which indicates an ability to control excess androgen production and associated symptoms (see FIG. 4). 100% of subjects demonstrated reduction in Androstenedione (at various doses). 60% of subjects demonstrated more than 25% reduction in Androstenedione. 50% of subjects were within normal reference range after treatment.

Example 5: 3-Month Phase 2 Study

[0169] This is a 3-month Phase 2 study to evaluate the safety and efficacy of Compound 1 in subjects with classic CAH. This study will investigate the extended use of Compound 1 over a 3-month period in combination with replacement glucocorticoids and mineralocorticoids in the treatment of CAH.

[0170] This study will enroll up to approximately 24 eligible subjects who will receive Compound 1 daily for up to 3-months. Compound 1 will be administered as an oral daily dose. At the end of each 2-week dosing period, patients will return for morning laboratory assessments. A follow-up outpatient visit will occur 30 days after their last dose.

Study Design

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

Outcome Measures

Primary Outcome Measure:

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

Second Outcome Measure:

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

Exploratory:

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

Eligibility:

- Minimum Age: 18 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Example 6: Adolescent Study

[0171] This is a Phase 2, open-label, multiple-dose study designed to provide proof of concept for the use of Compound 1 to treat adolescents 12 to 17 years of age with classic CAH. The study will evaluate the safety, efficacy, and PK of 2 weeks of treatment with Compound 1. Each subject will undergo a 2-week diary run-in period during screening, a 2-week treatment period, and a 30-day washout and safety follow-up period.

[0172] An adaptive design with up to 3 sequential dose cohorts (Cohorts 1, 2, and 3) is planned to identify an optimal dose strength and regimen in adolescents with classic CAH. Each cohort will initially enroll 3 subjects and may later enroll 3 more subjects based on interim data from the first 3 subjects, for a total of 6 subjects per cohort. However, if safety, efficacy, and PK results from 6 subjects are inconclusive, a cohort may be expanded up to a maximum of 12 subjects. Cohort 1 will receive study drug at 200 mg QD. Cohorts 2 and 3 will be sequentially activated only if further investigation of an optimal dose strength or regimen is required; the dose strength and frequency and timing of dosing for these cohorts will be determined based on interim data from the previous cohort(s). However, the dose strength administered to each successive cohort will be capped at twice the daily dose strength administered to the previous cohort.

[0173] This study will enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in many adolescent patients. In this population, GCs are associated with multiple well-described short- and long-term toxicities including: growth retardation, weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

[0174] The objective of treatment of this patient population with Compound 1 is reduction (or normalization) of key hormonal outcome measures which could allow reduction of their GC replacement requirements which will improve clinical outcomes of concern, including growth velocity. Improvement of hormonal outcome measures in this population are also expected to delay premature puberty and bone maturation, ultimately leading to improvements in height in adolescents with CAH.

Outcome Measures

Primary Outcome Measures:

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

Secondary Outcome Measures:

2. To evaluate the dose(s) of Compound 1 that cause changes in key pharmacodynamics bioamarkers in blood in adolescent subjects with CAH.

3. To investigate the effect of Compound 1 on quality of life in adolescent subjects with CAH.

4. To determine the pharmacokinetics of Compound 1 in adolescent subjects with CAH.

5. To investigate potential relationships between pharmacodynamics and pharmacokinetics in adolescent subjects with CAH.

Exploratory

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

Eligibility Criteria

Inclusion Criteria:

- Male and female subjects 12 to 17 years of age, inclusive
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable regimen of glucocorticoid replacement for minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Example 7: Phase 3 Clinical Studies

[0175] This is a 24-week, randomized, double-blind, placebo-controlled study of Compound 1 for the treatment of classic CAH. After screening, eligible patients will be enrolled into a 24-week treatment period followed by a 4-week safety follow-up period.

[0176] Subjects in the study will be randomized in a 1:1 ratio to either receive Compound 1 or a matching placebo for up to 24 weeks. Compound 1 or a placebo will be administered as an oral daily dose. Patients will return approximately monthly for study visits. A follow-up outpatient visit will occur 30 days after their last dose. It is initially planned that up to approximately 150 patients will be enrolled.

[0177] Consistent with the design of the Phase 2 study, the Phase 3 clinical study will seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated with supraphysiologic

doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

Study Design:

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

Outcome Measures

Primary Outcome Measures

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

Secondary Outcome Measures

2. Evaluate efficacy of Compound 1 in patients with CAH in terms of changes in key hormones.
3. Evaluate efficacy of Compound 1 in improving quality of life and/or mood in patients with CAH.
4. Evaluate efficacy of Compound 1 in improving hyperandrogenic symptoms in patients with CAH.
5. Evaluate efficacy of Compound 1 in improving metabolic parameters in patients with CAH.
6. Evaluate safety of Compound 1 in patients with CAH.

Eligibility

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

Criteria

Inclusion Criteria:

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

- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Example 8: Phase 3 OLE and steroid sparing studies

[0178] Upon completion of the study described in Example 7, eligible patients will then be offered the opportunity to enroll into an open label extension study lasting up to 1 year. The open label study will allow all eligible patients to receive active study drug during their participation in the Phase 3 program. Patients will undergo study assessments every 1-3 months during the open label phase, and will be evaluated for long-term safety and efficacy (including both hormonal endpoints and long-term clinical outcome measures of concern in this population).

[0179] A further study may seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). Such CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

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

[0181] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing

the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

ABSTRACT OF THE DISCLOSURE

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

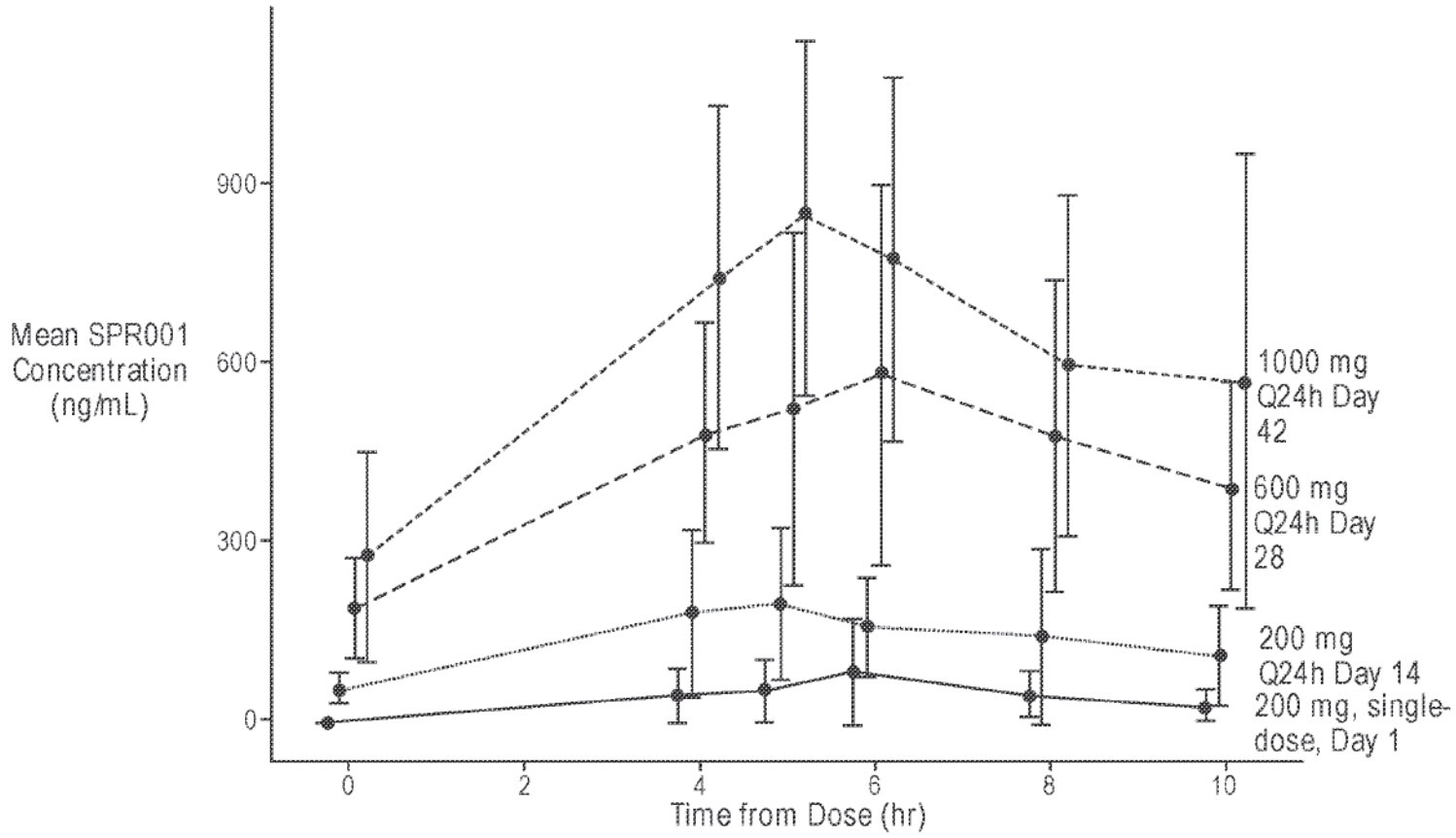

Mean SPR001 Concentration (ng/mL)
900
600
300
0
0
2
4
6
8
10
Time from Dose (hr)
1000 mg Q24h Day 42
600 mg Q24h Day 28
200 mg Q24h Day 14
200 mg, single-dose, Day 1

FIG. 1

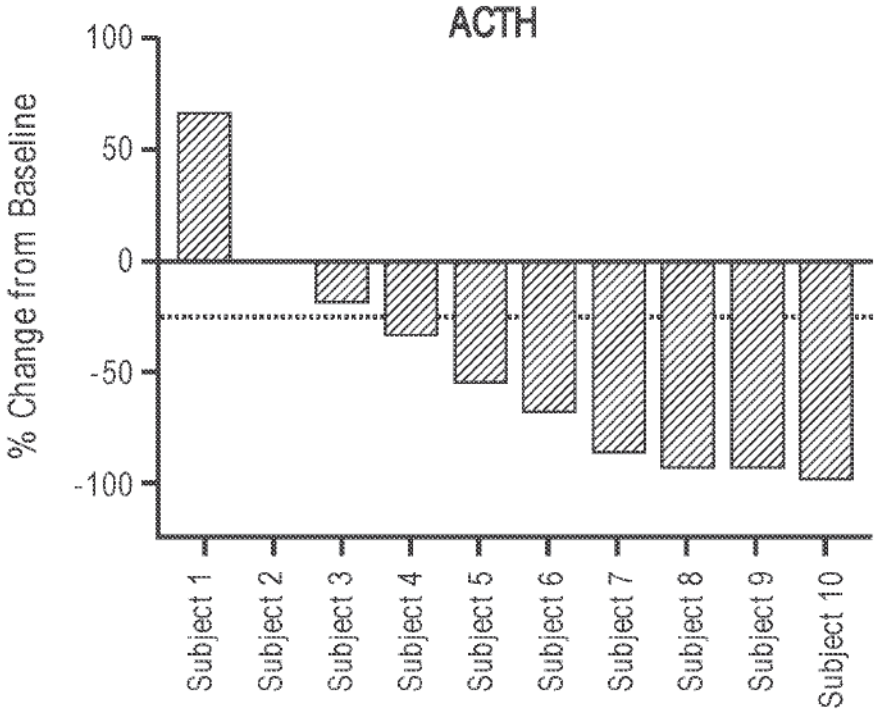

ACTH
% Change from Baseline
100
50
0
-50
-100
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
Subject 9
Subject 10

FIG. 2

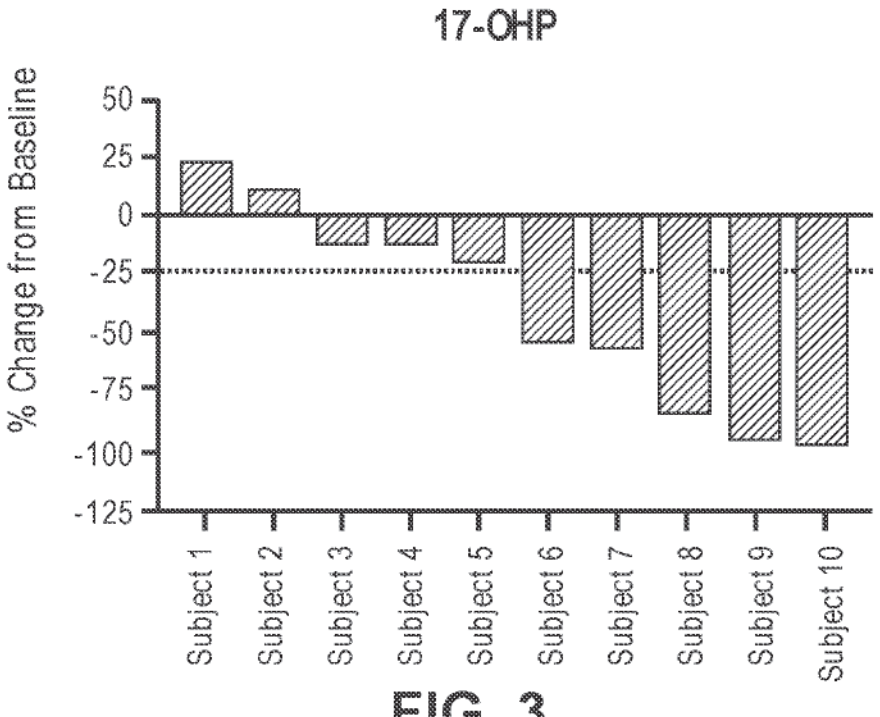

17-OHP
% Change from Baseline
50
25
0
-25
-50
-75
-100
-125
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
Subject 9
Subject 10

FIG. 3

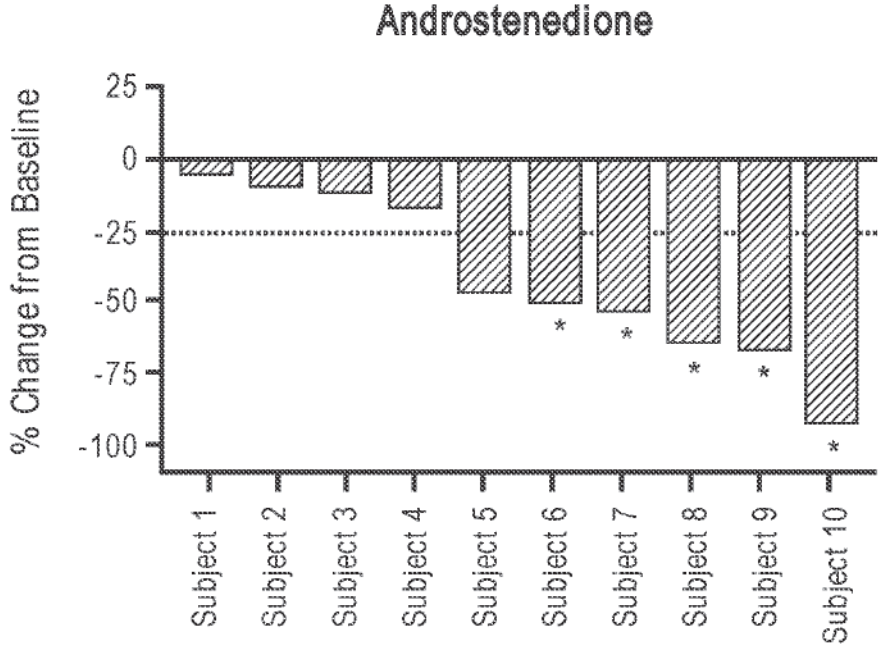

Androstenedione
% Change from Baseline
25
0
-25
-50
-75
-100
*
*
*
*
*
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
Subject 9
Subject 10

FIG. 4

PTO/AIA/82A (07-13)
Approved for use through 03/31/2021. 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	Unassigned
Filing Date	Filed Herewith
First Named Inventor	Alexis HOWERTON
Title	CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	50535-709.307

SIGNATURE of Applicant or Patent Practitioner

Signature	/Stephen Olshemski/	Date (Optional)	April 26, 2023
Name	Stephen Olshemski	Registration Number	80,285
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

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.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 03/31/2021. 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: 021971

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		Date (Optional)	7/28/2020
Name	Richard King		
Title	Chief Executive Officer		

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.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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.

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 #
18/307,718	04/26/2023 07:29:38 PM ET	50535-709.307

Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9067	FILED BY	John Bereznak
PATENT CENTER #	61992108	AUTHORIZED BY	Stephen Olshemski
CUSTOMER #	21971	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 232415	E20234PJ31006927	John Bereznak

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
232415	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	140.00	1	140.00
1817	REQUEST FOR PRIORITIZED EXAMINATION	4200.00	1	4200.00
1111	UTILITY PATENT APPL. SEARCH FEE	700.00	1	700.00
1011	BASIC FILING FEE - UTILITY (PAPER FILING ALSO REQUIRES NON-	320.00	1	320.00

	ELECTRONIC FILING FEE UNDER 1.16(T))			
1311	PATENT APPL. EXAMINATION FEE	800.00	1	800.00
1202	EACH CLAIM IN EXCESS OF 20	100.00	1	100.00
			TOTAL AMOUNT:	**$6,260.00**

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.

PTO/AIA/01 (09-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

As the below named inventor, I hereby declare that

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number 16/388,620 filed on April 18, 2019.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Alexis HOWERTON Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1.11 and 1.14. This collection is estimated to take 1 minute 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.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 16/388,620

filed on April 18, 2019

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Hal GERBER Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1.11 and 1.14. This collection is estimated to take 1 minute 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.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 16/388,620 filed on April 18, 2019.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Michael HUANG Date (Optional): 4/25/2019

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1.11 and 1.14. This collection is estimated to take 1 minute 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.

Application Data Sheet	Attorney Docket Number	50535-709.307
	Application Number	
Title of Invention	CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS	

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1					
Legal Name					
Prefix	**Given Name**	**Middle Name**		**Family Name**	**Suffix**
	Alexis			HOWERTON	
Residence Information	☒ US Residency	☐ Non US Residency	☐ Active US Military Service		
City	South San Francisco	**State/Province**	CA	**Country of Residence**	US
Mailing Address of Inventor					
Address 1	611 Gateway Blvd., Suite #740				
Address 2					
City	South San Francisco	**State/Province**	CA		
Postal Code	94080	**Country**	US		

Inventor 2					
Legal Name					
Prefix	**Given Name**	**Middle Name**		**Family Name**	**Suffix**
	Hal			GERBER	
Residence Information	☒ US Residency	☐ Non US Residency	☐ Active US Military Service		
City	South San Francisco	**State/Province**	CA	**Country of Residence**	US
Mailing Address of Inventor					
Address 1	611 Gateway Blvd., Suite #740				
Address 2					
City	South San Francisco	**State/Province**	CA		
Postal Code	94080	**Country**	US		

Inventor 3					
Legal Name					
Given Name	**Middle Name**		**Family Name**	**Suffix**	
Michael			HUANG		
Residence Information	☒ US Residency	☐ Non US Residency	☐ Active US Military Service		
South San Francisco	**State/Province**	CA	**Country of Residence**	US	

Mailing Address of Inventor			
Address 1	611 Gateway Blvd., Suite #740		
Address 2			
City	South San Francisco	**State/Province**	CA
Postal Code	94080	**Country**	US

Correspondence Information:

☐ An Address is being provided for the correspondence information of this application	
Customer Number	021971
Email Address	

Application Information:

Title of the Invention	CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS		
Attorney Docket Number	50535-709.307	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets	3	**Suggested Figure for Publication**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section is application papers including a specification any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 1229b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Please Select One	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition
Customer Number	021971		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78. When referring to the current application, please leave the "Application Number" field blank

Prior Application Status	Pending		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	18/078,649	2022-12-09
Prior Application Status	Abandoned		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
18/078,649	Continuation of	17/586,228	2022-01-27
Prior Application Status	Patented		

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17/586,228	Division of	17/359,411	2021-06-25	11,351,177	2022-06-07
Prior Application Status	Patented				
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17/359,411	Continuation of	17/063,592	2020-10-05	11,344,557	2022-05-31
Prior Application Status	Patented				
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17/063,592	Continuation of	16/388,620	2019-04-18	10,849,908	2020-12-01
Prior Application Status	Expired				

Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/388,620	Continuation of	PCT/US2018/046760	2018-08-14
Prior Application Status	Expired		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2018/046760	Claims the benefit of provisional	62/545,406	2017-08-14

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country	Filing Date (YYYY-MM-DD)	Access Code

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claim invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection1 below, application **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) – Unless box A in subsection 2 (opt-out authorization) is checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japanese Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the filing date of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO – Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

☒ Assignee	☐ Legal Representative under 35 U.S.C. 117	☐ Joint Inventor
☐ Person to whom the inventor is obligated to assign	☐ Person who shows sufficient proprietary interest	

If the applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Choose an item.

Name of the Deceased or Legally Incapacitated Inventor

If the Applicant is an Organization check here. ☒			
Organization Name	Spruce Biosciences, Inc.		
Mailing Address Information for Applicant:			
Address 1	611 Gateway Blvd., Suite #740		
Address 2			
City	South San Francisco	**State/Province**	CA
Country	US	Postal Code	94080
Phone Number		Fax Number	
Email Address			

Assignee Information Including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.			
Assignee 1			
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.			
If the Assignee or Non-Applicant Assignee is an Organization check here. ☐			
Organization Name			
Mailing Address Information For Assignee including Non-Applicant Assignee:			
Address 1			
Address 2			
City		**State/Province**	
Country		Postal Code	
Phone Number		Fax Number	
Email Address			

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Stephen Olshemski/			Date (YYYY-MM-DD)	2023-04-26
First Name	Stephen	Last Name	Olshemski	Registration Number	80,285

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 #
18/307,718	**04/26/2023 07:29:38 PM ET**	**50535-709.307**

Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9067	FILED BY	John Bereznak
PATENT CENTER #	61992108	FILING DATE	-
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Stephen Olshemski

Documents

TOTAL DOCUMENTS: 6

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Spruce Biosciences, Inc. 50535-709.307 Drawings - FILED.pdf	3	Drawings-only black and white line drawings	106 KB
Spruce Biosciences, Inc. 50535-709.307 Track One Request.pdf	1	Track One Request	129 KB
Spruce Biosciences, Inc. 50535-709.307 Declaration.pdf	3	Oath or Declaration filed	494 KB
Spruce Biosciences, Inc. 50535-709.307 Power of Attorney.pdf	2	Power of Attorney	1662 KB

Spruce 50535-709.307 Application Data Sheet.pdf	7	Application Data Sheet	140 KB

Warning: This is not a USPTO supplied ADS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Spruce Biosciences, Inc. 50535-709.307 Specification - FILED.pdf	62	Specification	320 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce Biosciences, Inc. 50535-709.307 Drawings - FILED.pdf	B2F87D5B858FCE70AE18DB3989658FDAC909EFD15F918AB0 B66611F850BF4CC7F23D69D03034CA48E8FBE1F8303FD3615 B833071661F09F5DA0B43D7EEAD9E78
Spruce Biosciences, Inc. 50535-709.307 Track One Request.pdf	9741019F9F5E795575709B0CA339A9437C36D94F5B63A13F97 309DF96CC6C16A5DC204C0F32C10BF368B9B1F8B5569E5570 96548E93D9765CB66171EAA9E8BE6
Spruce Biosciences, Inc. 50535-709.307 Declaration.pdf	083427D7A04AD6F11BBAAE87303DE9FCA2CD03FE055BBE8A 89133224FAC5BED4A2A559BD70549081EC5DF046151822BEE 05F959E0D4064F1836857356DD3A650
Spruce Biosciences, Inc. 50535-709.307 Power of Attorney.pdf	114399308EF69F66F39D081C8691E0796CA4783770460A81016 BA3430755CE5EBAB97F761DCC68B3D5077DCC9817BEBA9A3 32F2D69CC278454EA612A85F0D3BD
Spruce 50535-709.307 Application Data Sheet.pdf	DA70733E8D85B4264177F93F651961C7FBB21D1DA58247CDE A06529C131F5C5308C85D4AE70C9CDBE51356304F2EEC6429 4CBD1B572BA3D566EE3F8869C1BEFF
Spruce Biosciences, Inc. 50535-709.307 Specification - FILED.pdf	D49E9431BAF3CC358A07EF963A514417CD7C0F5E47E204C43 4DE2B355278105B4E7EBB6AF65918C574A7583461855F445AE 670BFB42783824C49BD29FDAE1D53

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: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Alexis HOWERTON	Nonprovisional Application Number (if known):	
Title of Invention:	CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Stephen Olshemski/	Date April 26, 2023
Name (Print/Typed) Stephen Olshemski	Practitioner Registration Number 80,285

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

WSGR Docket No. 50535-709.307

PATENT APPLICATION

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

Inventor(s): Alexis HOWERTON
Citizen of USA, Residing at
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

Hal GERBER
Citizen of USA, Residing at
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

Michael HUANG
Citizen of USA, Residing at
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

Assignee: Spruce Biosciences, Inc.
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

a Delaware Corporation

Entity: Large business concern

WILSON
SONSINI

650 Page Mill Road
Palo Alto, CA 94304
(650) 493-9300 (Main)
(650) 493-6811 (Facsimile)

Filed Electronically on: April 26, 2023

4893-7748-9247

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

CROSS-REFERENCE

[0001] This patent application is a continuation of U.S. Patent Application No. 18/078,649, filed December 9, 2022; which is a continuation of U.S. Patent Application No. 17/586,228, filed January 27, 2022; which is a divisional of U.S. Patent Application No. 17/359,411, filed on June 25, 2021, now U.S. Patent No. 11,351,177; which is a continuation of U.S. Patent Application No. 17/063,592, filed on October 5, 2020, now U.S. Patent No. 11,344,557; which is a continuation of U.S. Patent Application No. 16/388,620, filed on April 18, 2019, now U.S. Patent No. 10,849,908; which is a continuation of PCT Application No. PCT/US2018/046760, filed on August 14, 2018; which claims the benefit of U.S. Provisional Patent Application No. 62/545,406, filed August 14, 2017; all of which are incorporated herein by reference in their entirety.

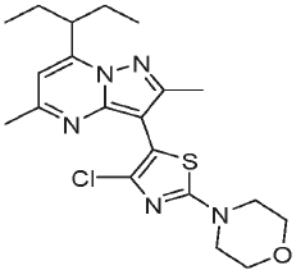
BACKGROUND OF THE INVENTION

[0002] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

SUMMARY OF THE INVENTION

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

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



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

[0005] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

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

[0007] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0008] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0009] In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more

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

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

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

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

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

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

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

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

[0016] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are

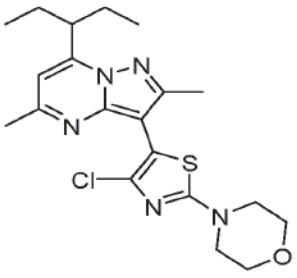
administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid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

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

[0018] In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 mins before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night. In some embodiments, the pharmaceutical composition is administered at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the pharmaceutical composition is administered about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

[0019] In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

[0020] In one aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering Compound 1:



or a pharmaceutically acceptable salt or solvate thereof; and

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

[0021] In some embodiments, the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione. In some embodiments,

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

[0022] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

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

In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 50 mg /day.

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

[0025] In some embodiments, Compound 1 is formulated in a pharmaceutical composition in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0026] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

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

embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0028] In some embodiments the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments,the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, he pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

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

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

[0031] In some embodiments, the method further comprises administering a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or

solvate thereof. In some embodiments, the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount. In some embodiments, the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.

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

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

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

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

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

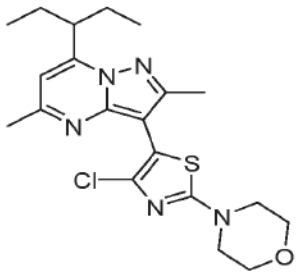
solvate thereof, is administered in the evening. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at 10 pm at night.

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

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

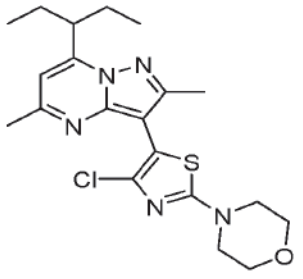
[0039] In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

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



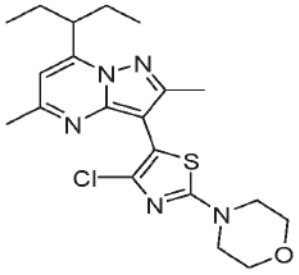
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0041] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

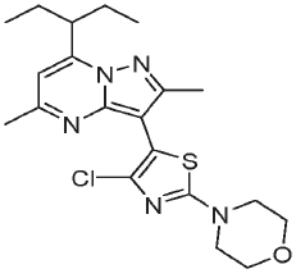


; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

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

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

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

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

INCORPORATION BY REFERENCE

[0044] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

[0050] CRF has been implicated in psychiatric disorders and neurological diseases including depression and anxiety, as well as the following: Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and associated withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia (CAH), Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulceration, premenstrual syndrome, sexual dysfunction, premature labor, inflammatory disorders, allergies, multiple sclerosis, visceral pain, sleep disorders, pituitary tumors or ectopic pituitary derived tumors, chronic fatigue syndrome, and fibromyalgia.

[0051] CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors. A more discrete septallhypothalmic distribution and the availability of alternative endogenous ligands suggest a different functional role for the CRF2 receptor. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF 1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism. In other cases, CRF2 agonism produces similar effects to those reported for CRF 1 antagonists or CRF 1 gene deletion. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well.

[0052] Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous Cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which Cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment

include Cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

[0053] The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient Cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of Addisonian syndrome due to under-treatment. Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione, testosterone, renin activity, and electrolytes.

[0054] Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance. A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes. Treatment of CAH includes efforts to normalize the Cortisol deficiency with glucocorticoids (usually hydrocortisone in children but often more potent agents with narrow therapeutic indices, such as dexamethasone, in adults) and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for Cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients.

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

[0056] 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.

[0057] The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21 -hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-hydroxyprogesterone (17-OHP). Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21 -hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically Cortisol and aldosterone. Cortisol is a critical negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

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

Certain Definitions

[0059] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[0060] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

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

[0062] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or."

[0063] The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[0064] "Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. "Administering" a pharmaceutical composition may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

[0065] By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

[0066] The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as Compound 1, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

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

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

[0069] A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or

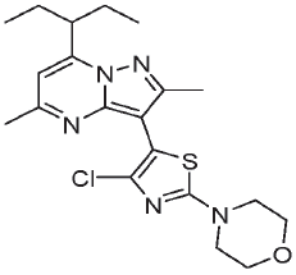
displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

[0070] The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

[0071] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Compound

[0072] Disclosed herein is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine (or alternatively 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine), a pharmaceutically acceptable salt, and/or a solvate thereof:



. In some embodiments, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine is referred to as Compound 1. In some embodiments, 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine is referred to as Compound 1.

Pharmaceutical Compositions

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

Dosage Form

[0074] In some embodiments, the pharmaceutical compositions described herein are provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of Compound 1 that is suitable for administration to an animal, preferably mammal, subject in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

[0075] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0076] In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more

additional pharmaceutically acceptable excipients. *See, e.g., Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

Capsule

[0077] In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

[0078] In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents, flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or delayed release coatings, sustained release coatings, barrier coatings, seal coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary according to the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

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

[0080] In some embodiments, a capsule is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if

solubility is less than 0.002 mg/mL in water. In some embodiments, the capsule has a dose strength of up to 200 mg. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus II.

Tablet

[0081] Poorly soluble drugs may be difficult to formulate using standard technologies such as high shear wet granulation. Optimum delivery of poorly soluble drugs may require complex technologies such as solid solutions amorphous dispersions (hot melt extrusion or spray drying), nano-formulations or lipid-based formulations. Hydrophobic drug substances may be considered poorly soluble according to USP criteria and may be known to be difficult to granulate with water and other excipients. This is likely due to most known excipients for immediate release formulations being water soluble or water-swellable. Making a tablet of a high dose drug substance that is poorly soluble may require a high concentration of the drug substance. However, as the drug concentration is increased above a certain level, formation of granules may become more and more difficult. Furthermore, at a certain drug load, it may become impossible.

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

[0083] In some embodiments, the tablet is made by compression, molding, or extrusion, optionally with one or more pharmaceutically acceptable excipient. In some embodiments, compressed tablets are prepared by compressing Compound 1 in a free-flowing form, optionally mixed with pharmaceutically acceptable excipients. In some embodiments, molded tablets are made by molding a mixture of the powdered Compound 1 moistened with an inert liquid diluent. In some embodiments, the tablet is prepared by hot-melt extrusion. In some embodiments, extruded tablets are made by forcing a mixture comprising Compound 1 through an orifice or die under controlled conditions. In some embodiments, the tablet is coated or scored. In some embodiments, the tablet is formulated so as to provide slow or controlled release of Compound 1. In some embodiments, a tablet is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the tablet has a dose strength of up to 200 mg. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus II.

[0084] In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg,

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

[0085] 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.

[0086] In some embodiments, the tablet is produced at a commercial scale.

[0087] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[0088] In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of Compound 1. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone, polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

Pharmaceutically Acceptable Excipients

[0089] 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.

[0090] 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

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

acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 1 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0092] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the

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

[0093] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0094] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0095] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or

solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0096] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

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

mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0098] In some embodiments, the pharmaceutical composition comprises about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

Particle size

[0099] In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises Compound 1, or a pharmaceutically acceptable salt or solvate thereof, in the form of microparticles. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 100 μm. In some embodiments, microparticles of Compound 1

have an average size from about 1 μm to about 50 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 30 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 20 μm. In some embodiments, microparticles of Compound 1 have an average size from about 5 μm to about 15 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 3 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 4 μm to about 9 μm.

[0100] In some embodiments, microparticles of Compound 1 have an average size less than about 100 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 80 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 60 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 50 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 40 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 30 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 20 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 10 μm.

Pharmacokinetics

[0101] In some embodiments, Compound 1 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, Compound 1 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, Compound 1 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, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

[0102] In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

Stability

[0103] The pharmaceutical compositions described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to pharmaceutical compositions having about 95% or greater of the initial Compound 1 amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of Compound 1. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable pharmaceutical compositions have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable pharmaceutical compositions have about 5% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 4% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 3% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 2% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 1% w/w total impurities or related substances.

[0104] At refrigerated condition, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±5 °C. In some embodiments, refrigerated condition is about 0 °C, about 0.1 °C, about 0.2 °C, about 0.3 °C, about 0.4 °C, about 0.5 °C, about 0.6 °C, about 0.7 °C, about 0.8 °C, about 0.9 °C, about 1 °C, about 1.1 °C, about 1.2 °C, about 1.3 °C, about 1.4 °C, about 1.5 °C, about 1.6 °C, about 1.7 °C, about 1.8 °C, about 1.9 °C, about 2 °C, about 2.1 °C, about 2.2 °C, about 2.3 °C, about 2.4 °C, about 2.5 °C, about 2.6 °C, about 2.7 °C, about 2.8 °C, about 2.9 °C, about 3 °C, about 3.1 °C, about 3.2 °C, about 3.3 °C, about 3.4 °C, about 3.5 °C, about 3.6 °C, about 3.7 °C, about 3.8 °C, about 3.9 °C, about 4 °C, about 4.1 °C, about 4.2 °C, about 4.3 °C, about 4.4 °C, about 4.5 °C, about 4.6 °C, about 4.7 °C, about 4.8 °C, about 4.9 °C, about 5 °C, about 5.1 °C, about 5.2 °C, about 5.3 °C, about 5.4 °C, about 5.5 °C, about 5.6 °C, about 5.7 °C, about 5.8 °C, about 5.9 °C, about 6 °C, about 6.1 °C, about 6.2 °C, about 6.3 °C, about 6.4 °C, about 6.5 °C, about 6.6 °C, about 6.7 °C, about 6.8 °C, about 6.9 °C, about 7 °C, about 7.1 °C, about 7.2 °C, about 7.3 °C, about 7.4 °C, about 7.5 °C, about 7.6 °C, about 7.7 °C, about 7.8 °C, about 7.9 °C, about 8 °C, about 8.1 °C, about 8.2 °C, about 8.3 °C, about 8.4 °C, about 8.5 °C, about 8.6 °C, about 8.7 °C, about 8.8 °C, about 8.9 °C, about 9 °C, about 9.1 °C, about 9.2 °C, about 9.3 °C, about 9.4 °C,

about 9.5 ºC, about 9.6 ºC, about 9.7 ºC, about 9.8 ºC, about 9.9 ºC, or about 10 ºC. At accelerated conditions, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, or at least 24 month. Accelerated conditions for the pharmaceutical compositions described herein include temperatures that are at or above ambient levels (e.g. 25±5 °C). In some instances, an accelerated condition is at about 40±2 °C. In some instances, an accelerated condition is at about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C, or about 60 °C. Accelerated conditions for the pharmaceutical compositions described herein also include relative humidity (RH) that are at or above ambient levels (55±10% RH). In other instances, an accelerated condition is above about 65% RH, about 70% RH, about 75% RH, or about 80% RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40±2 °C at 75±5% RH humidity.

[0105] In some embodiments, the pharmaceutical compositions are stable at about 5±5 ºC to about 25±5 ºC for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 ºC for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 ºC for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 ºC for at least 24 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 ºC for at least 24 months.

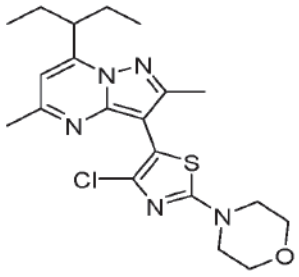
Methods of Use

[0106] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.In some embodiments, the methods described herein result in the reduction of a hormone level. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17α-hydroxy progesterone (17-OHP), dehydroepiandrosterone, androstenediol, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein result in the reduction of 17α-hydroxy progesterone (17-OHP). In some embodiments, the methods described herein result in the reduction of adrenocorticotropic hormone (ACTH), also known as corticotropin.

[0107] Also disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising:

(i) measuring a hormone level in the subject in need thereof;

(ii) administering Compound 1:



or a pharmaceutically acceptable salt or solvate thereof;

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

[0108] In some embodiment, the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione.

[0109] In some embodiment, the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL. In some embodiment, the hormone is 17-OHP, and the pre-determined range is less than about 400 ng/dL, less than about 350 ng/dL, less than about 300 ng/dL, less than about 250 ng/dL, or less than about 200 ng/dL.

[0110] In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL. In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL, below about 90 pg/mL, or below about 80 pg/mL.

[0111] In some embodiment, the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL. In some embodiment, the hormone is testosterone and the pre-determined range is less than about 76 ng/dL, less than about 70 ng/dL, less than about 65 ng/dL, less than about 60 ng/dL, less than about 55 ng/dL, less than about 50 ng/dL, less than about 45 ng/dL, less than about 40 ng/dL, less than about 35 ng/dL, less than about 30 ng/dL, less than about 25 ng/dL, less than about 20 ng/dL, or less than about 15 ng/dL.

[0112] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 200 ng/dL in males. In some embodiment, the hormone is androstenedione and the pre-determined range is less than about 200 ng/dL, less than about 150 ng/dL, less than about 100 ng/dL, less than about 50 ng/dL, or less than about 30 ng/dL in males.

[0113] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 150 ng/dL in females. In some embodiment, the hormone is

androstenedione and the pre-determined range is less about 150 ng/dL, less about 100 ng/dL, less about 50 ng/dL, or less about 40 ng/dL in females.

[0114] In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a month, twice a month, three times a month, once a week, twice a week, three times a week, once every two days, once a day, twice a day, three times a day, or four times a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof twice a day.

[0115] In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1500 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1400 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1300 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1100 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 900 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 60 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 70 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 80 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 90 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 700 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 150 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200

mg/day and about 500 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 400 mg/day.

[0116] 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.

[0117] In some embodiments, about 100 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

[0118] In some embodiments, less than about 2000 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered

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

[0119] 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.

[0120] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

[0121] 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.

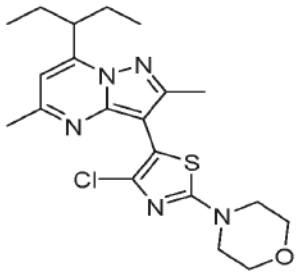
[0122] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

[0123] 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.

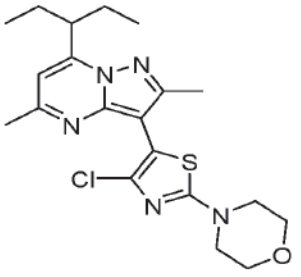
[0124] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

[0125] In one aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



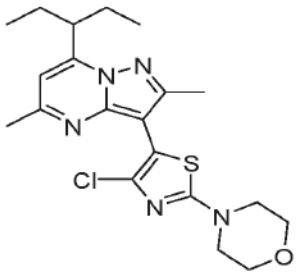
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0126] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

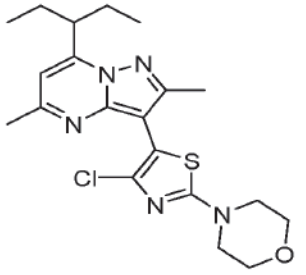


; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

[0127] In one aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition

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

[0128] In one aspect, the present disclosure provides a method of improving quality of life in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

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

Combination Therapy

[0129] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; and a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0130] In some embodiments, the methods described herein reduce the amount of a glucocorticoid administered from a supraphysiologic amount to a physiologic amount.

[0131] In some embodiments, the methods described herein reduce the symptoms associated with high-dose glucocorticoid therapy. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.

[0132] In some embodiments, the amount of glucocorticoid administered is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about

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

[0133] In some embodiments, the amount of glucocorticoid administered is reduced by about 1% to about 90%, about 1% to about 60%, about 1% to about 30%, about 1% to about 10%, about 10% to about 50%, about 10% to about 40%, about 10% to about 30%, about 15% to about 25%, about 20% to about 30%, about 5% to about 25%, about 20% to about 50%, about 30% to about 60%, or about 40% to about 70% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0134] In some embodiments, the glucocorticoid is administered at a dose between about 0.1 mg/day and about 25 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 20 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 15 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 12 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 9 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 8 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 7 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 6 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 5 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 4 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 3 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 2 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 3 mg/day and about 13 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 8 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 9 mg/day and about 12 mg/day. In some embodiments, the

glucocorticoid is administered at a dose between about 9 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 10 mg/day.

[0135] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered in one pharmaceutical composition. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently in separate pharmaceutical compositions.

[0136] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 12 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 8 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 6 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 4 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 2 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 1 hour. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 30 minutes. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 10 minutes.

[0137] In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

[0138] In some embodiments, the glucocorticoid is hydrocortisone and the dose administered is less than the recommended dose of 15-25 mg/day.

[0139] In some embodiments, the glucocorticoid is prednisone and the dose administered is less than the recommended dose of 5-7.5 mg/day.

[0140] In some embodiments, the glucocorticoid is prednisolone and the dose administered is less than the recommended dose of 4-6 mg/day.

[0141] In some embodiments, the glucocorticoid is dexamethasone and the dose administered is less than the recommended dose of 0.25-0.5 mg/day.

[0142] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; a glucocorticoid; and optionally a mineralcorticoid. In some embodiments, the mineralocorticoid is fludrocortisone and the dose is less than the recommended dose of 0.05-0.2 mg/day.

EXAMPLES

[0143] 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.

[0144] All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

Example 1: Pharmaceutical Composition

[0145] The pharmaceutical composition is manufactured as size 1 white hard gelatin capsules containing 200 mg of Compound 1 micronized to and average size of 10 microns or less. The pharmaceutical composition contains no additional excipients.

Example 2: Stability of the Pharmaceutical Composition

Stability Data Summary

[0146] A summary of the pharmaceutical composition stability studies is provided in Table 1. The pharmaceutical composition is a Compound 1 neat-filled into size 0 capsules with no added excipients, in 3 strength configurations: 1-mg, 5-mg, and 50-mg. The capsules were blister packaged in a polyvinyl chloride (PVC)-based film.

[0147] Under long term and accelerated conditions, no significant trend was observed in the three lots for any of the attributes evaluated throughout the course of the stability study.

Table 1. Summary of Stability

Lot Number	Strength	CCS	Stability Conditions	Available Data
#1	1-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#2	5-mg	PVC-based	25 °C/60% RH	6 months

		blister pack	40 °C/75% RH	6 months
#3	50-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#4	200-mg	75 mL HDPE bottle	25 °C/60% RH	1 month
			40 °C/75% RH	9 months
#5	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#6	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months

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

Stability Protocols

[0148] The stability protocol for various pharmaceutical compositions is provided in Table 2, 3, and 4.

Table 2. Stability Protocol

Test	**Acceptance Criteria**	**Time (months)**			
		T_0	1	**3**	**6**
Appearance	Size 0 blue capsule containing yellow powder, blister pack and foil backing intact	X	A,B	A,B	A,B
Assay	Report (% Label Claim)	X	A,B	A,B	A,B
Related Substances	Report RRT and % each individual species and total	X	A,B	A,B	A,B
Disintegration	Report	X	A,B	A,B	A,B

RRT = relative retention time
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

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

Test	**Acceptance Criteria**	**Time (months)**			
		T_0	1	3	6
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	A,B	A,B	A,B

Assay (%LC)	90.0 – 110.0	X	A,B	A,B	A,B
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	A,B	A,B	A,B
Disintegration (min)	NMT 15	X	A,B	A,B	A,B
Water Activity	Report result	X	A,B	A,B	A,B

LC = label claim; NMT = not more than
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

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

Test	**Acceptance Criteria**	**Time (months)**					
		T_0	**1**	**3**	**6**	**9**	**12**
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	B	A,B	A,B	A	A
Assay (%LC)	90.0 – 110.0	X	B	A,B	A,B	A	A
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	B	A,B	A,B	A	A
Disintegration (min)	NMT 15	X	B	A,B	A,B	A	A
Water Activity	Report result	X	n/a	n/a	n/a	A	A
Microbial Enumeration Total Aerobic Microbial Count (CFU/g) Total Combined Yeast and Mold (CFU/g) Count	 NMT 2000 CFU/g NMT 200 CFU/g	X	n/a	n/a	n/a	A	A

Test	Acceptance Criteria	Time (months)					
		T_0	1	3	6	9	12
Test for Specified Microorganisms *E. coli* (/g)	Absent	X	n/a	n/a	n/a	A	A

CFU = colony forming units; LC = label claim; n/a = not applicable; NMT = not more than
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

[0149] The supportive data demonstrate that the pharmaceutical composition is stable for a minimum of 6 months (end of study). No adverse trends were observed under long term and accelerated conditions. The assay results were consistent through the entire study and no new related substances species were observed during the stability study. The reported stability results for lots stored in a blister packaging configuration are considered supportive for the updated packaging configuration of a 30-mL HDPE bottle, induction seal, and a child resistant cap. There are no excipients in either configuration and both configurations provide protection from light.

Example 3: Phase 1 Clinical Studies

[0150] Compound 1 has been investigated in 2 Phase 1 studies in healthy adult volunteers.

[0151] Study 1 was the first-in-human study that investigated the safety, tolerability, and PK of single-escalating doses of Compound 1, given orally, to healthy adult subjects. Safety and tolerability assessments were made over a wide range of single oral doses, and dose escalation did not proceed until safety data from the preceding doses had been reviewed. The data from this study were used for the selection of doses for Study 2.

[0152] The 2-part multiple-dose study, Study 2, determined the safety and tolerability of repeated daily doses of Compound 1 and investigated the effects on biomarkers of relevance for the treatment of alcohol dependence. Part B investigated the interaction of Compound 1 with midazolam (a cytochrome P450 3A4 [CYP3A4] substrate), determining whether Compound 1 significantly inhibited the metabolism of drugs that are metabolized by CYP3A4.

[0153] In Study 1, Compound 1 was administered to healthy adult subjects as a single PO dose of 2, 10, 50, 150, 400, or 800 mg in the fed state and 150 mg in the fasted state. Absorption occurred moderately late, achieving peak C_{max} between 4 to 6 hours following dosing in the fed state.

[0154] Table 5 provides a summary of the PK parameters at each dose level. When Compound 1 was given in the fed state, median time to reach maximum plasma concentration (T_{max}) occurred between 4 and 6 hours. The median T_{max} was 10.05 hours when Compound 1 was given in the fasted state at 150 mg and ranged between 6 and 12 hours, suggesting possible

delayed absorption in the fasted state. Mean half-life ($t_{1/2}$) after a single PO dose (fed and fasted state) was between 31 and 44 hours, ranging from 11 to 101 hours. Apparent volume of distribution (V_z/F) was large and appeared highly variable with greatest variability observed at the 2 highest dose levels of 400 mg and 800 mg.

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

PK Parameters	Geometric Mean (CV%) Analyte = Plasma Compound 1					
	2 mg	**10 mg**	**50 mg**	**150 mg**	**400 mg**	**800 mg**
N	6	6	6	6	6	6
C_{max} (ng/mL)	0.867 (53)	3.01 (87)	19.5 (39)	93.4 (22)	207 (92)	382 (110)
T_{max}[a] (h)	6.00 (4.00-6.00)	4.00 (2.00 -6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	6.00 (4.00 - 6.00)
$t_{1/2}$[b] (h)	NC (NC)	NC (NC)	31 (10.8-53.4)	29.2 (20.0 - 41.5)	44.2 (20.2 - 101)	41.9 (24.1 - 67.8)
$AUC_{0\text{-}tlast}$ (ng•h/mL)	NC (NC)	NC (NC)	152 (60)	891 (26)	2300 (103)	4390 (100)
$AUC_{0\text{-}\infty}$ (ng•h/mL)	NC (NC)	NC (NC)	165 (64)	956 (25)	2580 (93)	4850 (95)
CL/F (L/h)	NC (NC)	NC (NC)	302 (64)	157 (25)	155 (93)	165 (95)
V_z/F (L)	NC (NC)	NC (NC)	13500 (45)	6620 (38)	9890 (212)	9970 (144)
V_{ss}/F (L)	NC (NC)	NC (NC)	8080 (36)	4600 (33)	6580 (152)	6820 (120)

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

a Median (range)

b Geometric mean (range)

[0155] As part of this single-dose escalation study, a food effect PK investigation was performed to examine Compound 1 exposures in both the fed and fasted states at the 150-mg dose level. A total of 6 subjects were administered 150 mg Compound 1 in each of these 2 dosing groups. Of these 6 subjects, 4 subjects received Compound 1 at the same dose in both fed and fasted states. The administration of Compound 1 in the fasted state resulted in a much flatter mean concentration-time (i.e., with significantly lower absorption) profile when compared against the mean profile at the same dose, given within 5 minutes after a standardized breakfast meal. The mean $AUC_{0\text{-}\infty}$, and C_{max} values for a 150-mg dose in the fed state was approximately 3- and 11-fold greater than that of the fasted state, respectively. Table 6 provides a summary of the PK parameters at the 150-mg dose level under both fed and fasted state conditions.

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

Pharmacokinetic Parameters	Geometric Mean (CV %)	
	Analyte = Plasma Compound 1	
	150 mg Fed	150 mg Fasted
N	6	6
C_{max} (ng/mL)	93.4 (22)	8.22 (83)
T_{max}[a] (h)	4.00 (3.00 – 6.00)	10.05 (6.00 – 12.00)
$t_{1/2}$[b] (h)	29.2 (20.0 – 41.5)	38.4 (24.2 – 88.5)
$AUC_{0\text{-tlast}}$ (ng•h/mL)	891 (26)	288 (48)
$AUC_{0\text{-}\infty}$ (ng•h/mL)	956 (25)	331 (44)
CL/F (L/h)	157 (25)	454 (44)
Vz/F (L)	6620 (38)	25100 (81)
Vss/F (L)	4600 (33)	25200 (68)

AUC = area under the plasma concentration-time curve; CL/F = apparent total body clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; N = number of subjects; NC = not calculable; PK = pharmacokinetic; T_{max} = time to reach maximum plasma concentration; t1/2 = elimination half-life; $V_{ss}F$ = apparent volume of distribution at steady state during the terminal phase after extravascular administration; V_z/F = apparent volume of distribution during the terminal phase after extravascular administration.

a Median (range)

b Geometric mean (range)

[0156] PK parameters $AUC_{0\text{-}\infty}$ and C_{max} were analyzed separately for dose proportionality for Compound 1 from 50 to 800 mg when administered in the fed state. The analysis results suggested that for every doubling of dose, $AUC_{0\text{-}\infty}$ can be expected to increase 1.74 times more than what would be expected under dose proportionality. C_{max} appeared more than dose proportional but the formal test was inconclusive as the 90% confidence interval were partially within the 0.8 – 1.25 interval. Dose proportionality across administered doses in the fed state could not be concluded on the basis of $AUC_{0\text{-}\infty}$ or C_{max}.

[0157] PK were also evaluated in the multiple-dose, dose-escalation study, Study 2. In Part A of the study, subjects were divided into 3 cohorts and received 50, 150, or 200 mg Compound 1 or placebo for 14 consecutive days (at least 6 subjects received Compound 1 and 2 subjects received placebo in each cohort). Blood concentrations of Compound 1 were close to steady-state levels after 2 weeks of dosing and the accumulation ratio was between 2.51 to 3.65. Part B investigated the interaction of Compound 1 with midazolam (a CYP3A4 substrate), thereby determining whether this compound significantly inhibited the metabolism of drugs that are metabolized by CYP3A4 serial blood samples were collected to determine plasma concentrations of study drug after a single dose of Compound 1 had been administered and at steady state. All dosing occurred in the fed state. An assessment of diurnal cortisol levels, plus when under conditions of glucose clamp, were also carried out both prior to and during the dosing period.

[0158] Overall concentration time profiles of Compound 1 showed that absorption was moderately delayed with C_{max} achieved at a median of 5 hours following oral dosing. Consistent with the single-dose study (Study 1), concentrations appeared to decline in a bi-exponential manner, characterized by a rapid decrease within the first 24 hours. Following multiple daily dosing for 2 weeks, the $t_{1/2}$ of Compound 1 exceeded 100 hours; therefore, an accumulation ratio of Compound 1 was between 2.51 to 3.65 (see Table 7). The T_{max} appeared to be consistent across doses. Overall half-lives, weight normalized CL/F and V/F were consistent for 150 and 200 mg. However, the values for these latter 2 parameters were almost doubled at the 50-mg dose level. Variability (CV%) for apparent clearance and volume of distribution were large and not reduced with weight-normalization.

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

	Geometric Mean (CV%)					
	50 mg Day 1	**150 mg Day 1**	**200 mg Day 1**	**50 mg Day 14**	**150 mg Day 14**	**200 mg Day 14**
N	**8**	**9**	**7**	**8**	**9**	**6**
C_{max} (ng/mL)	22.7 (59)	127 (52)	143 (62)	50.3 (56)	222 (58)	314 (93)
T_{max} [a] (hr)	4.52 (3.00 – 10.00)	5.00 (5.00 - 6.00)	5.00 (2.00 - 5.00)	5.00 (3.00 - 5.00)	5.00 (3.00 - 5.03)	5.00 (3.00 - 5.00)
Effective $t_{1/2}$ [b] (hr)	NC NC	NC NC	NC NC	37.7 (27.4)	32.7 (29.7)	52.0

$AUC_{0-\infty}$ (ng•hr/mL)	NC NC	NC NC	NC NC	980 (53.8)	4680 (104)	5660 (122)
AUC_{0-24h} (ng•hr/mL)	97.6 (58)	590 (56)	559 (55[c])	273 (56)	1480 (66)	2040 (98)
C_{avg} (ng/mL)	NC NC	NC NC	NC NC	11.4 (56)	61.7 (66)	85.0 (98)
CL_{aa}/F (L/hr)	NC NC	NC NC	NC NC	183 (56)	101 (66)	98 (98)
WT-norm						
Cl_{aa}/F (L/hr/kg)	NC NC	NC NC	NC NC	2.88 (46.9)	1.42 (72.9)	1.50 (89.9)
Vz/F (L)	NC NC	NC NC	NC NC	33500 (90)	17600 (59)	16300 (76)
Vss/F (L)	NC NC	NC NC	NC NC	12900 (91)	6170 (40)	5080 (78)
WT-norm						
Vss/F (L/kg)	NC NC NC	NC NC NC	NC NC NC	204 (71.3) 2.80	86.5 (41.0) 2.51	77.4 (68.6) 3.65
R_A	NC	NC	NC	(27.4)	(29.7)	(34.4)

AUC = area under the plasma concentration-time curve; CL/F = apparent clearance; C_{max} = maximum plasma concentration; RA = accumulation ratio calculated as Day 14 AUC_{0-24}/Day 1 AUC_{0-24}; t1/2 = terminal half-life; effective t1/2 = half-life calculated by accumulation ratio; Tmax = time to maximum plasma concentration; Vss/F = volume of distribution at steady state; Vz/F = volume of distribution at terminal phase; WT-norm = weight normalized

[a] Median (range).

[b] Geometric mean (range).

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

[0159] Table 8 presents the results of the dose proportionality assessment for the AUC_{0-24} and C_{max} over the tested dose range. For AUC_{0-24} and C_{max}, the adjusted mean slope at Day 1 and Day 14 were all above the value of 1, suggesting a slightly more than proportional increase of AUC_{0-24} and C_{max} values with increasing doses.

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

Parameter	Day	Mean Slope	Standard Error	90% CI for Slope	CV%
AUC_{0-24} (ng hr/mL)	1	1.40	0.194	(1.069, 1.737)	59.3
	14	1.48	0.221	(1.104, 1.864)	69.1
C_{max} (ng/mL)	1	1.41	0.185	(1.092, 1.728)	57.5

	14	1.33	0.210	(0.972, 1.693)	64.8

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

Safety

[0160] The safety of Compound 1 was evaluated in 2 Phase 1 studies in healthy adult volunteers (Study 1 and Study 2). In both studies, adverse events (AEs), clinical laboratory tests, vital signs (supine blood pressure and pulse rate), and electrocardiograms (ECGs) were evaluated. Overall, in Study 1, Compound 1 was well-tolerated.

[0161] Compound 1, when administered as multiple doses up to 200 mg, was generally well tolerated in the healthy subject population studied. In Study 1, the effects upon biomarkers of relevance for the treatment of alcohol dependence were investigated. Five clusters of an Addiction Research Center Inventory Questionnaire (ARCI-49) were used to compare the effect of Compound 1 vs. placebo: Morphine-Benzedrine Group Scale measuring euphoria; Lysergic-Acid-Diethylamide Group Scale estimating dysphoric and somatic changes; Pentobarbital-Chlorpromazine-Alcohol Group Scale measuring sedation; Benzedrine Group (BG) Scale measuring intellectual efficiency and energy; Amphetamine Group Scale measuring effects of d-amphetamine, respectively. No systematic pattern or dose-response for the change from baseline or for the difference over placebo in each cluster was observed.

[0162] In summary, single, oral doses up to 800 mg and multiple doses up to 200 mg of Compound 1 were well-tolerated by healthy male and female subjects.

Example 4: Phase 2 Clinical Studies

[0163] Cohort A of the Phase 2 Study includes a 6-week, multiple-dose, dose escalation study of Compound 1 for the treatment of adults with classic CAH. After screening, eligible patients will be enrolled into a 6-week treatment period followed by a 4-week washout/safety follow-up period.

[0164] This cohort will be conducted in approximately 9 patients, who will receive Compound 1 daily for up to 6 weeks. Compound 1 will be administered as an oral daily dose. Patients will undergo titration of Compound 1 through three escalating dosage strengths at 2-week intervals. Patients will have overnight PK/PD assessments performed at baseline, which include an pre-dose overnight assessment and a post-dose overnight assessment for PK/PD following administration of the first dose. At the end of each 2-week dosing period, patients will return for single overnight visits for steady-state PK/PD assessments. A follow-up outpatient visit will occur 30 days after their last dose. Upon completion of the initial cohort (Cohort A), the study will proceed to a multiple ascending dose (MAD) design with up to 3 sequential cohorts (Cohorts B, C, and D) to further evaluate the safety, PK, and PD of various SPR001 dosing regimens and to identify an optimal dose regimen. Each cohort will undergo a 2-week run-in

period, a 2-week treatment period, and a 30-day washout and safety follow-up period. During the run-in period, which will occur during screening, subjects will document in a paper diary each dose of glucocorticoid medication taken, the time of each meal, and the time they went to bed and woke up each day, to ensure compliance with background glucocorticoid regimens and the stability of their daily routine.

[0165] Patients in Cohort B will receive study drug at 200 mg BID, with a dose in the morning and a dose in the evening, either with a meal or consumption of a standardized snack. For Cohorts C and D, the dose level and the frequency and timing of dosing will be determined based on interim data from the previous cohorts. However, the dose level of each successive cohort will be capped at twice the daily dose level of the previous cohort.

Study Design

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

Arms and Interventions

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

Outcome Measures

Primary Outcome Measure:

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

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

Secondary Outcome Measure:

3. To explore the dose(s) of Compound 1 that cause pharmacodynamics changes in plasma concentrations of ACTH, androstenedione, and testosterone, as measured by the absolute and percent change from baseline by dose.

4. To determine pharmacokinetics of Compound 1 in subjects with CAH.

5. To explore potential relationships between pharmacodynamics and pharmacokinetics.

Exploratory

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

Eligibility

- Minimum Age: 18 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Results:

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

[0166] With respect to patient-level response to Compound 1, 80% showed reduced ACTH (see FIG. 2). Generally, attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of patient subjects demonstrated reduction in ACTH. 70% of subject demonstrated more than 25% reduction in ACTH. 40% of subjects were in the normal range after treatment.

[0167] A reduction of 17-OHP demonstrates "control" of the disease based on Standard guidelines. This allows for steroid taper. 80% of subjects demonstrated reduction in 17-OHP (see FIG. 3). 50% of subjects demonstrated more than 25% reduction in 17-OHP. 50% of subjects were within the guideline range (1200 ng/dL) after treatment.

[0168] Compound 1 attenuates morning rise in A4 which indicates an ability to control excess androgen production and associated symptoms (see FIG. 4). 100% of subjects demonstrated reduction in Androstenedione (at various doses). 60% of subjects demonstrated more than 25% reduction in Androstenedione. 50% of subjects were within normal reference range after treatment.

Example 5: 3-Month Phase 2 Study

[0169] This is a 3-month Phase 2 study to evaluate the safety and efficacy of Compound 1 in subjects with classic CAH. This study will investigate the extended use of Compound 1 over a 3-month period in combination with replacement glucocorticoids and mineralocorticoids in the treatment of CAH.

[0170] This study will enroll up to approximately 24 eligible subjects who will receive Compound 1 daily for up to 3-months. Compound 1 will be administered as an oral daily dose. At the end of each 2-week dosing period, patients will return for morning laboratory assessments. A follow-up outpatient visit will occur 30 days after their last dose.

Study Design

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

Outcome Measures

Primary Outcome Measure:

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

Second Outcome Measure:

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

Exploratory:

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

Eligibility:

- Minimum Age: 18 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Example 6: Adolescent Study

[0171] This is a Phase 2, open-label, multiple-dose study designed to provide proof of concept for the use of Compound 1 to treat adolescents 12 to 17 years of age with classic CAH. The study will evaluate the safety, efficacy, and PK of 2 weeks of treatment with Compound 1. Each subject will undergo a 2-week diary run-in period during screening, a 2-week treatment period, and a 30-day washout and safety follow-up period.

[0172] An adaptive design with up to 3 sequential dose cohorts (Cohorts 1, 2, and 3) is planned to identify an optimal dose strength and regimen in adolescents with classic CAH. Each cohort will initially enroll 3 subjects and may later enroll 3 more subjects based on interim data from the first 3 subjects, for a total of 6 subjects per cohort. However, if safety, efficacy, and PK results from 6 subjects are inconclusive, a cohort may be expanded up to a maximum of 12 subjects. Cohort 1 will receive study drug at 200 mg QD. Cohorts 2 and 3 will be sequentially activated only if further investigation of an optimal dose strength or regimen is required; the dose strength and frequency and timing of dosing for these cohorts will be determined based on interim data from the previous cohort(s). However, the dose strength administered to each successive cohort will be capped at twice the daily dose strength administered to the previous cohort.

[0173] This study will enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in many adolescent patients. In this population, GCs are associated with multiple well-described short- and long-term toxicities including: growth retardation, weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

[0174] The objective of treatment of this patient population with Compound 1 is reduction (or normalization) of key hormonal outcome measures which could allow reduction of their GC replacement requirements which will improve clinical outcomes of concern, including growth velocity. Improvement of hormonal outcome measures in this population are also expected to delay premature puberty and bone maturation, ultimately leading to improvements in height in adolescents with CAH.

Outcome Measures

Primary Outcome Measures:

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

Secondary Outcome Measures:

2. To evaluate the dose(s) of Compound 1 that cause changes in key pharmacodynamics bioamarkers in blood in adolescent subjects with CAH.

3. To investigate the effect of Compound 1 on quality of life in adolescent subjects with CAH.

4. To determine the pharmacokinetics of Compound 1 in adolescent subjects with CAH.

5. To investigate potential relationships between pharmacodynamics and pharmacokinetics in adolescent subjects with CAH.

Exploratory

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

Eligibility Criteria

Inclusion Criteria:

- Male and female subjects 12 to 17 years of age, inclusive
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable regimen of glucocorticoid replacement for minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Example 7: Phase 3 Clinical Studies

[0175] This is a 24-week, randomized, double-blind, placebo-controlled study of Compound 1 for the treatment of classic CAH. After screening, eligible patients will be enrolled into a 24-week treatment period followed by a 4-week safety follow-up period.

[0176] Subjects in the study will be randomized in a 1:1 ratio to either receive Compound 1 or a matching placebo for up to 24 weeks. Compound 1 or a placebo will be administered as an oral daily dose. Patients will return approximately monthly for study visits. A follow-up outpatient visit will occur 30 days after their last dose. It is initially planned that up to approximately 150 patients will be enrolled.

[0177] Consistent with the design of the Phase 2 study, the Phase 3 clinical study will seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated with supraphysiologic

doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

Study Design:

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

Outcome Measures

Primary Outcome Measures

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

Secondary Outcome Measures

2. Evaluate efficacy of Compound 1 in patients with CAH in terms of changes in key hormones.
3. Evaluate efficacy of Compound 1 in improving quality of life and/or mood in patients with CAH.
4. Evaluate efficacy of Compound 1 in improving hyperandrogenic symptoms in patients with CAH.
5. Evaluate efficacy of Compound 1 in improving metabolic parameters in patients with CAH.
6. Evaluate safety of Compound 1 in patients with CAH.

Eligibility

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

Criteria

Inclusion Criteria:

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

- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Example 8: Phase 3 OLE and steroid sparing studies

[0178] Upon completion of the study described in Example 7, eligible patients will then be offered the opportunity to enroll into an open label extension study lasting up to 1 year. The open label study will allow all eligible patients to receive active study drug during their participation in the Phase 3 program. Patients will undergo study assessments every 1-3 months during the open label phase, and will be evaluated for long-term safety and efficacy (including both hormonal endpoints and long-term clinical outcome measures of concern in this population).

[0179] A further study may seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). Such CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

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

[0181] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing

the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A method for treating congenital adrenal hyperplasia (CAH) in a human, comprising:

administering to said human a therapeutically-effective amount of a CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof,

wherein said human has received or has been previously determined to receive a first dose of a glucocorticoid, and

administering to said human a second dose of a glucocorticoid, wherein said second dose of a glucocorticoid is reduced compared to said first dose of a glucocorticoid,

wherein an androstenedione (A4) level in said subject is reduced from baseline, or

wherein an adrenocorticotropic hormone (ACTH) level in said subject is reduced from baseline, or

wherein a 17-hydroxyprogesterone (17-OHP) level in said subject is reduced from baseline.

2. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 5% from baseline.

3. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 10% from baseline.

4. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 15% from baseline.

5. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 20% from baseline.

6. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 25% from baseline.

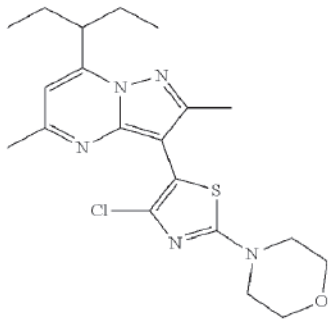
7. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 24 hours.

8. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 4 weeks.

9. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 6 weeks.

10. The method of claim 1, wherein said administering of said first dose of said glucocorticoid is concurrently or sequentially within 2 hours of said administering of said therapeutically-effective amount of a CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof.

11. The method of claim 1, wherein said CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof is Compound 1:



or a pharmaceutically acceptable salt thereof.

12. The method of claim 1, wherein said glucocorticoid is selected from beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone.

13. The method of claim 1, wherein said glucocorticoid is hydrocortisone.

14. The method of claim 1, wherein said first dose of said glucocorticoid comprises a supraphysiologic amount of said glucocorticoid.

15. The method of claim 1, wherein said second dose of said glucocorticoid comprises a physiologic amount of said glucocorticoid.

16. The method of claim 1, wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day.

17. The method of claim 1, wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is orally administered.

18. The method of claim 17, wherein said oral administration is once a day.

19. The method of claim 17, wherein said oral administration is twice a day.

20. The method of claim 1, wherein said first dose is a first daily dose and said second dose is a second daily dose.

21. The method of claim 1, wherein said second dose of said glucocorticoid is at least about 5%, at least about 10%, or at least about 20% lower than said first dose of said glucocorticoid.

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.

WSGR Docket No. 50535-709.307

PATENT APPLICATION

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

Inventor(s): Alexis HOWERTON
Citizen of USA, Residing at
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

Hal GERBER
Citizen of USA, Residing at
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

Michael HUANG
Citizen of USA, Residing at
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

Assignee: Spruce Biosciences, Inc.
611 Gateway Blvd., Suite #740
South San Francisco, CA 94080

a Delaware Corporation

Entity: Large business concern

WILSON
SONSINI

650 Page Mill Road
Palo Alto, CA 94304
(650) 493-9300 (Main)
(650) 493-6811 (Facsimile)

Filed Electronically on: April 26, 2023

4893-7748-9247

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

CROSS-REFERENCE

[0001] This patent application is a continuation of U.S. Patent Application No. 18/078,649, filed December 9, 2022; which is a continuation of U.S. Patent Application No. 17/586,228, filed January 27, 2022; which is a divisional of U.S. Patent Application No. 17/359,411, filed on June 25, 2021, now U.S. Patent No. 11,351,177; which is a continuation of U.S. Patent Application No. 17/063,592, filed on October 5, 2020, now U.S. Patent No. 11,344,557; which is a continuation of U.S. Patent Application No. 16/388,620, filed on April 18, 2019, now U.S. Patent No. 10,849,908; which is a continuation of PCT Application No. PCT/US2018/046760, filed on August 14, 2018; which claims the benefit of U.S. Provisional Patent Application No. 62/545,406, filed August 14, 2017; all of which are incorporated herein by reference in their entirety.

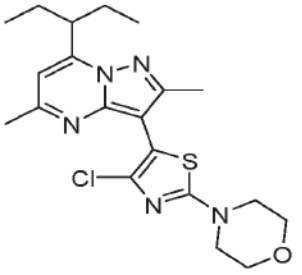
BACKGROUND OF THE INVENTION

[0002] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

SUMMARY OF THE INVENTION

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

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



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

[0005] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

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

[0007] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0008] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0009] In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more

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

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

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

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

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

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

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

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

[0016] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are

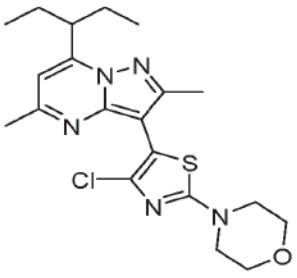
administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid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

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

[0018] In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 mins before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night. In some embodiments, the pharmaceutical composition is administered at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the pharmaceutical composition is administered about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

[0019] In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

[0020] In one aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering Compound 1:



or a pharmaceutically acceptable salt or solvate thereof; and

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

[0021] In some embodiments, the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione. In some embodiments,

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

[0022] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

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

In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 50 mg /day.

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

[0025] In some embodiments, Compound 1 is formulated in a pharmaceutical composition in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0026] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

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

embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0028] In some embodiments the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments,the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, he pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

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

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

[0031] In some embodiments, the method further comprises administering a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or

solvate thereof. In some embodiments, the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount. In some embodiments, the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.

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

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

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

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

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

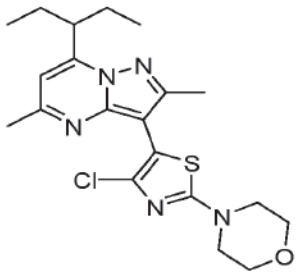
solvate thereof, is administered in the evening. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at 10 pm at night.

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

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

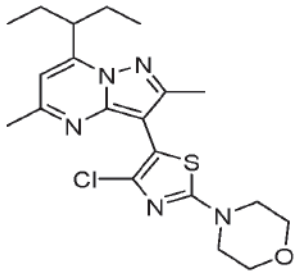
[0039] In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

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



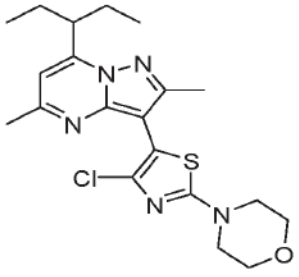
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0041] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

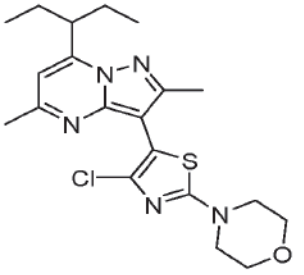


; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

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

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

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

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

INCORPORATION BY REFERENCE

[0044] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

[0050] CRF has been implicated in psychiatric disorders and neurological diseases including depression and anxiety, as well as the following: Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and associated withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia (CAH), Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulceration, premenstrual syndrome, sexual dysfunction, premature labor, inflammatory disorders, allergies, multiple sclerosis, visceral pain, sleep disorders, pituitary tumors or ectopic pituitary derived tumors, chronic fatigue syndrome, and fibromyalgia.

[0051] CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors. A more discrete septallhypothalmic distribution and the availability of alternative endogenous ligands suggest a different functional role for the CRF2 receptor. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF 1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism. In other cases, CRF2 agonism produces similar effects to those reported for CRF 1 antagonists or CRF 1 gene deletion. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well.

[0052] Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous Cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which Cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment

include Cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

[0053] The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient Cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of Addisonian syndrome due to under-treatment. Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione, testosterone, renin activity, and electrolytes.

[0054] Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance. A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes. Treatment of CAH includes efforts to normalize the Cortisol deficiency with glucocorticoids (usually hydrocortisone in children but often more potent agents with narrow therapeutic indices, such as dexamethasone, in adults) and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for Cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients.

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

[0056] 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.

[0057] The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21 -hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-hydroxyprogesterone (17-OHP). Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21 -hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically Cortisol and aldosterone. Cortisol is a critical negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

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

Certain Definitions

[0059] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[0060] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

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

[0062] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or."

[0063] The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[0064] "Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. "Administering" a pharmaceutical composition may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

[0065] By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

[0066] The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as Compound 1, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

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

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

[0069] A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or

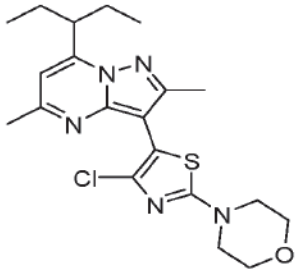
displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

[0070] The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

[0071] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Compound

[0072] Disclosed herein is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine (or alternatively 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine), a pharmaceutically acceptable salt, and/or a solvate thereof:


. In some embodiments, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine is referred to as Compound 1. In some embodiments, 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine is referred to as Compound 1.

Pharmaceutical Compositions

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

Dosage Form

[0074] In some embodiments, the pharmaceutical compositions described herein are provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of Compound 1 that is suitable for administration to an animal, preferably mammal, subject in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

[0075] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0076] In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more

additional pharmaceutically acceptable excipients. *See, e.g., Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

Capsule

[0077] In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

[0078] In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents, flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or delayed release coatings, sustained release coatings, barrier coatings, seal coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary according to the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

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

[0080] In some embodiments, a capsule is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if

solubility is less than 0.002 mg/mL in water. In some embodiments, the capsule has a dose strength of up to 200 mg. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus II.

Tablet

[0081] Poorly soluble drugs may be difficult to formulate using standard technologies such as high shear wet granulation. Optimum delivery of poorly soluble drugs may require complex technologies such as solid solutions amorphous dispersions (hot melt extrusion or spray drying), nano-formulations or lipid-based formulations. Hydrophobic drug substances may be considered poorly soluble according to USP criteria and may be known to be difficult to granulate with water and other excipients. This is likely due to most known excipients for immediate release formulations being water soluble or water-swellable. Making a tablet of a high dose drug substance that is poorly soluble may require a high concentration of the drug substance. However, as the drug concentration is increased above a certain level, formation of granules may become more and more difficult. Furthermore, at a certain drug load, it may become impossible.

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

[0083] In some embodiments, the tablet is made by compression, molding, or extrusion, optionally with one or more pharmaceutically acceptable excipient. In some embodiments, compressed tablets are prepared by compressing Compound 1 in a free-flowing form, optionally mixed with pharmaceutically acceptable excipients. In some embodiments, molded tablets are made by molding a mixture of the powdered Compound 1 moistened with an inert liquid diluent. In some embodiments, the tablet is prepared by hot-melt extrusion. In some embodiments, extruded tablets are made by forcing a mixture comprising Compound 1 through an orifice or die under controlled conditions. In some embodiments, the tablet is coated or scored. In some embodiments, the tablet is formulated so as to provide slow or controlled release of Compound 1. In some embodiments, a tablet is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the tablet has a dose strength of up to 200 mg. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus II.

[0084] In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg,

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

[0085] 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.

[0086] In some embodiments, the tablet is produced at a commercial scale.

[0087] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[0088] In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of Compound 1. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone, polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

Pharmaceutically Acceptable Excipients

[0089] 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.

[0090] 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

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

acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 1 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0092] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the

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

[0093] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0094] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0095] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or

solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0096] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

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

mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0098] In some embodiments, the pharmaceutical composition comprises about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

Particle size

[0099] In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises Compound 1, or a pharmaceutically acceptable salt or solvate thereof, in the form of microparticles. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 100 μm. In some embodiments, microparticles of Compound 1

have an average size from about 1 μm to about 50 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 30 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 20 μm. In some embodiments, microparticles of Compound 1 have an average size from about 5 μm to about 15 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 3 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 4 μm to about 9 μm.

[0100] In some embodiments, microparticles of Compound 1 have an average size less than about 100 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 80 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 60 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 50 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 40 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 30 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 20 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 10 μm.

Pharmacokinetics

[0101] In some embodiments, Compound 1 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, Compound 1 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, Compound 1 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, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

[0102] In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

Stability

[0103] The pharmaceutical compositions described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to pharmaceutical compositions having about 95% or greater of the initial Compound 1 amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of Compound 1. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable pharmaceutical compositions have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable pharmaceutical compositions have about 5% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 4% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 3% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 2% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 1% w/w total impurities or related substances.

[0104] At refrigerated condition, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±5 °C. In some embodiments, refrigerated condition is about 0 °C, about 0.1 °C, about 0.2 °C, about 0.3 °C, about 0.4 °C, about 0.5 °C, about 0.6 °C, about 0.7 °C, about 0.8 °C, about 0.9 °C, about 1 °C, about 1.1 °C, about 1.2 °C, about 1.3 °C, about 1.4 °C, about 1.5 °C, about 1.6 °C, about 1.7 °C, about 1.8 °C, about 1.9 °C, about 2 °C, about 2.1 °C, about 2.2 °C, about 2.3 °C, about 2.4 °C, about 2.5 °C, about 2.6 °C, about 2.7 °C, about 2.8 °C, about 2.9 °C, about 3 °C, about 3.1 °C, about 3.2 °C, about 3.3 °C, about 3.4 °C, about 3.5 °C, about 3.6 °C, about 3.7 °C, about 3.8 °C, about 3.9 °C, about 4 °C, about 4.1 °C, about 4.2 °C, about 4.3 °C, about 4.4 °C, about 4.5 °C, about 4.6 °C, about 4.7 °C, about 4.8 °C, about 4.9 °C, about 5 °C, about 5.1 °C, about 5.2 °C, about 5.3 °C, about 5.4 °C, about 5.5 °C, about 5.6 °C, about 5.7 °C, about 5.8 °C, about 5.9 °C, about 6 °C, about 6.1 °C, about 6.2 °C, about 6.3 °C, about 6.4 °C, about 6.5 °C, about 6.6 °C, about 6.7 °C, about 6.8 °C, about 6.9 °C, about 7 °C, about 7.1 °C, about 7.2 °C, about 7.3 °C, about 7.4 °C, about 7.5 °C, about 7.6 °C, about 7.7 °C, about 7.8 °C, about 7.9 °C, about 8 °C, about 8.1 °C, about 8.2 °C, about 8.3 °C, about 8.4 °C, about 8.5 °C, about 8.6 °C, about 8.7 °C, about 8.8 °C, about 8.9 °C, about 9 °C, about 9.1 °C, about 9.2 °C, about 9.3 °C, about 9.4 °C,

about 9.5 ºC, about 9.6 ºC, about 9.7 ºC, about 9.8 ºC, about 9.9 ºC, or about 10 ºC. At accelerated conditions, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, or at least 24 month. Accelerated conditions for the pharmaceutical compositions described herein include temperatures that are at or above ambient levels (e.g. 25±5 °C). In some instances, an accelerated condition is at about 40±2 °C. In some instances, an accelerated condition is at about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C, or about 60 °C. Accelerated conditions for the pharmaceutical compositions described herein also include relative humidity (RH) that are at or above ambient levels (55±10% RH). In other instances, an accelerated condition is above about 65% RH, about 70% RH, about 75% RH, or about 80% RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40±2 °C at 75±5% RH humidity.

[0105] In some embodiments, the pharmaceutical compositions are stable at about 5±5 ºC to about 25±5 ºC for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 ºC for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 ºC for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 ºC for at least 24 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 ºC for at least 24 months.

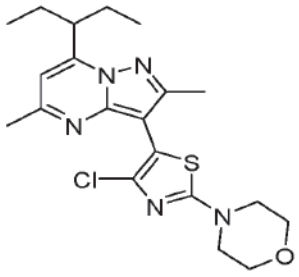
Methods of Use

[0106] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.In some embodiments, the methods described herein result in the reduction of a hormone level. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17α-hydroxy progesterone (17-OHP), dehydroepiandrosterone, androstenediol, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein result in the reduction of 17α-hydroxy progesterone (17-OHP). In some embodiments, the methods described herein result in the reduction of adrenocorticotropic hormone (ACTH), also known as corticotropin.

[0107] Also disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising:

(i) measuring a hormone level in the subject in need thereof;

(ii) administering Compound 1:



or a pharmaceutically acceptable salt or solvate thereof;

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

[0108] In some embodiment, the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione.

[0109] In some embodiment, the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL. In some embodiment, the hormone is 17-OHP, and the pre-determined range is less than about 400 ng/dL, less than about 350 ng/dL, less than about 300 ng/dL, less than about 250 ng/dL, or less than about 200 ng/dL.

[0110] In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL. In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL, below about 90 pg/mL, or below about 80 pg/mL.

[0111] In some embodiment, the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL. In some embodiment, the hormone is testosterone and the pre-determined range is less than about 76 ng/dL, less than about 70 ng/dL, less than about 65 ng/dL, less than about 60 ng/dL, less than about 55 ng/dL, less than about 50 ng/dL, less than about 45 ng/dL, less than about 40 ng/dL, less than about 35 ng/dL, less than about 30 ng/dL, less than about 25 ng/dL, less than about 20 ng/dL, or less than about 15 ng/dL.

[0112] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 200 ng/dL in males. In some embodiment, the hormone is androstenedione and the pre-determined range is less than about 200 ng/dL, less than about 150 ng/dL, less than about 100 ng/dL, less than about 50 ng/dL, or less than about 30 ng/dL in males.

[0113] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 150 ng/dL in females. In some embodiment, the hormone is

androstenedione and the pre-determined range is less about 150 ng/dL, less about 100 ng/dL, less about 50 ng/dL, or less about 40 ng/dL in females.

[0114] In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a month, twice a month, three times a month, once a week, twice a week, three times a week, once every two days, once a day, twice a day, three times a day, or four times a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof twice a day.

[0115] In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1500 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1400 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1300 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1100 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 900 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 60 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 70 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 80 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 90 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 700 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 150 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200

mg/day and about 500 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 400 mg/day.

[0116] 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.

[0117] In some embodiments, about 100 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

[0118] In some embodiments, less than about 2000 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered

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

[0119] 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.

[0120] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

[0121] 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.

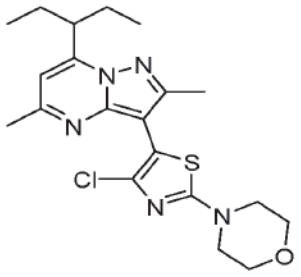
[0122] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

[0123] 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.

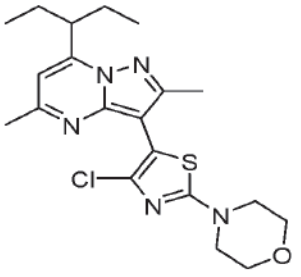
[0124] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

[0125] In one aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



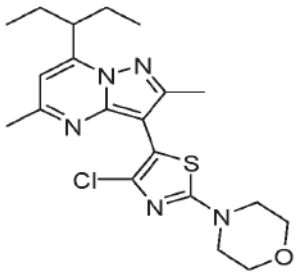
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0126] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

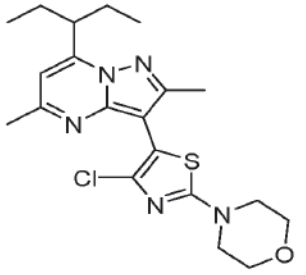


; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

[0127] In one aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition

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

[0128] In one aspect, the present disclosure provides a method of improving quality of life in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

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

Combination Therapy

[0129] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; and a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0130] In some embodiments, the methods described herein reduce the amount of a glucocorticoid administered from a supraphysiologic amount to a physiologic amount.

[0131] In some embodiments, the methods described herein reduce the symptoms associated with high-dose glucocorticoid therapy. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.

[0132] In some embodiments, the amount of glucocorticoid administered is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about

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

[0133] In some embodiments, the amount of glucocorticoid administered is reduced by about 1% to about 90%, about 1% to about 60%, about 1% to about 30%, about 1% to about 10%, about 10% to about 50%, about 10% to about 40%, about 10% to about 30%, about 15% to about 25%, about 20% to about 30%, about 5% to about 25%, about 20% to about 50%, about 30% to about 60%, or about 40% to about 70% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0134] In some embodiments, the glucocorticoid is administered at a dose between about 0.1 mg/day and about 25 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 20 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 15 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 12 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 9 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 8 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 7 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 6 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 5 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 4 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 3 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 2 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 3 mg/day and about 13 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 8 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 9 mg/day and about 12 mg/day. In some embodiments, the

glucocorticoid is administered at a dose between about 9 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 10 mg/day.

[0135] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered in one pharmaceutical composition. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently in separate pharmaceutical compositions.

[0136] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 12 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 8 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 6 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 4 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 2 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 1 hour. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 30 minutes. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 10 minutes.

[0137] In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

[0138] In some embodiments, the glucocorticoid is hydrocortisone and the dose administered is less than the recommended dose of 15-25 mg/day.

[0139] In some embodiments, the glucocorticoid is prednisone and the dose administered is less than the recommended dose of 5-7.5 mg/day.

[0140] In some embodiments, the glucocorticoid is prednisolone and the dose administered is less than the recommended dose of 4-6 mg/day.

[0141] In some embodiments, the glucocorticoid is dexamethasone and the dose administered is less than the recommended dose of 0.25-0.5 mg/day.

[0142] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; a glucocorticoid; and optionally a mineralcorticoid. In some embodiments, the mineralocorticoid is fludrocortisone and the dose is less than the recommended dose of 0.05-0.2 mg/day.

EXAMPLES

[0143] 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.

[0144] All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

Example 1: Pharmaceutical Composition

[0145] The pharmaceutical composition is manufactured as size 1 white hard gelatin capsules containing 200 mg of Compound 1 micronized to and average size of 10 microns or less. The pharmaceutical composition contains no additional excipients.

Example 2: Stability of the Pharmaceutical Composition

Stability Data Summary

[0146] A summary of the pharmaceutical composition stability studies is provided in Table 1. The pharmaceutical composition is a Compound 1 neat-filled into size 0 capsules with no added excipients, in 3 strength configurations: 1-mg, 5-mg, and 50-mg. The capsules were blister packaged in a polyvinyl chloride (PVC)-based film.

[0147] Under long term and accelerated conditions, no significant trend was observed in the three lots for any of the attributes evaluated throughout the course of the stability study.

Table 1. Summary of Stability

Lot Number	Strength	CCS	Stability Conditions	Available Data
#1	1-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#2	5-mg	PVC-based	25 °C/60% RH	6 months

		blister pack	40 °C/75% RH	6 months
#3	50-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#4	200-mg	75 mL HDPE bottle	25 °C/60% RH	1 month
			40 °C/75% RH	9 months
#5	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#6	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months

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

Stability Protocols

[0148] The stability protocol for various pharmaceutical compositions is provided in Table 2, 3, and 4.

Table 2. Stability Protocol

Test	**Acceptance Criteria**	**Time (months)**			
		T_0	1	**3**	**6**
Appearance	Size 0 blue capsule containing yellow powder, blister pack and foil backing intact	X	A,B	A,B	A,B
Assay	Report (% Label Claim)	X	A,B	A,B	A,B
Related Substances	Report RRT and % each individual species and total	X	A,B	A,B	A,B
Disintegration	Report	X	A,B	A,B	A,B

RRT = relative retention time
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

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

Test	**Acceptance Criteria**	**Time (months)**			
		T_0	1	3	6
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	A,B	A,B	A,B

Assay (%LC)	90.0 – 110.0	X	A,B	A,B	A,B
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	A,B	A,B	A,B
Disintegration (min)	NMT 15	X	A,B	A,B	A,B
Water Activity	Report result	X	A,B	A,B	A,B

LC = label claim; NMT = not more than
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

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

Test	**Acceptance Criteria**	**Time (months)**					
		T_0	**1**	**3**	**6**	**9**	**12**
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	B	A,B	A,B	A	A
Assay (%LC)	90.0 – 110.0	X	B	A,B	A,B	A	A
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	B	A,B	A,B	A	A
Disintegration (min)	NMT 15	X	B	A,B	A,B	A	A
Water Activity	Report result	X	n/a	n/a	n/a	A	A
Microbial Enumeration Total Aerobic Microbial Count (CFU/g) Total Combined Yeast and Mold (CFU/g) Count	 NMT 2000 CFU/g NMT 200 CFU/g	X	n/a	n/a	n/a	A	A

Test	Acceptance Criteria	Time (months)					
		T_0	1	3	6	9	12
Test for Specified Microorganisms *E. coli* (/g)	Absent	X	n/a	n/a	n/a	A	A

CFU = colony forming units; LC = label claim; n/a = not applicable; NMT = not more than
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

[0149] The supportive data demonstrate that the pharmaceutical composition is stable for a minimum of 6 months (end of study). No adverse trends were observed under long term and accelerated conditions. The assay results were consistent through the entire study and no new related substances species were observed during the stability study. The reported stability results for lots stored in a blister packaging configuration are considered supportive for the updated packaging configuration of a 30-mL HDPE bottle, induction seal, and a child resistant cap. There are no excipients in either configuration and both configurations provide protection from light.

Example 3: Phase 1 Clinical Studies

[0150] Compound 1 has been investigated in 2 Phase 1 studies in healthy adult volunteers.

[0151] Study 1 was the first-in-human study that investigated the safety, tolerability, and PK of single-escalating doses of Compound 1, given orally, to healthy adult subjects. Safety and tolerability assessments were made over a wide range of single oral doses, and dose escalation did not proceed until safety data from the preceding doses had been reviewed. The data from this study were used for the selection of doses for Study 2.

[0152] The 2-part multiple-dose study, Study 2, determined the safety and tolerability of repeated daily doses of Compound 1 and investigated the effects on biomarkers of relevance for the treatment of alcohol dependence. Part B investigated the interaction of Compound 1 with midazolam (a cytochrome P450 3A4 [CYP3A4] substrate), determining whether Compound 1 significantly inhibited the metabolism of drugs that are metabolized by CYP3A4.

[0153] In Study 1, Compound 1 was administered to healthy adult subjects as a single PO dose of 2, 10, 50, 150, 400, or 800 mg in the fed state and 150 mg in the fasted state. Absorption occurred moderately late, achieving peak C_{max} between 4 to 6 hours following dosing in the fed state.

[0154] Table 5 provides a summary of the PK parameters at each dose level. When Compound 1 was given in the fed state, median time to reach maximum plasma concentration (T_{max}) occurred between 4 and 6 hours. The median T_{max} was 10.05 hours when Compound 1 was given in the fasted state at 150 mg and ranged between 6 and 12 hours, suggesting possible

delayed absorption in the fasted state. Mean half-life ($t_{1/2}$) after a single PO dose (fed and fasted state) was between 31 and 44 hours, ranging from 11 to 101 hours. Apparent volume of distribution (V_z/F) was large and appeared highly variable with greatest variability observed at the 2 highest dose levels of 400 mg and 800 mg.

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

PK Parameters	Geometric Mean (CV%) Analyte = Plasma Compound 1					
	2 mg	**10 mg**	**50 mg**	**150 mg**	**400 mg**	**800 mg**
N	6	6	6	6	6	6
C_{max} (ng/mL)	0.867 (53)	3.01 (87)	19.5 (39)	93.4 (22)	207 (92)	382 (110)
T_{max}[a] (h)	6.00 (4.00-6.00)	4.00 (2.00 -6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	6.00 (4.00 - 6.00)
$t_{1/2}$[b] (h)	NC (NC)	NC (NC)	31 (10.8-53.4)	29.2 (20.0 - 41.5)	44.2 (20.2 - 101)	41.9 (24.1 - 67.8)
$AUC_{0\text{-tlast}}$ (ng•h/mL)	NC (NC)	NC (NC)	152 (60)	891 (26)	2300 (103)	4390 (100)
$AUC_{0\text{-}\infty}$ (ng•h/mL)	NC (NC)	NC (NC)	165 (64)	956 (25)	2580 (93)	4850 (95)
CL/F (L/h)	NC (NC)	NC (NC)	302 (64)	157 (25)	155 (93)	165 (95)
V_z/F (L)	NC (NC)	NC (NC)	13500 (45)	6620 (38)	9890 (212)	9970 (144)
V_{ss}/F (L)	NC (NC)	NC (NC)	8080 (36)	4600 (33)	6580 (152)	6820 (120)

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

a Median (range)

b Geometric mean (range)

[0155] As part of this single-dose escalation study, a food effect PK investigation was performed to examine Compound 1 exposures in both the fed and fasted states at the 150-mg dose level. A total of 6 subjects were administered 150 mg Compound 1 in each of these 2 dosing groups. Of these 6 subjects, 4 subjects received Compound 1 at the same dose in both fed and fasted states. The administration of Compound 1 in the fasted state resulted in a much flatter mean concentration-time (i.e., with significantly lower absorption) profile when compared against the mean profile at the same dose, given within 5 minutes after a standardized breakfast meal. The mean $AUC_{0\text{-}\infty}$, and C_{max} values for a 150-mg dose in the fed state was approximately 3- and 11-fold greater than that of the fasted state, respectively. Table 6 provides a summary of the PK parameters at the 150-mg dose level under both fed and fasted state conditions.

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

Pharmacokinetic Parameters	Geometric Mean (CV %)	
	Analyte = Plasma Compound 1	
	150 mg Fed	150 mg Fasted
N	6	6
C_{max} (ng/mL)	93.4 (22)	8.22 (83)
T_{max}[a] (h)	4.00 (3.00 – 6.00)	10.05 (6.00 – 12.00)
$t_{1/2}$[b] (h)	29.2 (20.0 – 41.5)	38.4 (24.2 – 88.5)
$AUC_{0\text{-tlast}}$ (ng•h/mL)	891 (26)	288 (48)
$AUC_{0\text{-}\infty}$ (ng•h/mL)	956 (25)	331 (44)
CL/F (L/h)	157 (25)	454 (44)
Vz/F (L)	6620 (38)	25100 (81)
Vss/F (L)	4600 (33)	25200 (68)

AUC = area under the plasma concentration-time curve; CL/F = apparent total body clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; N = number of subjects; NC = not calculable; PK = pharmacokinetic; T_{max} = time to reach maximum plasma concentration; t1/2 = elimination half-life; $V_{ss}F$ = apparent volume of distribution at steady state during the terminal phase after extravascular administration; V_z/F = apparent volume of distribution during the terminal phase after extravascular administration.

a Median (range)

b Geometric mean (range)

[0156] PK parameters $AUC_{0\text{-}\infty}$ and C_{max} were analyzed separately for dose proportionality for Compound 1 from 50 to 800 mg when administered in the fed state. The analysis results suggested that for every doubling of dose, $AUC_{0\text{-}\infty}$ can be expected to increase 1.74 times more than what would be expected under dose proportionality. C_{max} appeared more than dose proportional but the formal test was inconclusive as the 90% confidence interval were partially within the 0.8 – 1.25 interval. Dose proportionality across administered doses in the fed state could not be concluded on the basis of $AUC_{0\text{-}\infty}$ or C_{max}.

[0157] PK were also evaluated in the multiple-dose, dose-escalation study, Study 2. In Part A of the study, subjects were divided into 3 cohorts and received 50, 150, or 200 mg Compound 1 or placebo for 14 consecutive days (at least 6 subjects received Compound 1 and 2 subjects received placebo in each cohort). Blood concentrations of Compound 1 were close to steady-state levels after 2 weeks of dosing and the accumulation ratio was between 2.51 to 3.65. Part B investigated the interaction of Compound 1 with midazolam (a CYP3A4 substrate), thereby determining whether this compound significantly inhibited the metabolism of drugs that are metabolized by CYP3A4 serial blood samples were collected to determine plasma concentrations of study drug after a single dose of Compound 1 had been administered and at steady state. All dosing occurred in the fed state. An assessment of diurnal cortisol levels, plus when under conditions of glucose clamp, were also carried out both prior to and during the dosing period.

[0158] Overall concentration time profiles of Compound 1 showed that absorption was moderately delayed with C_{max} achieved at a median of 5 hours following oral dosing. Consistent with the single-dose study (Study 1), concentrations appeared to decline in a bi-exponential manner, characterized by a rapid decrease within the first 24 hours. Following multiple daily dosing for 2 weeks, the $t_{1/2}$ of Compound 1 exceeded 100 hours; therefore, an accumulation ratio of Compound 1 was between 2.51 to 3.65 (see Table 7). The T_{max} appeared to be consistent across doses. Overall half-lives, weight normalized CL/F and V/F were consistent for 150 and 200 mg. However, the values for these latter 2 parameters were almost doubled at the 50-mg dose level. Variability (CV%) for apparent clearance and volume of distribution were large and not reduced with weight-normalization.

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

	Geometric Mean (CV%)					
	50 mg Day 1	**150 mg Day 1**	**200 mg Day 1**	**50 mg Day 14**	**150 mg Day 14**	**200 mg Day 14**
N	**8**	**9**	**7**	**8**	**9**	**6**
C_{max} (ng/mL)	22.7 (59)	127 (52)	143 (62)	50.3 (56)	222 (58)	314 (93)
T_{max} [a] (hr)	4.52 (3.00 – 10.00)	5.00 (5.00 - 6.00)	5.00 (2.00 - 5.00)	5.00 (3.00 - 5.00)	5.00 (3.00 - 5.03)	5.00 (3.00 - 5.00)
Effective $t_{1/2}$ [b] (hr)	NC NC	NC NC	NC NC	37.7 (27.4)	32.7 (29.7)	52.0

$AUC_{0-\infty}$ (ng•hr/mL)	NC NC	NC NC	NC NC	980 (53.8)	4680 (104)	5660 (122)
AUC_{0-24h} (ng•hr/mL)	97.6 (58)	590 (56)	559 (55[c])	273 (56)	1480 (66)	2040 (98)
C_{avg} (ng/mL)	NC NC	NC NC	NC NC	11.4 (56)	61.7 (66)	85.0 (98)
CL_{aa}/F (L/hr)	NC NC	NC NC	NC NC	183 (56)	101 (66)	98 (98)
WT-norm						
Cl_{aa}/F (L/hr/kg)	NC NC	NC NC	NC NC	2.88 (46.9)	1.42 (72.9)	1.50 (89.9)
Vz/F (L)	NC NC	NC NC	NC NC	33500 (90)	17600 (59)	16300 (76)
Vss/F (L)	NC NC	NC NC	NC NC	12900 (91)	6170 (40)	5080 (78)
WT-norm						
Vss/F (L/kg)	NC NC NC	NC NC NC	NC NC NC	204 (71.3) 2.80	86.5 (41.0) 2.51	77.4 (68.6) 3.65
R_A	NC	NC	NC	(27.4)	(29.7)	(34.4)

AUC = area under the plasma concentration-time curve; CL/F = apparent clearance; C_{max} = maximum plasma concentration; RA = accumulation ratio calculated as Day 14 AUC_{0-24}/Day 1 AUC_{0-24}; t1/2 = terminal half-life; effective t1/2 = half-life calculated by accumulation ratio; Tmax = time to maximum plasma concentration; Vss/F = volume of distribution at steady state; Vz/F = volume of distribution at terminal phase; WT-norm = weight normalized

[a] Median (range).

[b] Geometric mean (range).

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

[0159] Table 8 presents the results of the dose proportionality assessment for the AUC_{0-24} and C_{max} over the tested dose range. For AUC_{0-24} and C_{max}, the adjusted mean slope at Day 1 and Day 14 were all above the value of 1, suggesting a slightly more than proportional increase of AUC_{0-24} and C_{max} values with increasing doses.

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

Parameter	Day	Mean Slope	Standard Error	90% CI for Slope	CV%
AUC_{0-24} (ng hr/mL)	1	1.40	0.194	(1.069, 1.737)	59.3
	14	1.48	0.221	(1.104, 1.864)	69.1
C_{max} (ng/mL)	1	1.41	0.185	(1.092, 1.728)	57.5

	14	1.33	0.210	(0.972, 1.693)	64.8

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

Safety

[0160] The safety of Compound 1 was evaluated in 2 Phase 1 studies in healthy adult volunteers (Study 1 and Study 2). In both studies, adverse events (AEs), clinical laboratory tests, vital signs (supine blood pressure and pulse rate), and electrocardiograms (ECGs) were evaluated. Overall, in Study 1, Compound 1 was well-tolerated.

[0161] Compound 1, when administered as multiple doses up to 200 mg, was generally well tolerated in the healthy subject population studied. In Study 1, the effects upon biomarkers of relevance for the treatment of alcohol dependence were investigated. Five clusters of an Addiction Research Center Inventory Questionnaire (ARCI-49) were used to compare the effect of Compound 1 vs. placebo: Morphine-Benzedrine Group Scale measuring euphoria; Lysergic-Acid-Diethylamide Group Scale estimating dysphoric and somatic changes; Pentobarbital-Chlorpromazine-Alcohol Group Scale measuring sedation; Benzedrine Group (BG) Scale measuring intellectual efficiency and energy; Amphetamine Group Scale measuring effects of d-amphetamine, respectively. No systematic pattern or dose-response for the change from baseline or for the difference over placebo in each cluster was observed.

[0162] In summary, single, oral doses up to 800 mg and multiple doses up to 200 mg of Compound 1 were well-tolerated by healthy male and female subjects.

Example 4: Phase 2 Clinical Studies

[0163] Cohort A of the Phase 2 Study includes a 6-week, multiple-dose, dose escalation study of Compound 1 for the treatment of adults with classic CAH. After screening, eligible patients will be enrolled into a 6-week treatment period followed by a 4-week washout/safety follow-up period.

[0164] This cohort will be conducted in approximately 9 patients, who will receive Compound 1 daily for up to 6 weeks. Compound 1 will be administered as an oral daily dose. Patients will undergo titration of Compound 1 through three escalating dosage strengths at 2-week intervals. Patients will have overnight PK/PD assessments performed at baseline, which include an pre-dose overnight assessment and a post-dose overnight assessment for PK/PD following administration of the first dose. At the end of each 2-week dosing period, patients will return for single overnight visits for steady-state PK/PD assessments. A follow-up outpatient visit will occur 30 days after their last dose. Upon completion of the initial cohort (Cohort A), the study will proceed to a multiple ascending dose (MAD) design with up to 3 sequential cohorts (Cohorts B, C, and D) to further evaluate the safety, PK, and PD of various SPR001 dosing regimens and to identify an optimal dose regimen. Each cohort will undergo a 2-week run-in

period, a 2-week treatment period, and a 30-day washout and safety follow-up period. During the run-in period, which will occur during screening, subjects will document in a paper diary each dose of glucocorticoid medication taken, the time of each meal, and the time they went to bed and woke up each day, to ensure compliance with background glucocorticoid regimens and the stability of their daily routine.

[0165] Patients in Cohort B will receive study drug at 200 mg BID, with a dose in the morning and a dose in the evening, either with a meal or consumption of a standardized snack. For Cohorts C and D, the dose level and the frequency and timing of dosing will be determined based on interim data from the previous cohorts. However, the dose level of each successive cohort will be capped at twice the daily dose level of the previous cohort.

Study Design

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

Arms and Interventions

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

Outcome Measures

Primary Outcome Measure:

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

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

Secondary Outcome Measure:

3. To explore the dose(s) of Compound 1 that cause pharmacodynamics changes in plasma concentrations of ACTH, androstenedione, and testosterone, as measured by the absolute and percent change from baseline by dose.

4. To determine pharmacokinetics of Compound 1 in subjects with CAH.

5. To explore potential relationships between pharmacodynamics and pharmacokinetics.

Exploratory

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

Eligibility

- Minimum Age: 18 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Results:

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

[0166] With respect to patient-level response to Compound 1, 80% showed reduced ACTH (see FIG. 2). Generally, attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of patient subjects demonstrated reduction in ACTH. 70% of subject demonstrated more than 25% reduction in ACTH. 40% of subjects were in the normal range after treatment.

[0167] A reduction of 17-OHP demonstrates "control" of the disease based on Standard guidelines. This allows for steroid taper. 80% of subjects demonstrated reduction in 17-OHP (see FIG. 3). 50% of subjects demonstrated more than 25% reduction in 17-OHP. 50% of subjects were within the guideline range (1200 ng/dL) after treatment.

[0168] Compound 1 attenuates morning rise in A4 which indicates an ability to control excess androgen production and associated symptoms (see FIG. 4). 100% of subjects demonstrated reduction in Androstenedione (at various doses). 60% of subjects demonstrated more than 25% reduction in Androstenedione. 50% of subjects were within normal reference range after treatment.

Example 5: 3-Month Phase 2 Study

[0169] This is a 3-month Phase 2 study to evaluate the safety and efficacy of Compound 1 in subjects with classic CAH. This study will investigate the extended use of Compound 1 over a 3-month period in combination with replacement glucocorticoids and mineralocorticoids in the treatment of CAH.

[0170] This study will enroll up to approximately 24 eligible subjects who will receive Compound 1 daily for up to 3-months. Compound 1 will be administered as an oral daily dose. At the end of each 2-week dosing period, patients will return for morning laboratory assessments. A follow-up outpatient visit will occur 30 days after their last dose.

Study Design

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

Outcome Measures

Primary Outcome Measure:

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

Second Outcome Measure:

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

Exploratory:

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

Eligibility:

- Minimum Age: 18 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Example 6: Adolescent Study

[0171] This is a Phase 2, open-label, multiple-dose study designed to provide proof of concept for the use of Compound 1 to treat adolescents 12 to 17 years of age with classic CAH. The study will evaluate the safety, efficacy, and PK of 2 weeks of treatment with Compound 1. Each subject will undergo a 2-week diary run-in period during screening, a 2-week treatment period, and a 30-day washout and safety follow-up period.

[0172] An adaptive design with up to 3 sequential dose cohorts (Cohorts 1, 2, and 3) is planned to identify an optimal dose strength and regimen in adolescents with classic CAH. Each cohort will initially enroll 3 subjects and may later enroll 3 more subjects based on interim data from the first 3 subjects, for a total of 6 subjects per cohort. However, if safety, efficacy, and PK results from 6 subjects are inconclusive, a cohort may be expanded up to a maximum of 12 subjects. Cohort 1 will receive study drug at 200 mg QD. Cohorts 2 and 3 will be sequentially activated only if further investigation of an optimal dose strength or regimen is required; the dose strength and frequency and timing of dosing for these cohorts will be determined based on interim data from the previous cohort(s). However, the dose strength administered to each successive cohort will be capped at twice the daily dose strength administered to the previous cohort.

[0173] This study will enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in many adolescent patients. In this population, GCs are associated with multiple well-described short- and long-term toxicities including: growth retardation, weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

[0174] The objective of treatment of this patient population with Compound 1 is reduction (or normalization) of key hormonal outcome measures which could allow reduction of their GC replacement requirements which will improve clinical outcomes of concern, including growth velocity. Improvement of hormonal outcome measures in this population are also expected to delay premature puberty and bone maturation, ultimately leading to improvements in height in adolescents with CAH.

Outcome Measures

Primary Outcome Measures:

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

Secondary Outcome Measures:

2. To evaluate the dose(s) of Compound 1 that cause changes in key pharmacodynamics bioamarkers in blood in adolescent subjects with CAH.

3. To investigate the effect of Compound 1 on quality of life in adolescent subjects with CAH.

4. To determine the pharmacokinetics of Compound 1 in adolescent subjects with CAH.

5. To investigate potential relationships between pharmacodynamics and pharmacokinetics in adolescent subjects with CAH.

Exploratory

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

Eligibility Criteria

Inclusion Criteria:

- Male and female subjects 12 to 17 years of age, inclusive
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable regimen of glucocorticoid replacement for minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Example 7: Phase 3 Clinical Studies

[0175] This is a 24-week, randomized, double-blind, placebo-controlled study of Compound 1 for the treatment of classic CAH. After screening, eligible patients will be enrolled into a 24-week treatment period followed by a 4-week safety follow-up period.

[0176] Subjects in the study will be randomized in a 1:1 ratio to either receive Compound 1 or a matching placebo for up to 24 weeks. Compound 1 or a placebo will be administered as an oral daily dose. Patients will return approximately monthly for study visits. A follow-up outpatient visit will occur 30 days after their last dose. It is initially planned that up to approximately 150 patients will be enrolled.

[0177] Consistent with the design of the Phase 2 study, the Phase 3 clinical study will seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated with supraphysiologic

doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

Study Design:

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

Outcome Measures

Primary Outcome Measures

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

Secondary Outcome Measures

2. Evaluate efficacy of Compound 1 in patients with CAH in terms of changes in key hormones.
3. Evaluate efficacy of Compound 1 in improving quality of life and/or mood in patients with CAH.
4. Evaluate efficacy of Compound 1 in improving hyperandrogenic symptoms in patients with CAH.
5. Evaluate efficacy of Compound 1 in improving metabolic parameters in patients with CAH.
6. Evaluate safety of Compound 1 in patients with CAH.

Eligibility

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

Criteria

Inclusion Criteria:

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

- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Example 8: Phase 3 OLE and steroid sparing studies

[0178] Upon completion of the study described in Example 7, eligible patients will then be offered the opportunity to enroll into an open label extension study lasting up to 1 year. The open label study will allow all eligible patients to receive active study drug during their participation in the Phase 3 program. Patients will undergo study assessments every 1-3 months during the open label phase, and will be evaluated for long-term safety and efficacy (including both hormonal endpoints and long-term clinical outcome measures of concern in this population).

[0179] A further study may seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). Such CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

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

[0181] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing

the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A method for treating congenital adrenal hyperplasia (CAH) in a human, comprising:

administering to said human a therapeutically-effective amount of a CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof,

wherein said human has received or has been previously determined to receive a first dose of a glucocorticoid, and

administering to said human a second dose of a glucocorticoid, wherein said second dose of a glucocorticoid is reduced compared to said first dose of a glucocorticoid,

wherein an androstenedione (A4) level in said subject is reduced from baseline, or

wherein an adrenocorticotropic hormone (ACTH) level in said subject is reduced from baseline, or

wherein a 17-hydroxyprogesterone (17-OHP) level in said subject is reduced from baseline.

2. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 5% from baseline.

3. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 10% from baseline.

4. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 15% from baseline.

5. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 20% from baseline.

6. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced by at least 25% from baseline.

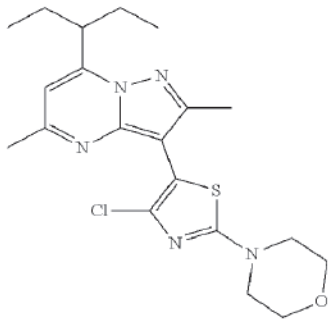
7. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 24 hours.

8. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 4 weeks.

9. The method of claim 1, wherein said A4 level, said ACTH level, or said 17-OHP level in said human is reduced from baseline and is maintained at a reduced level post 6 weeks.

10. The method of claim 1, wherein said administering of said first dose of said glucocorticoid is concurrently or sequentially within 2 hours of said administering of said therapeutically-effective amount of a CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof.

11. The method of claim 1, wherein said CRF_1 receptor antagonist or a pharmaceutically acceptable salt thereof is Compound 1:



or a pharmaceutically acceptable salt thereof.

12. The method of claim 1, wherein said glucocorticoid is selected from beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone.

13. The method of claim 1, wherein said glucocorticoid is hydrocortisone.

14. The method of claim 1, wherein said first dose of said glucocorticoid comprises a supraphysiologic amount of said glucocorticoid.

15. The method of claim 1, wherein said second dose of said glucocorticoid comprises a physiologic amount of said glucocorticoid.

16. The method of claim 1, wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is administered at a dose between about 50 mg/day and about 200 mg/day.

17. The method of claim 1, wherein said CRF1 receptor antagonist or a pharmaceutically acceptable salt thereof is orally administered.

18. The method of claim 17, wherein said oral administration is once a day.

19. The method of claim 17, wherein said oral administration is twice a day.

20. The method of claim 1, wherein said first dose is a first daily dose and said second dose is a second daily dose.

21. The method of claim 1, wherein said second dose of said glucocorticoid is at least about 5%, at least about 10%, or at least about 20% lower than said first dose of said glucocorticoid.

Approved for use through 11/30/2020. 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)

Sheet 1 of 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

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-8030304	10-04-2011	CHEN et al.	
	002	US-8563718	10-22-2013	RIZZO; John Robert et al.	
	003	US-10849908	12-01-2020	HOWERTON; Alexis et al.	
	004	US-11007201	05-18-2021	HOWERTON; Alexis et al.	
	005	US-11311549	04-26-2022	HOWERTON; Alexis et al.	
	006	US-11344557	05-31-2022	HOWERTON; Alexis et al.	
	007	US-11351177	06-07-2022	HOWERTON; Alexis et al.	
	008	US-20020013357	01-31-2002	NADKARNI; Sreekant et al.	
	009	US-20030008885	01-09-2003	HE; Liqi et al.	
	010	US-20060078623	04-13-2006	DHOOT; Nikhil et al.	
	011	US-20090076266	03-19-2009	DAUGULIS; Olafs et al.	
	012	US-20100022560	01-28-2010	CHEN; Zhaogen et al.	
	013	US-20100155595	06-24-2010	GHOSHAL; Amit [Us] et al.	
	014	US-20130045979	02-21-2013	SANFILIPPO; Louis	
	015	US-20170020877	01-26-2017	GRIGORIADIS; Dimitri E.	
	016	US-20170333126	11-23-2017	SOBOTKA; Paul	
	017	US-20180110554	04-26-2018	ZARINS; Denise Marie et al.	
	018	US-20200255436	08-13-2020	HOWERTON; Alexis et al.	
	019	US-20210015827	01-21-2021	HOWERTON; Alexis et al.	
	020	US-20210038604	02-11-2021	HOWERTON; Alexis et al.	
	021	US-20210137935	05-13-2021	HOWERTON; Alexis et al.	
	022	US-20210322430	10-21-2021	HOWERTON; Alexis et al.	

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] 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.

Approved for use through 11/30/2020. 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)

Sheet 2 of 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

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
	023	US-20210361664	11-25-2021	HOWERTON; Alexis et al.	
	024	US-20220133742	05-05-2022	GHOSH; Sangita et al.	
	025	US-20220143037	05-12-2022	HOWERTON; Alexis et al.	

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-2094709-B1	09-15-2010	LILLY CO ELI [US]		☐
	002	JP-2000302693-A	10-31-2000	PFIZER PROD INC.		☒
	003	JP-2000503661-A	03-28-2000	JANSSEN PHARMACEUTICA NV.	Machine Translation:	☒
	004	JP-2002501922-A	01-22-2002	DUPONT PHARMACEUTICALS COMPANY.	Machine Translation:	☒
	005	JP-2002513382-A	05-08-2002	DUPONT PHARMACEUTICALS COMPANY.	Machine Translation:	☒
	006	JP-2008533201-A	08-21-2008	ELI LILLY AND CO.	Machine Translation:	☒

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] 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.

Approved for use through 11/30/2020. 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)

Sheet 3 of 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[2]-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]
	007	JP-2010504344-A	02-12-2010	ELI LILLY AND CO.	Machine Translation:	☒
	008	JP-2012504626-A	02-23-2012	ELI LILLY AND CO.	Machine Translation:	☒
	009	JP-2017503030-A	01-26-2017	NEUROCRINE BIOSCIENCES, INC.	Machine Translation:	☒
	010	WO-0059908-A2	10-12-2000	DU PONT PHARM CO [US]		☐
	011	WO-0123388-A2	04-05-2001	NEUROGEN CORP [US], et al.		☐
	012	WO-02072202-A1	09-19-2002	BRISTOL MYERS SQUIBB PHARMA CO [US]		☐
	013	WO-2005063755-A1	07-14-2005	SB PHARMCO INC [US], et al.		☐
	014	WO-2006102194-A1	09-28-2006	LILLY CO ELI [US], et al.		☐
	015	WO-2008036579-A1	03-27-2008	LILLY CO ELI [US], et al.		☐
	016	WO-2010039678-A1	04-08-2010	LILLY CO ELI [US], et al.		☐

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] 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.

Approved for use through 11/30/2020. 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)

Sheet 4 of 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

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]
	017	WO-2015112642-A1	07-30-2015	NEUROCRINE BIOSCIENCES INC [US]		☐
	018	WO-2019036472-A1	02-21-2019	SPRUCE BIOSCIENCES INC [US]		☐
	019	WO-2019036503-A1	02-21-2019	SPRUCE BIOSCIENCES INC [US]		☐
	020	WO-2021016208-A1	01-28-2021	SPRUCE BIOSCIENCES INC [US]		☐
	021	WO-2022036123-A1	02-17-2022	SPRUCE BIOSCIENCES INC [US]		☐
	022	WO-9413676-A1	06-23-1994	PFIZER [US], et al.		☐
	023	WO-9729109-A1	08-14-1997	JANSSEN PHARMACEUTICA NV [BE], et al.		☐
	024	WO-9803510-A1	01-29-1998	DU PONT MERCK PHARMA [US]		☐
	025	WO-9808847-A1	03-05-1998	PFIZER [US], et al.		☐

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] 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.

Approved for use through 11/30/2020. 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)

Sheet 5 of 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

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	BORNSTEIN et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 101(2):364-389 (2016).	☐
	002	CHEN et al. Design of 2,5-Dimethyl-3-(6-dimethyl-4-methylpyridin-3-yl)-7-dipropyl aminopryazolo[1,5-a]pyrimidine (NBI 30775/R121919) and Structure-Activity Relationships of a Series of Potent and Orally Active Corticotropin- Releasing Factor Receptor Antagonists. J. O Medicinal Chemistry Society 47(19) 4787-4798 XP001206057 (2004).	☐
	003	Co-pending U.S. Application No. 17/720,074, inventors REDDY; Dasharatha et al., filed on April 13, 2022.	☐
	004	Co-pending U.S. Application No. 18/078,649, inventors HOWERTON; Alexis et al., filed on December 09, 2022.	☐
	005	Co-pending U.S. Application No. 18/310,463, inventor REDDY; Dasharatha, filed on May 01, 2023.	☐
	006	DAVE. Overview of pharmaceutical excipients used in tablets and capsules. https://www.drugtopics.com/view/overview-pharmaceutical-excipients-used-tablets-and-capsules (10/24/2008).	☐
	007	EP18846043.0 Extended Search Report dated February 10, 2021.	☐
	008	EP18846689.0 Extended European Search Report dated December 22, 2020.	☐
	009	ESCOBAR-MORREALE, HF., Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 14(5):270-284 (2018).	☐

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 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.

Approved for use through 11/30/2020. 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)

Sheet 6 of 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

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]
	010	FUQUA et al. Duration of suppression of adrenal steroids after glucocorticoid administration. Int J Pediatr Endocrinol 2010:712549 (2010).	☐
	011	GEHLERT et al. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-y1)-8-(1-ethylpropy1)-2,6-dimethyl-imidazo[l ,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 27(10):2718-2726 (2007).	☐
	012	GENNARO. Remington: The Science and Practice of Pharmacy. 21st Ed. Mack Pub. Co., Easton, PA (2005).	☐
	013	GILLIGAN P. et al., The Discovery of 4-(3-Pentylamino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-pyrazolo-[1,5-alpha]-pyrimidine: A corticotrophin-Releasing Factor (hCRF1)Antagonist. Bioorganic & Medicinal Chemistry 181-189 (2000).	☐
	014	HE LIQI et al. 4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine: A Potent, Orally Bioavailable CRF1 Receptor Antagonist. J. Of Medicinal Chem. American Chem. Society. Washington, US, Vol. 43, 449-456 XP002196777 (2000).	☐
	015	HIEN-QUANG DO. A General Method for Copper-Catalyzed Arylation of Arene C-H Bonds. J Am Chem Soc. 2008 November 12; 130(45): 15185-15192.	☐
	016	HIEN-QUANG DO. Copper-Catalyzed Arylation and Alkenylation of Polyfluoroarene C-H Bonds. Journal of American Chemical Society 2008, 1128-1129.	☐
	017	HIEN-QUANG DO. Copper-Catalyzed Arylation of Heterocycle C-H Bonds. J Am Chem Soc. 2007 October 17; 129(41): 12404-12405.	☐

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 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.

Approved for use through 11/30/2020. 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)

Sheet 7 of 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

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]
	018	HODGETTS et al. Discovery of N-(1-ethylpropyl)-[3-methoxy-5-(2-methoxy-4-trifluoromethoxyphenyl)-6-methyl-pyrazin-2-yl]amine 59 (NGD 98-2): an orally active corticotropin releasing factor-1 (CRF-1) receptor antagonist. J Med Chem 54:4187-4206 (2011).	☐
	019	KHADILKAR et al., Can polycystic ovarian syndrome be cured? Unfolding the concept of secondary polycystic ovarian syndrome. J Obstet Gynaecol India 69(4):297-302 (2019).	☐
	020	LEE et al. Attenuated Forms of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. J Clin Endocrinol Metab. 55(5):866-871 (1982).	☐
	021	MAJO et al. Facile Palladium-Catalyzed Synthesis of 3-Arylpyrazolo-[1,5-a]pyrimidines. Adv. Synth. Catal. 2003, 620-624.	☐
	022	Malvern Instruments Worldwide. A Basic Guide to Particle Characterization. Inform - White Paper. 2012. 26 Pages.	☐
	023	O'REILLY et al., 11-oxygenated C19 steroids are the predominant androgens in polycystic ovary syndrome. J Clin Endocrinol Metab. 102(3):840-848 (2017).	☐
	024	PCT/US2007/078605 Written Opinion dated March 20, 2009.	☐
	025	PCT/US2009/058722 International Search Report dated April 8, 2010.	☐
	026	PCT/US2009/058722 Written Opinion dated April 2, 2011.	☐
	027	PCT/US2018/046707 International Search Report and Written Opinion dated October 24, 2018.	☐
	028	PCT/US2018/046760 International Search Report and Written Opinion dated October 24, 2018.	☐

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 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.

Approved for use through 11/30/2020. 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)

Sheet 8 of 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

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]
	029	PCT/US2020/042820 International Search Report and Written Opinion dated November 25, 2020.	☐
	030	PCT/US2021/045780 International Search Report and Written Opinion dated December 17, 2021.	☐
	031	PCT/US2022/050436 International Search Report and Written Opinion dated November 18, 2022.	☐
	032	ROSENFIELD et al., The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocrine Reviews 37(5):467-520 (2016).	☐
	033	SARAFOGLOU et al. 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.	☐
	034	THAKRAL et al. Salt Disproportionation in the Solid State: Role of Solubility and Counterion Volatility. Mol Pharm 13(12):4141-4151 (2016).	☐
	035	TURCU et al. Single-Dose Study of a Corticotripin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency. J Clin Endocrinol Metab 101(3):1174-1180 (2016).	☐
	036	U.S. 16/388,620 Notice of Allowance dated September 30, 2020.	☐
	037	U.S. 17/063,592 Notice of Allowance dated March 25, 2022.	☐
	038	U.S. 17/078,054 Notice of Allowance dated March 9, 2021.	☐
	039	U.S. 17/359,414 Notice of Allowance dated March 4, 2022.	☐

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 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.

Approved for use through 11/30/2020. 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)

Sheet 9 of 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

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]
	040	U.S. Serial No. 17/586,228 Office Action dated June 10, 2022.	☐
	041	U.S. Serial No. 12/377,733 Notice of Allowance dated May 27, 2011.	☐
	042	U.S. Serial No. 16/388,620 Office Action dated July 15, 2019.	☐
	043	U.S. Serial No. 16/388,620 Office Action dated November 25, 2019.	☐
	044	U.S. Serial No. 16/639,540 Office Action dated July 11, 2022.	☐
	045	U.S. Serial No. 16/639,540 Office Action dated November 16, 2021.	☐
	046	U.S. Serial No. 17/063,592 Office Action dated December 7, 2021.	☐
	047	U.S. Serial No. 17/078,054 Office Action dated December 14, 2020.	☐
	048	U.S. Serial No. 17/359,411 Notice of Allowance dated April 28, 2022.	☐
	049	U.S. Serial No. 17/359,411 Notice of Allowance dated April 4, 2022.	☐
	050	U.S. Serial No. 17/359,411 Notice of Allowance dated March 22, 2022.	☐
	051	U.S. Serial No. 17/359,411 Office Action dated January 6, 2022.	☐
	052	U.S. Serial No. 17/359,414 Office Action dated November 16, 2021.	☐
	053	U.S. Serial No. 17/720,074 Notice of Allowance dated March 28, 2023.	☐
	054	U.S. Serial No. 17/720,074 Office Action dated August 26, 2022.	☐

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 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.

Approved for use through 11/30/2020. 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)

Sheet | 10 | of | 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

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]
	055	VARMA. Excipients used in the Formulation of Tablets. https://www.rroij.com/openaccess/excipients-used-in-the-formulationof-tablets-.php?aid=78260 Revised date: 26/07/2016.	☐
	056	ZHANG et al. D-Level Essay in Statistics, 2009, How to Analyze Change from Baseline. Available at http://www.statistics.du.se/essays/D09 Zhang%20Ling%20&%20Han%20Kun.pdf (6/10/2009).	☐

Examiner Signature		Date Considered	

*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. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 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.

Approved for use through 11/30/2020. 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)

Sheet | 11 | of | 12

Complete if Known	
Application Number	US18/307,718
Filing Date	04-26-2023
First Named Inventor	HOWERTON; Alexis
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	50535-709.307

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 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 certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Stephen Olshemski/	Date (YYYY-MM-DD)	2023-05-10
Name/Print	Stephen Olshemski	Registration Number	80,285

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.

Thiazolepyrazolopyrimidines as CRF1 receptor antagonists

Abstract

translated from Japanese

The present invention relates to compounds of formula I, pharmaceutical compositions thereof and their use as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric and neuroendocrine disorders, nervous system diseases and metabolic syndrome. .

Classifications

- C07D487/04 Ortho-condensed systems

View 22 more classifications

JP2010504344A

Japan

Download PDF Find Prior Art Similar

Other languages: Japanese

Inventor: チャオダン・チェン, チャフィク・アムドウチ・アムドウチ, エリック・ジェイムズ・ヘンプル, フィリップ・アーサー・ヒップスカインド, ジェイソン・ケネス・マイヤーズ, 錢子亮&錢Y, ジェイムズ・リー・トス

Worldwide applications

2007 JP BR CA AU MX US RS DE CN PL NZ SI WO EP ES EA DK UA MY PT HR AT AR CL PE TW 2009 IL TN GP NO MA 2010 HK HR CY

Application JP2009529316A events

2006-09-20 Priority to US82626406P

2007-09-17 Application filed by イーライ リリー アンド カンパニー

2008-06-17 First worldwide family litigation filed

2010-02-12 Publication of JP2010504344A

2010-10-28 Publication of JP2010504344A5

2013-03-13 Application granted

2013-03-13 Publication of JP5612082B2

Status Active

2027-09-17 Anticipated expiration

Show all events

Info: Patent citations (10), Non-patent citations (1), Cited by (14), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

Claims (17)

Hide Dependent

translated from Japanese

Compound of formula I

(Where

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, $R^a R^b N$-, methoxymethyl, n-butyl, acetamide, pyridin-4-yl, morpholin-4-yl,

And

R^a and R^b are independently hydrogen, C_1-C_3 alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-)

Or a pharmaceutically acceptable salt thereof. R^3 is Cl, Br, or trifluoromethyl, a compound or a pharmaceutically acceptable salt thereof according to claim 1. The compound or a pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein R^3 is Cl or Br. R^4 is $R^a R^b N$-, pyridin-4-yl, morpholin-4-yl, or

The compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof. R^4 is morpholin-4-yl or

The compound according to any one of claims 1 to 4 or a pharmacologically acceptable salt thereof. The compound according to any one of claims 1 to 4, or a pharmacological thereof, wherein R^4 is $R^a R^b N$-, and R^a and R^b are independently C_1-C_3 alkyl. Acceptable salt. 3- [4-Bromo-2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl] -2,5-dimethyl-7- (1-propyl- The compound or a pharmaceutically acceptable salt thereof according to claim 1, which is (butyl) -pyrazolo [1,5-a] pyrimidine. 3- (4-Bromo-2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl) -7- (1-ethyl-propyl) -2,5 The compound according to claim 1, which is -dimethyl-pyrazolo [1,5-a] pyrimidine, or a pharmaceutically acceptable salt thereof. 3- (4-Chloro-2-morpholin-4-yl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine, The compound according to claim 1 or a pharmaceutically acceptable salt thereof. A pharmaceutical composition comprising the compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, and a pharmacologically acceptable excipient. Patient depression, anxiety, alcohol abuse or drug abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, seizures, sleep disorders,

allergies, migraine, premenstrual syndrome, infertility, sexual dysfunction, Congenital adrenal hyperplasia, Cushing's disease, premature birth, stress-induced gastric ulcer, inflammatory disorder, pituitary or ectopic tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis A method of treatment comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof. ,Method. A method for treating anxiety or depression in a patient, wherein the patient in need thereof has a therapeutically effective amount of the compound of any one of claims 1 to 9 or a pharmacologically acceptable salt thereof. Administering a possible salt. A method of treating a patient's alcohol or drug abuse, wherein the patient in need thereof has a therapeutically effective amount of the compound of any one of claims 1 to 9 or a pharmacologically acceptable salt thereof. Administering a possible salt. 10. A compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof for use in therapy. Depression, anxiety, alcohol abuse or drug abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, seizures, sleep disorders, allergies, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital In the treatment of adrenal hyperplasia, Cushing's disease, premature birth, stress-induced gastric ulcer, inflammatory disorder, pituitary or ectopic pituitary tumor, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis The compound or pharmacologically acceptable salt thereof according to any one of claims 1 to 9, for use. 10. 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. 10. A compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof for use in the treatment of alcohol abuse or drug abuse.

Description

translated from Japanese

The present invention relates to novel thiazolepyrazolopyrimidine compounds, pharmaceutical compositions thereof and their use as CRF1 receptor antagonists in the treatment of psychiatric and neuroendocrine disorders, nervous system diseases and metabolic syndrome.

Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is a major physiological regulator of proopiomelanocortin (POMC) -derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role in the pituitary gland, due to the immunohistochemical localization of CRF, this hormone has a broad extrahypothalamic distribution of the central nervous system and as a neurotransmitter or neuromodulator in the brain Proven to produce a wide range of autonomic effects, electronic physiological effects and effects on action consistent with the role. There is also evidence that CRF plays an important role in integrating responses to physiological, psychological and immunological stressors in the immune system.

CRF is a psychiatric and nervous system disease, including depression and neuroanxiety, and Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol abuse And drug abuse and related withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia, Cushing disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulcer, premenstrual syndrome, sexual dysfunction, premature birth, It has been associated with inflammatory disorders. allergies, multiple sclerosis. visceral pain, sleep disorders, pituitary or ectopic pituitary tumors. chronic fatigue syndrome and fibromyalgia.

CRF receptor subtypes (CRF1 and CRF2) have been identified and these are heterogeneously distributed in the brain, suggesting a possible functional diversity For example, widely distributed brain CRF1 receptors are strongly associated with the emotion associated with exposure to environmental stressors. Importantly, the CRF1 receptor, but not the CRF2 receptor, appears to mediate the selection of anxiety-like behavior. The more discrete septal / hypothalamic distribution and availability of another endogenous ligand suggests a different functional role for the CRF2 receptor. For example, a novel CRF family of neuropeptides with a preferential affinity for the CRF2 receptor over the CRF1 receptor may cause an appetite without producing the behavior-activated appearance observed with selective CRF1 agonism. It has been reported to suppress. In other cases, CRF2 agonism produces effects similar to those reported for CRF1 antagonists or CRF1 gene deletions. For example, although CRF2 agonists have been proposed as anti-obesity agents, CRF1 antagonists may also be important treatments for obesity.

Certain pyrrolo [2,3-d] pyrimidines, pyrrolo [3,2-d] pyrimidines, pyrazolo [1,5-a] pyrimidines, 1,2,3-triazolo [4,5-b useful as CRF antagonists] Pyridine and pyrazolo [1,5-a] -1,3,5-triazine are described in Patent Document 1, Patent Document 2, Patent Document 3, and Patent Document 4.

International Publication No. 94/13676 Pamphlet International Publication No. 97/29109 Pamphlet International Publication No. 98/08847 Pamphlet International Publication No. 98/03510 Pamphlet

The present invention provides novel thiazolepyrazolopyrimidines useful as CRF1 receptor antagonists. In view of the above, it would be desirable to discover new effective and selective antagonists of CRF1 as potentially beneficial therapeutics for the treatment of psychiatric and neuroendocrine disorders, nervous system diseases and metabolic syndrome. In addition, novel compounds with preferred bioavailability and pharmacokinetic profiles over known CRF antagonists (eg CP154526 and NBI30775) because the majority of commercially available CNS drugs and cardiovascular drugs exhibit unfavorable bioavailability and pharmacokinetic profiles. It is also desirable to discover.

In one embodiment, the invention provides a compound of 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, $R^a R^b N$-, methoxymethyl, n-butyl, acetamide, pyridin-4-yl, morpholin-4-yl,

R^a and R^b are independently hydrogen, C_1 -C_3 alkyl, $H_2NCH_2CH_2$ —, $(CH_3)_3COC(O)NHCH_2CH_2$ —, or $CH_3CH_2CH_2NHCH_2CH_2$ - in which) or to provide a

pharmaceutically acceptable salt thereof.

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

In another embodiment, the invention relates to patient depression, anxiety, alcohol abuse or drug abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, seizures, sleep disorders, allergies, migraine, premenstrual Syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature birth, stress-induced gastric ulcer, inflammatory disorder, pituitary or ectopic pituitary tumor, chronic fatigue syndrome, fibromuscular A method of treating pain, visceral pain or multiple sclerosis comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. About.

In another embodiment, the present invention relates to depression, anxiety, alcohol abuse or drug abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, seizures, sleep disorders, allergies, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature birth, stress-induced gastric ulcer, inflammatory disorder, pituitary or ectopic pituitary tumor, chronic fatigue syndrome, fibromyalgia, It relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of visceral pain or multiple sclerosis.

In another embodiment, the present invention relates to depression, anxiety, alcohol abuse or drug abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, seizures, sleep disorders, allergies, migraine, premenstrual syndrome, Infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature birth, stress-induced gastric ulcer, inflammatory disorder, pituitary or ectopic pituitary tumor, chronic fatigue syndrome, fibromyalgia, It relates to a compound of formula I or a pharmaceutically acceptable salt thereof for use in the treatment of visceral pain or multiple sclerosis.

In another embodiment, the present invention relates to a therapeutic compound of formula I or a pharmaceutically acceptable salt thereof.

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

"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 pharmacologically acceptable pharmaceutical carrier, solution, or additive to enhance pharmaceutical properties. Such excipients must be compatible with the other ingredients of the formulation and not deleterious to the user. Such excipients are well known to those skilled in the art (see, eg, Remingtons Pharmaceutical Sciences, 19th Edition, Mack Publishing Company, 1995).

"Pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid addition salts and base addition salts of the compounds of the present invention. These salts can be prepared in situ in the final isolation and purification steps of the compound. In particular, acid addition salts can be prepared by reacting the purified compound in the free base form separately with a suitable organic or inorganic acid and isolating the resulting salt (see, eg, Remingtons Pharmaceutical Sciences, No. 1), 19th edition, see Mack Publishing Company, 1995).

A "therapeutically effective amount" or "effective amount" is the biological or medical response of a tissue, system, animal or human being sought by a researcher, veterinarian, physician or other clinician, or the desired response thereto It means the amount of a compound of formula I of the invention or a pharmaceutical composition containing a compound of formula I of the invention that causes a therapeutic effect.

Terms such as "treatment", "treat", "treating" and the like are intended to include both slowing the progression of the disorder and directing recovery. These terms also refer to one or more symptoms of the disorder or condition, even if the disorder or condition is not actually resolved, and the progression of the disorder or condition is not slowed by itself and is not likely to recover. Also includes mitigating, improving, mitigating, eliminating or reducing. The term "treatment" and similar terms also include preventive (eg, prophylactic) treatment and treatment for pain relief. Prevention of a disease results in prolonging or delaying the onset of symptoms of the disease.

Symbols in molecular structure
indicates the bonding position for the specific substituent.

When any variable occurs more than one time in any constituent or in formula I, its definition when each appears is independent of its definition when it appears elsewhere. Also, combinations of substituents and / or variables are acceptable only if such combinations result in stable compounds. In selecting the compounds of the present invention, those skilled in the art will recognize that various substituents, ie R^1, R^2, etc., should be selected in accordance with the well-known principles of chemical structure connectivity. I will.

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 the following embodiments, which can be further combined differently:

(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) R^3 is Cl, Br, compound of formula I is methyl or trifluoromethyl;

(D) the compound of formula I, wherein R^3 is Cl;

(E) the compound of formula I, wherein R^3 is Br;

(F) R^4 is $R^a R^b N$-, pyridin-4-yl, morpholin-4-yl, or
A compound of formula I which is

(G) the compound of formula I, wherein R^4 is morpholin-4-yl;

(H) R^4 is
A compound of formula I which is

(I) the compound of formula I, wherein R^a and R^b are independently C_1 -C_3 alkyl;

(J) the compound of formula I, wherein R^1 and R^2 are ethyl, R^3 is Cl, and R^4 is morpholin-4-yl;

(K) the 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) R^1 and R^2 are n- propyl, R^3 is Br, compound of formula I R^4 is morpholin-4-yl;

(N) R^1 and R^2 are ethyl, R^3 is Cl, R^4 is
A compound of formula I which is

(O) R^1 and R^2 are n-propyl, R^3 is Cl, and R^4 is
A compound of formula I which is

(P) R^1 and R^2 are ethyl, R^3 is Br, and R^4 is
A compound of formula I which is

(Q) R^1 and R^2 are n-propyl, R^3 is Br, and R^4 is
A compound of formula I which is

(R) the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the treatment of depression or neuroanxiety;

(S) the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the treatment of alcohol abuse or drug abuse;

(T) the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the treatment of alcohol or drug abuse and related withdrawal symptoms;

(U) a compound of formula I or a pharmaceutically acceptable salt thereof showing a Ki value of 500 nM or less for CRF1 binding;

(V) a compound of formula I or a pharmaceutically acceptable salt thereof showing a Ki value of 50 nM or less for CRF1 binding;

(W) a compound of formula I or a pharmaceutically acceptable salt thereof showing a Ki value of 5 nM or less for CRF1 binding;

(X) a compound of formula I or a pharmaceutically acceptable salt thereof that exhibits a Ki value of 500 nM or less for CRF1 binding and selectively binds to CRF1 over CRF2 (ie, a smaller Ki);

(Y) a compound of formula I or a pharmaceutically acceptable salt thereof that exhibits a Ki value of 50 nM or less for CRF1 binding and selectively binds to CRF1 over CRF2 (ie, a smaller Ki);

(Z) a compound of formula I or a pharmaceutically acceptable salt thereof that exhibits a Ki value of 5 nM or less for CRF1 binding and selectively binds to CRF1 over

CRF2 (ie, a smaller Ki); and / or Alternatively (aa) certain exemplified compounds (such as Example 15) that have better bioavailability and pharmacokinetic profiles than some known CRF antagonists (eg, CP154526 and NBI30775).

The compounds of the present invention are preferably formulated as pharmaceutical compositions that are administered by a variety of routes. Such compositions are preferably for oral administration. Such pharmaceutical compositions and processes for preparing such pharmaceutical compositions are well known in the art (see, eg, Remington: The Science and Practice of Pharmacy, A. Gennaro et al , 19th Edition, Mack Publishing Co. , 1995).

The compounds of formula I are generally effective over a wide dosage range. For example, daily dosages typically range from about 0.0001 to about 30 mg / kg body weight. In some cases, dosage levels below the lower limit of the aforementioned range may be sufficient, while in some cases even higher doses may be used without causing any harmful side effects, and therefore The above dosage ranges are not intended to limit the scope of the invention in any way. The amount of the compound actually administered will depend on the condition being treated, the route of administration selected, the actual compound (s) being administered, the age, weight and response of the individual patient, It should be understood that it will be determined by the physician in view of the relevant circumstances, including the severity of the patient's symptoms.

The compounds of formula I are CRF-1 antagonists and are therefore useful for the treatment of medical conditions that can be treated by reducing CRF1 receptor tone or stimulation. Corticotropin releasing factor (CRF), a 41 amino acid peptide that is a major physiological regulator of peptide secretion from proopiomelanocortin (POMC) from the anterior pituitary gland [J. Rivier et al., Proc. Nati. Acad. Sci (USA) 80: 4851 (1983); Vale et al., Science 213: 1394 (1981)] has been associated with a number of medical conditions. For example, in addition to its endocrine role in the pituitary gland, because of the immunohistochemical localization of CRF, this hormone has a broad extra-thalamic distribution of the central nervous system and is a neurotransmitter or neuromodulator in the brain It has been demonstrated to produce a wide range of autonomic effects, electrophysiological effects and action effects consistent with its role as [W. Vale et al., Rec. Prog. Horm. Res. 39: 245 (1983); F. Koob, Persp. Behav. Med. 2:39 (1985); B. De Souza et al., J. Mol. Neurosci. 5: 3169 (1985)]. There is also evidence that CRF plays an important role in integrating responses to physiological, psychological and immunological stressors in the immune system [see, for example, J. et al. E. Black, Physiological Reviews 69: 1 (1989); E. Morley, Life Sci. 41: 527 (1987)].

CRF is associated with psychiatric disorders and nervous system disorders, including depression and neuroanxiety [D. M.M. Nielsen, Life Sci. 78: 909-919; E. Kunzel et al. Psychiatr. Res. 37: 525-533; R. Gehlert et al., Eur. J. et al. Pharmacol. 509: 145-153]. The role of CRF has also been postulated in the pathogenesis and pathophysiology of Alzheimer's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis. Because they are related to dysfunction of CRF neurons in the central nervous system [for review, see E.C. B. De Souze, Hosp. Practice 23:59 (1988)]. Chronic administration of CRF has been shown to produce dysfunction 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 involving CRF include sputum [Y. Z. Baram et al., Brain Res. 770. 89-95 (1997)] and migraine [Y. C. Theoharides et al , Endocrinology 136: 5745-5750 (1995)]. CRF has been associated with alcohol and drug abuse and related withdrawal symptoms [D. H. Overstreet et al., Pharmacol. Biochem. Behav. 77: 405-413; Shaham et al., Psychopharmacology (Berr) 137: 184-190]. In addition, CRF is associated with various endocrine disorders and cardiovascular diseases such as obesity [E. Timofeva and D. Richard, Neuroendocrinology 66: 327-340 (1997)], metabolic syndrome [AM Ward et al., Metabolism 53: 720. -726 (2004)], congenital adrenal hyperplasia [GP Merke and GB Cutler Jr., Endocrinol. Metab. Clin. North Am. 30: 121-135 (2001)], Cushing's disease [M Labeur et al., Curr. Drug Targets Immunod Endocr. Metabol. Disord. 4: 335-342 (2004)], hypertension [RJ Briscoe et al , Brai. Res.881: 204-207 (2000)], and seizures [S.L.Stevens et al , J.Cereb.Blood Flow Metab 23: 1151-1159 play a role in (2003)]), there is evidence that. Gastric disorders (eg, irritable bowel syndrome [Y. Tache et al., Eur J. Surg. Suppl: 16-22 (2002)] and stress-induced gastric ulcer [KE Gabry et al., Mol. Psychiatry 7: 474| -483,433 (2002)]) has been shown to be related to CRF. In addition, CRF has been identified in various areas of human female health, such as 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. et al. Physiol. Regul. Integr. Comp. Physiol. 283: R591-597 (2002)], and preterm birth [F. D. Wadhwa et al., Am. J. et al. Obstet. Gynecol. 191: 1063-1069 (2004)]. There is also evidence that CRF plays an important role in the immune system. This is because inflammatory disorders [A. Gravanis and A.M. 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. Immunol. 174: 5407-5413 (2005)]. In addition to the above, CRF is a visceral pain [M. Nijsen et al , Neurogastroenterol. Motil. 17: 423-432 (2005)], sleep disorders [T. M.M. Buckley and A.M. F. Schatzberg, J.A. Clin. Endocrinol. Metab. 90: 3106-3114 (2005)], pituitary tumors or ectopic pituitary tumors [K. D. Dieterich et al., J. Mol. Clin. Endocrinol. Metab. 83: 3327-3331 (1998)], chronic fatigue syndrome and fibromyalgia [G. Neeck and L.M. J. et al. Croford, Rheum. Dis. Clin. North Am. 26: 989-1002 (2000)].

CRF receptor subtypes (CRF1 and CRF2) have been identified and these are heterogeneously distributed in the brain [D. T.A. Chalmers et al., TIPS 17: 166-72 (1996)], suggesting the possibility of functional diversity [S. C. Heinrichs et al., Regul. Peptides 71:15 (1997)]. For example, widely distributed brain CRF1 receptors are strongly associated with the emotionality associated with exposure to environmental stressors [G. Liebsch et al., Regul. Peptides 59: 229-39 (1995); W. Schulz, PNAS 93: 10477-82 (1996)]. Importantly, the CRF1 receptor, but not the CRF2 receptor, appears to mediate selection of anxiety-like behavior [Heinrichs et al., 1997]. A more discrete septum / hypothalamus distribution [D. T.A. Chalmers et al. Neurosci. 15 (10): 6340-50 (1995)] and the availability of other endogenous ligands [J. Vaughan et al , Nature 378: 287-92 (1995)] suggests a different functional role for the CRF2 receptor [Heinrichs et al., 1997]. For example, a novel CRF family of neuropeptides with a preferential affinity for the CRF2 receptor over the CRF1 receptor may cause an appetite without producing the behavior-activated appearance observed with selective CRF1 agonism. [H. Tezval et al., PNAS 101 (25): 9468-9473 (2004)]. In some cases, CRF2 agonism produces effects similar to those reported for CRF1 antagonists or CRF1 gene deletion [S. C. Heinrichs, Trends in Pharmacological Sciences 20 (8): 311-5 (1999)]. For example, CRF2 agonists have been proposed as anti obesity agents, but CRF1 antagonists may also be important treatments for obesity [C. Contoreggi et al., Neuroendocrinology 80 (2): 111-23 (2004)].

(Preparation of compounds of the invention)

All of the compounds of the present invention can be chemically prepared, for example, according to the synthetic routes shown below. However, the following discussion is in no way intended to limit the scope of the present invention. For example, the specific synthetic steps for each of the described routes may be combined in different ways to prepare additional compounds of formula I or may be combined in conjunction with steps from different schemes. . The product of each step can be recovered by conventional methods including extraction, evaporation, precipitation, chromatography, filtration, powdering, crystallization and the like. In the schemes below, all substituents are as previously defined unless otherwise stated, and suitable reagents are well known and recognized in the art.

Formation of compounds of formula (6a, b), formula (7), or formula 8 (ac) can be carried out according to the reaction shown in Scheme 1. Suitable compounds of formula (6a, b), formula (7), or formula (8a-c) are those where R^1 and R^2 are as defined for formula I and R^{3a} = H or CH_3 , R^{3b} = Br or CH_3 and R^{3c} = H, CH_3 , or Br.

In Scheme 1, Step 1, pyrazolo [1,5-a] pyrimidin-7-one of formula (1) uses phosphorus oxychloride and dimethylaniline in an inert solvent (such as toluene) at the reflux temperature of the solvent. To 7-chloro-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine.

In Step 2, the Grignard reagent of formula (3) (X = Cl or Br) is reacted with the chloride of formula (2) at reflux temperature in an inert solvent (such as toluene) to yield the 7-alkyl of formula (4). Give pyrazolopyrimidine.

Alternatively, the 7-alkylpyrazolopyrimidine of formula (4) can be obtained as shown in Step 3, Step 4, and Step 5. In Step 3, ethyl acetoacetate is acylated with an acid halide of formula (4a) in the presence of magnesium chloride to give a diketo-ester of formula (4b). The diketo-ester of formula (4b) is decarboxylated under Krapcho conditions to give the diketone of formula (4c). For example, (4b) is heated in dimethyl sulfoxide at a temperature of about 130-170 ° C. to effect this decarboxylation. In

step 5, the diketone of formula (4c) is cyclized with 3-amino-5-methylpyrazole in a protic solvent (such as methanol, ethanol, or acetic acid) to give a 7-alkylpyrazolopyrimidine of formula (4). give. In preferred conditions, acetic acid is used at a temperature of about 0-60 ° C.

The pyrazolopyrimidine of formula (4) is functionalized in step 6 to an iodopyrazolopyrimidine of formula (5) using an excess of N-iodosuccinimide in acetonitrile.

In Scheme 1, Step 7 or Step 8, iodopyrazolopyrimidine of formula (5) is reacted with thiazole zinc halide in a Negishi cross-coupling reaction to form thiazolylpyrazolopyrimidine of formula (6a) or formula (6b) (Jensen, J .; Skjaerbaek, N .; Vedso, P. Synthesis 2001, 128). The thiazole zinc halide is produced using methods well known to those skilled in the art. For example, in step 7, 2-trimethylsilanyl two thiazole is treated with n- butyllithium, sec- butyllithium or tert- butyllithium, and then lithium $ZnCl_2$ - zinc replacement is made. The organozinc reagent is present 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 at reflux temperature for about 12-36 hours. Below "coupled with iodopyrazolopyrimidines of formula (5)" to give thiazole pyrazolopyrimidines of formula (6a).

Alternatively, in step 8, thiazole zinc bromide is generated using 5 bromo-4-methylthiazole and zinc metal and is used for Negishi cross coupling essentially as described for step 7 to obtain the formula (6b) Thiazolepyrazolopyrimidine.

In Scheme 1, Step 9, the thiazole of formula (6a, b) is brominated to give the bromothiazole or dibromothiazole of formula (7) where R^{3b} = Br or CH_3 . This thiazole is brominated with 1 or 2 equivalents of N-bromosuccinimide, depending on whether R^{3a} is CH_3 or H, respectively.

The alkyl thiazole of formula (8a-c) is obtained in step 11 from the thiazole of formula (6a, b) or in step 10 from the formula (7) bromothiazole. In step 10, halogen-lithium exchange with n-butyllithium, sec-butyllithium, or t-butyllithium provides a thiazole lithium reagent, which is then subjected to an electrophile (an alkyl such as iodomethyl methyl ether or iodobutane). Reaction with halide). In step 11, the thiazole lithium reagent is generated by deprotonation using n-butyllithium, sec-butyllithium, or tert-butyllithium, followed by an electrophile such as iodomethyl methyl ether or iodobutane. React with.

The thiazole ring system is easily functionalized and that thiazole intermediates such as 2-trimethylsilanyl-thiazole (Dondoni, A. et al., J. Org. Chem. 1988, 53, 1748) can be easily prepared. Those skilled in the art will understand. 5-Bromo-4-methylthiazole is obtained by bromination of 4-methylthiazole with bromine in acetic acid (Collins, IJ et al., WO2003099522, Nov. 13, 2003). . 2,5-Dimethyl-4H-pyrazolo [1,5-a] pyrimidin-7-one (1) is obtained by condensation of ethyl acetoacetate and 5-methyl-2H-pyrazol-3-ylamine in refluxing acetic acid. Easy to prepare.

Formation of the compound of formula (9), formula (10), or formula (11) is carried out according to the reaction shown in Scheme 2. Suitable compounds of formula (9), formula (10), or formula (11) are as R^1 , R^2 , R^5 , and R^b are as defined for formula I, and R^{3b} = Br or CH_3 , R^{4a} = --$NR^a R^b$ or --N-morpholinyl, a compound defined as "het".

In Step 1, the bromothiazole of formula (7) is coupled with a heterocyclic zinc reagent in a Negishi cross-coupling reaction to give a thiazole heterocycle of formula (9). For example, 1-methyl-1,2,4-triazole is treated with n-butyllithium, sec-butyllithium, or tert-butyllithium at about −80 to −65 ° C. and then with zinc chloride, React with bromothiazole of formula (7) in situ. This reaction is carried out in an inert solvent (such as THF) with a palladium catalyst (such as dichloro [1,1'-bis (diphenyl-phosphino) ferrocene] palladium (II) dichloromethane or tetrakis (triphenylphosphine) palladium (0)). Is preferably carried out in the presence of The reaction is warmed to reflux temperature. Alternatively, the heterocyclic zinc reagent is formed from a haloheterocycle (such as 4-iodopyridine) and zinc metal.

In Scheme 2, Step 2, the intermediate 2-formylthiazole is formed by halogen-lithium exchange using n-butyllithium, sec-butyllithium, or t-butyllithium, followed by reaction with N-formylmorpholine. . This formylthiazole is subjected to reductive amination in the presence of an organic amine (such as morpholine) to give the morpholinylmethylthiazole of formula (10). Reductive amination is well known in the art and is usually performed 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.

In Step 3, the bromothiazole of formula (7) undergoes a substitution reaction with an amine or morpholine of formula --$NR^a R^b$ to give an aminothiazole of formula (11). This reaction is carried out at 70-110 ° C. using an inorganic base (such as cesium carbonate) in an inert solvent (such as THF or dioxane).

Formation of the compound of formula (13), formula (14), or formula (15) can be carried out according to the reaction shown in Scheme 3. Suitable compounds of formula (13), formula (14), or formula (15) are those where R^1 , R^2 , and R^4 are as defined for formula I.

One skilled in the art will recognize that 4-bromothiazole (such as that of formula (12)) is readily manipulated for other functionalizations. For example, in Step 1, the bromide can be dehalogenated with copper (I) chloride to give the thiazole of formula (13), which is then chlorinated with N-chlorosuccinimide to obtain the formula 4-chlorothiazole of (14) is obtained.

In Scheme 3, Step 3, 4-bromothiazole of formula (12) is dissolved in sodium methoxide in the presence of copper (I) iodide in methanol at about 100-120 ° C. in an inert solvent (such as dimethylformamide). To give 4-methoxythiazole of formula (15).

Formation of the compound of formula (17), formula (18), formula (19), formula (20), formula (20a), or formula (21) can be carried out according to the reaction shown in Scheme 4. Suitable compounds of formula (17), formula (18), formula (19), formula (20), formula (20a), or formula (21) are those wherein R^1 , R^2 , R^a , and R^b are of formula A compound as defined for I, wherein R^{4a} is --$NR^a R^b$ or --N-morpholinyl and "het" is indicated.

In Scheme 4, Step 1, iodopyrazolopyrimidine of formula (5) and 5-bromothiazole of formula (16) undergo Negishi cross-coupling to produce dimethylpyrrolylthiazole of formula (17). For example, 5-bromothiazole of formula (16) is treated with n-butyllithium, sec-butyllithium, or tert-butyllithium at about −80 to −65 ° C. and then with zinc chloride. This organozinc reagent is reacted in situ with the iodopyrazolopyrimidine of formula (5). This coupling reaction is preferably carried out in an inert solvent (such as THF) at the reflux temperature in the presence of a palladium catalyst (such as bis (tri-t-butylphosphine) palladium (0)).

In Step 2, the dimethylpyrrolylthiazole of formula (17) is deprotected to give the aminothiazole of formula (19). The dimethylpyrrole is treated with hydroxylamine in acetic acid at a temperature of about 60-100 ° C. for about 4-8 hours, preferably about 6 hours. In step 3, the same conditions as in step 2 are used except that the reaction is continued for about 72 hours to produce thiazoleacetamide of formula (18)

In Scheme 4, Step 4, 2-aminothiazole of formula (19) is converted to 2-bromothiazole of formula (20) using a modified Sandmeyer reaction. Preferred conditions use alkyl nitrite (such as t-butyl nitrite) and copper (II) bromide in acetonitrile at a temperature of about 60-80 ° C.

In Step 5, 2-bromothiazole of formula (20) undergoes a substitution reaction with an amine or morpholine of formula --$NR^a R^b$ to give an aminothiazole of formula (21). The reaction is carried out in an inert solvent (such as methanol, THF, or dioxane) or treated neat with an excess of amine at a temperature of about 70-110 ° C. Alternatively, this reaction is carried out using an amine as a reactant and an excess of triethylamine or an inorganic base (such as cesium carbonate). Various deprotection steps are also envisaged in the synthesis of the aminothiazole of formula (21). For example, if --$NR^a R^b$ possesses additional amine functionality as defined

in Formula I, if necessary or beneficial to carry out the above reaction, tert-butyl ester carbamic acid (BOC) is removed. The selection and use of suitable protecting groups is well known and recognized in the art (see, eg, Protection Groups in Organic Synthesis, Theodora Greene (Wiley-Interscience)).

In Scheme 4, Step 6, the 2-bromothiazole of formula (20) is coupled with a heterocyclic zinc reagent in a Negeshi cross-coupling reaction and is analogous to that described in Scheme 2, Step 1 (20a).) Thiazole heterocycle.

One skilled in the art will recognize that the functionalized thiazole of formula (16) can be prepared by means known in the art. For example, cyclization of thiourea with bromoketones (such as 3-bromo-1,1,1-trifluoropropan-2-one) provides 4-trifluoromethyl-thiazol-2-ylamine. Subsequent bromination and protection of the amine with hexane-2,5-dione gives (16).

Formation of the compound of formula (23) can be carried out according to the reaction shown in Scheme 5. Suitable compounds of formula (23) are those compounds in which R^1 and R^2 are as defined for formula I and R^{4b} is indicated.

An iodopyrazolopyrimidine of formula (5) and for example 4-chloro-2-morpholino-thiazole of formula (22) undergo cross-coupling to produce a pyrazolopyrimidine thiazole of formula (23). For example, these reactants are coupled with a base (such as cesium carbonate) in the presence of copper iodide, palladium acetate, and triphenylphosphine. This coupling reaction is preferably carried out in an inert solvent (such as DMF) at about 100 to 150 ° C. for 4 to 24 hours.

One skilled in the art will recognize that the functionalized thiazole of formula (22) can be prepared by means known in the art. For example, 2-morpholino thiazole of formula (22) can be obtained by reacting 2,4-dichlorothiazole with morpholine. In addition, 2,5-dichlorothiazole can be all brominated to obtain 2,5-dibromo-4-chlorothiazole. Subsequent bromine-lithium exchange with n-butyllithium and quench with water at −90 ° C. in THF yields 2-bromo-4-chlorothiazole [J. Chem. Soc. Perkin Trans I: Org Bioorg. Chem. (1972-1999), (2): 215-219 (1992)]. 2-Bromo-4-chlorothiazole can also undergo a Negishi cross-coupling reaction with a heterocyclic zinc reagent to give thiazol-2-yltriazole or thiazol-2-ylpyridine.

Formation of the compound of formula (27) can be carried out according to the reaction shown in Scheme 6. Suitable compounds of formula (27) are those wherein R^1 and R^2 are as defined for formula I and "het" is defined as indicated for step 1 or step 3, respectively.

In Scheme 6, Step 1, for example, a heterocyclic thiazole of formula (25) is obtained by reaction of iodopyrazolopyrimidine of formula (5) with bromothiazole of formula (24). This reaction is carried out using palladium catalyst (such as palladium acetate) and tris (2,4-di-tert-butyl-phenyl) -phosphane in the presence of N-butylammonium bromide and base (such as potassium acetate). It is carried out in an active solvent (such as N-methylpyrrolidinone) at a temperature of about 100-150 ° C.

Alternatively, in step 2, the thiazolyl pyrazolopyrimidine of formula (6a) is iodinated to give 2-iodothiazole of formula (26). The thiazole is treated with lithium diisopropylamide for about 1 hour at a temperature of -70 to -80 ° C in an inert solvent (such as THF) and then with N-iodosuccinimide at about the same temperature. This is followed by step 3, in which triazolylthiazole or 4-pyridylthiazole of formula (25) is formed using Negishi cross-coupling conditions similar to those described for Scheme 2, Step 1. .

In Scheme 6, Step 4, the thiazolylpyrazolopyrimidine of formula (25) is brominated to give the bromothiazole of formula (27). This bromination is performed using N-bromosuccinimide in the presence of a small amount of acetic acid in an inert solvent (such as acetonitrile).

The compound of formula (27), where het = 2,5-dimethyl-pyrrol-1-yl, is further converted as described in Scheme 4, Step 2, Step 3, Step 4, and Step 5, A compound can be obtained.

One skilled in the art will recognize that the heterocyclic thiazole of formula (24) can be readily prepared by means known in the art. For example, thiazole-2 carboxylic acid amide can be cyclized with 1,1-dimethoxy-N, N-dimethyl-methanamine to form a triazole, which is then treated with N-methyl-hydrazine to give a triazolyl. Luthiazole is provided, which can then be brominated with N-bromosuccinimide. Literature procedures give 4-thiazol-2-yl-pyridine, which can be brominated to give 4- (5-bromo-thiazol-2-yl) -pyridine. 5-Bromo-2- (2,5-dimethyl-pyrrol-1-yl) -thiazole can be easily obtained by reacting 2-amino-5-bromothiazole with hexane-2,5-dione.

As used herein, "TLC" refers to thin layer chromatography, "HPLC" refers to high performance liquid chromatography, "LC / MS" refers to liquid chromatography / mass spectrometry, and "GC / MS". Refers to gas chromatography / mass spectrometry, "HR-ToF" refers to high-resolution time-of-flight, "APCI" refers to atmospheric pressure chemical ionization, and "δ" refers to the transition from tetramethylsilane to a low magnetic field. ppm, "THF" refers to tetrahydrofuran, "EtOAc" refers to ethyl acetate, "MeOH" refers to methanol, "EtOH" refers to ethanol, and "DMF" refers to dimethylformamide .

Without further elaboration, it is believed that one skilled in the art can fully practice the invention using the foregoing description. The following preparations and examples are provided to further illustrate the present invention. They are intended to illustrate the invention and are not intended to limit the invention in any way. Reagents and starting materials are readily available to those skilled in the art or can be readily synthesized. Examples 1 to 35 provide representative compounds and illustrate their preparation. Examples A-D illustrate various biological tests that can be used to determine the biological properties of the compounds of the present invention. Those skilled in the art will readily recognize appropriate variations from the procedures described in the examples. The names of the compounds of the present invention are those provided by ChemDraw Ultra® version 7.0.1. The salt was named by adding the conjugate acid to the free base.

(Preparation Example 1)
2,5-Dimethyl-4H-pyrazolo [1,5-a] pyrimidin-7-one While maintaining the temperature at 25-28 ° C., ethyl acetoacetate (128 g, 0.98 mol) was replaced with 5-methyl-2H-pyrazole. The solution was added dropwise to an acetic acid solution (500 mL) of -3-ylamine (100 g, 0.95 mol). The mixture was heated at reflux for 10 hours and cooled to room temperature. The reaction was added to tert-butyl methyl ether (5 L) cooled to 5 ° C. keeping the temperature below 10 ° C. Stir at 5 ° C. for 1 hour and filter. The resulting material was dried in vacuo overnight to give a white solid (158 g, 96%).

(Preparation Example 2)
7-chloro-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine 2,5-dimethyl-4H-pyrazolo [1,5-a] pyrimidin-7-one (10.0 g) in toluene (150 mL) , 61.3 mmol) was added N, N-dimethylaniline (9.7 mL, 76.7 mmol). Phosphorus oxychloride (11.2 mL, 122.6 mmol) was added dropwise to the white suspension. Refluxed under an inert atmosphere for 3 hours, cooled to room temperature, and concentrated the reaction to a brown oil using reduced pressure. This oil was dissolved in ethyl acetate (250 mL) and made basic with 1.0 N NaOH. The organic phase was separated and the basic aqueous phase was extracted with ethyl acetate (2 × 100 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a brown solid. Use flash chromatography to elute from 80% hexane / 20% (30% THF / hexane) to 0% hexane / 100% (30% THF / hexane) with a step gradient in 20% increments. Was purified to give a pale green solid (6.65 g, 59%). ESI / MS m / z (35 Cl) 182.3 (M + 1) +.

(Alternative procedure)
2,5-Dimethylpyrazolo [1,5-a] pyrimidin-7-one (20 g, 122 mmol) was added to 1,4-dioxane (60 mL). The mixture was stirred at 22 ° C. for 10 minutes and then N, N-diethylaniline (20.8 mL, 126 mmol) was added. Stir for an additional 5 minutes and then add phosphorus oxychloride (11.7 mL, 126 mmol) over 15 minutes. The mixture was stirred at 22 ° C. for 15 minutes and then heated to 80-85 ° C. over 35 minutes and the reaction was held at this temperature for 1.5 hours. The cooled reaction mixture was slowly added to an aqueous solution (325 mL) of dipotassium hydrogen phosphate (106.7 g, 612.82 mmol) cooled to 0-5 ° C., keeping the temperature below

5 ° C. during the addition. The mixture was stirred at 22 ° C. and methyl-t-butyl ether (150 mL) was added. The organic layer was separated and the aqueous layer was extracted with methyl-t-butyl ether (2 × 100 mL). The organic portions were combined, dried over sodium sulfate, filtered and the solvent was evaporated. Purification by silica gel chromatography eluting with hexane / ethyl acetate (2/1) gave the title compound as a yellow solid (20.7 g, 88%). $^{ES / MS m / z (^{35} Cl)}$ 182 (M + 1) +.

(Preparation Example 3)
7- (1-Propyl-butyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine
An oven-dried flask equipped with a reflux condenser was charged with anhydrous THF (40 mL), iodine (catalytic amount), magnesium ribbon (1.92 g, 78.9 mmol) and 4-bromoheptane (9.4 mL, 52 mmol). The reaction solution was heated to reflux in an oil bath. The temperature of this reaction solution rose rapidly when the Grignard reaction started. The reaction was stirred at 90 ° C. for a further 4 hours and cooled to room temperature. Magnesium metal is allowed to settle (centrifuged) and the Grignard reagent is added to 7-chloro-2,5-dimethylpyrazolo [1,5-a] pyrimidine (in anhydrous toluene (20 mL) with positive argon pressure (The cannula was transferred to a flask containing 4.80 g, 26 3 mmol). The reaction was refluxed overnight under an inert atmosphere. The reaction was cooled to room temperature and quenched with water. Dilute with ethyl acetate (150 mL) and add water (100 mL) and saturated ammonium chloride (50 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (75 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Using flash chromatography, the residue produced using 80% hexane / 20% (20% ethyl acetate / hexane) to 0% hexane / 100% (20% ethyl acetate / hexane) with a step gradient in 20% increments. Elution was carried out to obtain yellow crystals (3.08 g, 48%). ES / MS m / z 246.3 (M + 1) $^{+}$.

(Alternative procedure)
A mixture of magnesium shavings (3.5 g, 144 mmol) and catalytic amount of iodine (100 mg) in THF (100 mL) was heated to 65 ° C. under a nitrogen atmosphere. A few drops of neat 4-bromoheptane was added and the mixture was heated until the reaction started. A solution of 4-bromoheptane (17 6 mL, 94.9 mmol) in THF (42 mL) was then added over 2 hours keeping the temperature at 65-70 ° C. The mixture was refluxed for an additional hour and the reaction was cooled to 22 ° C. Prepared Grignard reagent was added to a solution of 7-chloro-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (10.2 g; 58.3 mmol) in THF (60 mL) cooled to 0 ° C. under a nitrogen atmosphere. Added below. The magnesium reagent solution was added using a cannula over 45 minutes keeping the temperature below 10 ° C. The mixture was stirred at 5 ° C. for an additional 30 minutes. To this mixture was added 10% aqueous ammonium chloride (w / w) (125 mL), and the mixture was stirred at 22 ° C. for 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The organic layers were combined and dried over sodium sulfate. The mixture was filtered and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel using an eluent of hexane / ethyl acetate (5/1) to give the title compound (8 g, 62%). ES / MS m / z 246 (M + 1) $^{+}$.

(Preparation Example 3a)
7- (1-propyl-butyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (alternative route)
Step 1: 3-Acetyl-3-oxo-4-propyl-heptanoic acid ethyl ester Magnesium chloride (14.63 g, 153.70 mmol) was added to dichloromethane (500 mL), followed by ethyl acetoacetate (19.55 mL, 20.00 g). , 153.79 mmol) were added all at once and stirred at room temperature for 1 hour. The mixture was cooled in an ice-water bath and pyridine (24.86 mL, 24.32 g, 307.39 mmol) was added dropwise. Di-n-propylacetyl chloride (25.00 g, 153.70 mmol) was added dropwise to this white slurry at 0 ° C. under nitrogen. After the addition was complete, the cooling bath was removed, warmed to ambient temperature and stirred for 16 hours. The reaction was quenched with 1N HCl (400 mL) and the bottom layer was separated. The organic portion was dried over magnesium sulfate, filtered and concentrated in vacuo to give a yellow oil (34 g, 86%). This material was used directly in the next step without further purification.

Step 2: 5-propyl-octane-2,4-dione 3-acetyl-3-oxo-4-propyl-heptanoic acid ethyl ester (32.4 g, 126.39 mmol) in dimethyl sulfoxide (100 mL) and water (5 mL) Dissolved in. The solution was heated at 150 ° C. for 6-8 hours or the reaction was followed by GC / MS. The reaction was cooled and extracted with heptane (3 × 100 mL). The combined organic portions were washed with water (100 mL) and brine (100 mL). Concentration in vacuo at 50 ° C. removed most of the heptane. 23.29 g of an oil was obtained and used directly in the next step.

Step 3: 7- (1-propyl-butyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine 5-propyl-octane-2,4-dione (15 g, 81.40 mmol) was added to acetic acid (15 mL).) And cooled in an ice bath. 5-Amino-3-methylpyrazole (7.91 g, 81.40 mmol) was added in portions and stirred at ambient temperature. After 3 hours, the completion of the reaction was checked by GC / MS. GC showed correct regioisomer production by comparison with the reference sample. Excess acetic acid was distilled off. Water (50 mL) was added and extracted with heptane (50 mL). The heptane was washed with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude oil (15.8 g, 79%). ^{1} H 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).

The following compounds were prepared using either procedure, essentially as described in Preparative Example 3. Grignard reagent was prepared using 3-bromopentane.

(Preparation Example 5)
7- (1-propyl-butyl) -3-Iodo-2,5 dimethyl-pyrazolo [1,5-a] pyrimidine 7- (1-propyl-butyl) -2,5-dimethyl-pyrazolo [1,5 -A] Pyrimidine (3.08 g, 12.5 mmol) was dissolved in anhydrous acetonitrile (25 mL), and N-iodosuccinimide (4.2 g, 18.7 mmol) was added 6 times at intervals of 10 minutes (0.70 g each time)) And added. Stir at room temperature over the weekend. Acetonitrile was distilled off and the oil was diluted with dichloromethane (100 mL). Wash with saturated ammonium chloride solution (2 × 50 mL). The organic phase was collected, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a dark red oil. Use flash chromatography to elute from 100% hexane / 0% (20% ethyl acetate / hexane) to 0% hexane / 100% (20% ethyl acetate / hexane) with a step gradient in 50% increments. The oil was purified 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).

The following compounds were prepared essentially as described in Preparation Example 5.

(Alternative procedure for Preparation 5)
Acetic acid (1 mL) and N-iodosuccinimide (6.7 g, 29.9 mmol) were added to 7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] in acetonitrile (60 mL). To a solution of pyrimidine (6 g, 27.5 mmol) was added in one portion. The mixture was stirred at 22 ° C. for 2 hours. The solvent was evaporated and the residue was taken up in water (50 mL) and methyl-t-butyl ether (100 mL). The organic portion was separated, dried over sodium sulfate, filtered and the solvent was evaporated to give the title compound (9.2 g, 96%). ES / MS m / z 344 (M + 1) $^{+}$.

(Preparation Example 7)
2-Trimethylsilanyl-thiazole In a three-necked flask equipped with a dropping funnel and a thermometer, n-butyllithium (20.4 mL, 51.0 mmol, 2.5 M hexane solution) was mixed with diethyl ether (50 mL). . 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 was complete, the reaction mixture was stirred at −78 ° C. for 30 minutes and then chlorotrimethylsilane (5.4 g, 50.0 mmol) was added. Stir at −78 ° C. for 1 hour and then warm to room temperature. The reaction was quenched by adding saturated sodium bicarbonate. The aqueous layer was extracted with diethyl ether. The combined organic portions were washed with brine and dried over sodium sulfate. Filtration and concentration under reduced pressure gave a residue. Purification by distillation gave 8.33 g (52-56 ° C./15 mmHg) of the title compound. ^{1} H NMR (400MHz, $CDCl_3$) δ 8.13 (d, 1H, J = 2.6Hz), 7.54 (d, 1H, J = 2.6Hz), 0.43 (s, 9H).

(Preparation Example 8)
5-Bromo-4-methylthiazole Bromine (9.27 mL, 182 mmol) was added to a solution of 4-methylthiazole (15.0 g, 152 mmol) in acetic acid (30 mL) at 0 ° C. The reaction mixture was slowly warmed to room temperature and stirred overnight. Diluted with dichloromethane and washed with 1N NaOH and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography eluting with hexane / ethyl acetate (5/1) to give the title compound (9.94 g, 37%). ^{1} H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 2.43 (s, 3H).

(Preparation Example 9)
Thiazole-2-carboxylic acid ethyl ester To a mixture of 2-trimethylsilylthiazole (135 g, 858.1 mmol) in toluene (1350 mL) was added a solution of ethyl chloroformate (98.4 mL, 1.03 mol) in toluene (1350 mL). Added over 15 minutes. The reaction was stirred at 22 ° C. for 2 hours. This solution was added onto a 25% (w / w) aqueous solution of sodium carbonate (5 L) and stirred for 30 minutes. The organic layer was separated and the aqueous layer was re-extracted with methylene chloride (2 × 1 L). The organic layers were combined and the solvent was evaporated to give the title compound (134 g, 99%). ES / MS m / z 158 (M + 1) $^+$.

(Preparation Example 10)
Thiazole-2-carboxylic acid amide Thiazole-2-carboxylic acid ethyl ester (150 g, 0.9 mol) was added to a mixture of methanol (75 mL) and 30% aqueous ammonium hydroxide (750 mL) and the mixture was refluxed for 1 hour. Heated. Cool to 22 ° C. and evaporate the methanol under vacuum. The mixture was stirred at room temperature for 30 minutes and the solid was filtered. The isolated solid was dried under vacuum to give the title compound (98 g, 85%). ES / MS m / z 129 (M + 1) $^+$.

(Preparation Example 11)
1-methyl-5-thiazol-2-yl-1H- [1,2,4] triazole 1,1-dimethoxy-N, N-dimethyl-methanamine (240 mL) was cooled to 10 ° C. and thiazole-2-carboxylic acid Acid amide (60 g, 421 mmol) was added in three portions. The mixture was stirred at 10 ° C. for 30 minutes. The mixture was heated to reflux gradually over 45 minutes. The produced methanol was distilled off and the reaction solution was heated at 100 ° C. for 1.5 hours. The mixture was cooled to 60 ° C. and excess 1,1-dimethoxy-N, N-dimethyl-methanamine was removed by vacuum distillation. The residue was cooled to 22 ° C. and hexane (200 mL) was added. This mixture was pulverized for 15 minutes, filtered and the solid was dried to constant weight before being used in the next step.

The solid isolated above (58 g) was added to acetic acid (680 mL) and the mixture was cooled to 10 ° C. N-methyl-hydrazine (27 mL, 509 mmol) was added at a rate to keep the temperature below 15 ° C. The mixture was warmed to 20 ° C. over 30 minutes and then gradually heated to 90 ° C. The mixture was stirred at 90 ° C. for 30 minutes and cooled to 22 ° C. Acetic acid was removed by vacuum distillation. The residue was added to water and adjusted to pH = 8 by adding 25% aqueous sodium hydroxide. The aqueous layer was extracted with methyl-t-butyl ether (3 × 600 mL). The organic layers were combined and the solvent was evaporated. The resulting residue was purified by silica gel chromatography using an eluent of hexane / isopropanol (9/1) to give the title compound (49 g, 70%). ES / MS m / z 167 (M + 1) $^+$

(Preparation Example 12)
5- (5-Bromo-thiazol-2-yl) -1-methyl-1H- [1,2,4] triazole Methyl-5-thiazol-2-yl-1H- [1,2,4] triazole (6 0.55 g; 39.4 mmol) and dimethylformamide (32 mL) were added N-bromosuccinimide (14 g, 78.8 mmol) in three portions over 1 hour. The mixture was stirred at 22 ° C. for 18 hours and then added to water (300 mL) cooled to 0-5 ° C. The aqueous layer was separated and extracted with methyl-t-butyl ether (2 × 200 mL). The organic layers were combined, washed with 7% aqueous sodium hydrogen carbonate solution (100 mL), and dried over sodium sulfate. Filtration and evaporation of the solvent gave the title compound (9.5 g, 93%). $^{ES / MS m / z (7\%}$ 8r / 81 8r) 245/247 (M + 1) +.

(Preparation Example 13)
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 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) is mixed in N-methylpyrrolidinone (58 mL) and stirred under nitrogen for complete dissolution I let you. Tetra-N-butylammonium bromide (5.47 g, 16.7 mmol) and potassium acetate (11.8 g, 119 mmol) were added and the mixture was heated to 100 ° C. under a nitrogen atmosphere. The hot mixture was degassed by 3 cycles of vacuum / nitrogen purge. Palladium acetate (215 mg, 0.94 mmol) and tris 2,4-di-tert-butyl-phenyl) -phosphane (787 mg, 1.2 mmol) were added. The mixture was heated at 125 ° C. for 4 hours under nitrogen. The mixture was cooled to 22 ° C. and added to water (750 mL). The aqueous layer was extracted with methyl-t-butyl ether (3 × 200 mL), the organic portions were combined and evaporated. The residue was purified by filtration through a silica gel pad eluting with hexane / ethyl acetate (4/1). Fractions containing the product were combined and the solvent was evaporated to give the title compound (7 g, 72%). ES / MS m / z 410 (M + 1) $^+$.

(Preparation Example 14)
2,5-Dimethyl-7- (1-propyl-butyl) -3-thiazol-5-yl-pyrazolo [1,5-a] pyrimidine 2-Trimethylsilanylthiazole (1.1) dissolved in anhydrous THF (30 mL). 765 g, 11.24 mmol) was placed in an oven-dried flask and cooled to −78 ° C. under an inert atmosphere. n-Butyllithium (2.5 M hexane solution, 4.5 mL, 11.24 mmol) was slowly added, and the mixture was stirred at −78 ° C. for 30 minutes. Anhydrous zinc chloride (2.26 g, 16.58 mmol) was added in one portion and stirred at −78 ° C. for 30 minutes. The reaction was warmed to room temperature, stirred for 30 minutes, and 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) were added. Reflux overnight in an oil bath (90 ° C.) under an inert atmosphere. The reaction was cooled to room temperature, quenched with saturated sodium bicarbonate, and diluted with ethyl acetate (150 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (75 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. This product was generated using flash chromatography eluting with 100% hexane / 0% (30% THF / hexane) to 0% hexane / 100% (30% THF / hexane) with a step gradient in 10% increments. The residue was purified to give a white solid (0.720 g, 42%) ES / MS m / z 329.0 (M + 1) $^+$.

The following compounds were prepared essentially as described in Preparation Example 14.

(Alternative procedure for Preparation 15)
n-Butyllithium (76.5 mL, 191 mmol, 2.5 M hexane solution) was added to a solution of 2-trimethylsilylthiazole (30 g, 191 mmol) in THF (450 mL) at -78 ° C. under nitrogen. The temperature was kept below -74 ° C during the addition. The mixture was stirred at −78 ° C. for 30 minutes, then zinc chloride, dry powder (39.9 g, 286 mmol) was added in one portion and the mixture was warmed to 22 ° C. over 1 hour. 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) was added and the mixture was heated at reflux under nitrogen for 8 hours. The mixture was cooled to 22 ° C. and 10% aqueous ammonium chloride (450 mL) was added. The organic layer was separated and the aqueous layer was washed with methyl-t-butyl ether (2 × 100 mL). The organic portions were combined, dried over sodium sulfate, filtered, and the solvent was evaporated to give the title compound (20.4 g, 78%). ES / MS m / z 301 (M + 1) $^+$.

(Preparation Example 16)
7- (1-Ethyl-propyl) -3- (2-iodo-thiazol-5-yl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine lithium di-i-propylamide (150 ml, 62 .4 mmol, 0.6 M THF solution) was prepared as 7- (1-ethyl-propyl) -2,5-dimethyl-3-thiazol-5-yl-pyrazolo [1 in THF (100 mL). , 5-a] pyrimidine (17.8 g, 62.4 mmol) was added at −78 ° C. under a nitrogen atmosphere. The temperature was kept below -74 ° C during the addition. The mixture was stirred at −78 ° C. for 1 hour and then a solution of N-iodosuccinimide (15 g, 63 mmol) in THF (100 mL) was added keeping the temperature below −74 ° C. The reaction was gradually warmed to 22 ° C. and then a 10% aqueous solution of ammonium chloride (300 mL) was added. The organic layer was separated and the aqueous layer was washed with methyl-t-butyl ether (2 × 200 mL). The organic layers were combined, dried over

sodium sulfate, filtered and the solvent was evaporated. The resulting residue was purified by silica gel chromatography eluting with hexane / acetone (5/1) to give 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 Rieke® zinc (in 100 mL THF) 10 g, 13.2 mL, 18.48 mmol) was added to 5-bromo-4-methylthiazole (2.13 g, 18.48 mmol) and heated at reflux for 2 hours. The mixture was cooled to room temperature and the zinc was precipitated by centrifugation Nitrogen gas was blown into 7- (1-ethyl-propyl) -3-iodo-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (900 mg, 2.62 mmol) in anhydrous tetrahydrofuran (10 mL), The organozinc bromide solution was added followed by [1,1'-bis (diphenylphosphino) ferrocene] -dichloropalladium (II) (106 mg, 0.13 mmol). The reaction mixture was stirred at reflux overnight and cooled to room temperature. Ammonium chloride solution was added to the reaction mixture and extracted with dichloromethane. The organic portion was dried over sodium sulfate, filtered and the solvent removed in vacuo. The crude product was purified by silica gel column chromatography eluting with hexane / ethyl acetate (3/1) to give 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 = 7.3 Hz). ES / MS m / z 315 (M + 1) $^{+}$.

(Preparation Example 17)
3- (2,4-Dibromo-thiazol-5-yl) -2,5-dimethyl-7- (1-propyl-butyl) -pyrazolo [1,5-a] pyrimidine 2,5-dimethyl-7- (1-propyl-butyl) -3-thiazol-5-yl-pyrazolo [1,5-a] pyrimidine (3.15 g, 9.59 mmol) was dissolved in acetonitrile (100 mL) and N-bromosuccinimide (4.27 g). , 24.0 mmol) was added in one portion. The mixture was stirred overnight under an inert atmosphere, and the reaction was confirmed to be complete using TLC. Concentrated under reduced pressure and the oil was diluted with dichloromethane (150 mL) and washed with water (75 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Step gradient (0-10-15-20-25-30-30) from 100% hexane / 0% (30% THF / hexane) to 0% hexane / 100% (30% THF / hexane) using flash chromatography The resulting oil was purified by eluting with 35-40-45-50-100% 30% THF / hexanes to give yellow crystals (3.70 g, 79%). $^{ES / MS m / z (79}$ Br 81 Br) 486.7 (M + 1) +.

The following compounds were prepared essentially as described in Preparation Example 17 except that dichloromethane was used as the solvent.

[a] 1.1 equivalents of NBS was used and stirred 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
An oven-dried flask was charged 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 overnight in an oil bath (105 ° C.) under an inert atmosphere. LC / MS was used to confirm that the reaction was complete. Diluted with ethyl acetate (100 mL), washed with water (50 mL), and the aqueous layer was back extracted with ethyl acetate (50 mL). The organic phases were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Using flash chromatography with a step gradient in 10% increments from 100% hexane / 0% (40% dichloromethane / 20% ethyl acetate / 2% 7N ammonia in methanol / 38% hexane) to 0% hexane / 100% (The resulting residue was purified eluting with 40% dichloromethane / 20% ethyl acetate / 2% 7N ammonia in methanol / 38% hexane) to give an off-white solid (0.878 g, 89%). . $^{ES / MS m / z (79}$ Br) 491.7 (M + 1) +.

The following examples were prepared essentially as described in Example 4, using either 2.0 dimethylamine / THF or morpholine as the amine and THF or dioxane as the solvent. The reaction was carried out in a sealed tube or a Schlenk tube.

[a] 6 equivalents of cesium carbonate were used.

(Example 10)
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
An oven-dried flask was charged with 1-methyl-1,2,4-triazole (0.498, 6.00 mmol) and anhydrous THF (20 mL) and cooled to −78 ° C. under an inert atmosphere. n-Butyllithium (2.5 M hexane solution, 2.4 mL, 6.0 mmol) was slowly added and stirred for 30 minutes. Anhydrous zinc chloride (1.36 g, 10.0 mmol) was added in one portion and stirred at −78 ° C. for 30 minutes. The reaction was warmed to room temperature, stirred for 30 minutes, and 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) were added. The reaction was refluxed overnight in an oil bath (90 ° C.) under an inert atmosphere. The reaction was cooled to room temperature, quenched with water and diluted with ethyl acetate (100 mL). The layers were separated and the aqueous layer portion was extracted with dichloromethane (50 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Using flash chromatography with a step gradient in 10% increments from 100% hexane / 0% (10% acetonitrile / 40% THF / 50% hexane) to 0% hexane / 100% (10% acetonitrile / 40% THF / 50 The resulting residue was purified by elution with hexane to give a white solid (0.090 g, 9%). $^{ES / MS m / z (79}$ Br) 487.7 (M + 1) +.

(Alternative preparation example)
2,5-Dimethyl-3- [2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl] -7- (1- To a solution of propyl-butyl) -pyrazolo [1,5-a] pyrimidine (6 g, 14.65 mmol), N-bromosuccinimide (2.74 g, 15.4 mmol) was added in one portion and stirred at 22 ° C. for 10 hours. . The solvent was evaporated and the residue was dissolved in a mixture of water (50 mL) and methyl-t-butyl ether (100 mL). The organic layer was separated and the aqueous layer was extracted with additional methyl-t-butyl ether (2 × 50 mL). The organic portions were combined and the solvent was evaporated. The resulting material was purified by filtration through a silica gel pad eluting with hexane / ethyl acetate (3/1). Fractions containing product were combined and the solvent was evaporated. Heptane (25 mL) was added to powder this solid. The solid was filtered and dried under vacuum to give 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-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl] -2,5-dimethyl-7- (1-propyl- Butyl) -pyrazolo [1,5-a] pyrimidine, hydrochloride
3- [4-Bromo-2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl] -2,5-dimethyl-7- (1-propyl- Butyl) -pyrazolo [1,5-a] pyrimidine (750 mg, 1.54 mmol) was dissolved in acetone (5 mL) and 1M HCl diethyl ether solution (1.84 mL, 1.84 mmol) was added. The mixture was stirred at room temperature for 3 hours and concentrated in vacuo. The residue was dissolved in diethyl ether / hexane = 1/1 (5 mL) to 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).

The following compounds were prepared essentially as described in Example 10.

[a] 0.5M zinc chloride in THF was used instead of anhydrous zinc chloride. Stir 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
Under a nitrogen atmosphere, n-butyllithium (2.5 M hexane solution, 0.6 mL, 1.5 mmol) was added to 1-methyl-1,2,4-triazole (124.5 mg, 1.5 mmol) in THF (3 mL).) At −78

° C. and stirred for 30 minutes. Anhydrous zinc chloride (409 mg, 3.0 mmol) was added and stirring was continued for 30 minutes, warmed to room temperature and stirred for 2 hours. Add 3- (2,4-dibromo-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (229 mg, 0.5 mmol) Then tetrakis (triphenylphosphine) palladium (58 mg, 0.05 mmol) was added and refluxed overnight. Cool to room temperature, dilute with ethyl acetate and wash with saturated ammonium chloride. The organic portion was dried over sodium sulfate, filtered and concentrated to give a residue. The crude product was purified by flash chromatography eluting with hexane: 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) +.

(Alternative preparation from Example 21)
Acetic acid (1 mL) and N-bromosuccinimide (4.1 g, 22 mmol) were added to 7- (1-ethyl-propyl) -2,5-dimethyl-3- [2- (2-methyl-) in acetonitrile (80 mL). 2H- [1,2,4] triazol-3-yl) -thiazol-5-yl] -pyrazolo [1,5-a] pyrimidine (8 g, 21 mmol) was added. The mixture was stirred at 22 ° C. for 2 hours. The solvent was evaporated and water (50 mL) and methyl-t-butyl ether (100 mL) were added to the resulting residue. The organic portion was separated, dried over sodium sulfate, filtered and the solvent was evaporated. The resulting residue was recrystallized from isopropyl alcohol to give 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-toluenesulfonic acid 3- (4-bromo-2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazole- 5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (50 mg, 0.109 mmol) was dissolved in acetone (3 mL). A 0.25M aqueous solution of p-toluenesulfonic acid (434.4 µL, 0.109 mmol) was added and the resulting mixture was evaporated to dryness. Ethyl acetate (12 mL) was added to partially dissolve this solid. Methanol (1 mL) was added to give a clear solution. The solution was concentrated by gentle evaporation until crystals were observed. The crystals were isolated by filtration and dried under vacuum at 25 ° C. to give 50 mg of the title compound.

The stoichiometry of this salt was determined by ion chromatography using the following HPLC conditions: Column: Phenomenex Phenosphere SAX at 30 ° C., 4.6 × 150 mm; Mobile phase: 50% acetonitrile / 50% 0.025M phosphorus Sodium acid buffer (pH = 4.5); flow rate = 1.5 mL / min; detection: UV at 205 nm; injection volume = 5 µL; measurement time = 3 minutes. Calculated theoretical amount: 27.2% tosylate; Found: 28.4% tosylate (average of 3 HPLC measurements).

(Example 13)
(4-Chloro-5- [2,5-dimethyl-7- (1-propyl-butyl) -pyrazolo [1,5-a] pyrimidin-3-yl] -thiazol-2-yl) -dimethylamine oven dried In a prepared flask was (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) were charged and cooled to −78 ° C. under inert atmosphere n-Butyllithium (1.6M hexane solution, 0.42 mL, 0.67 mmol) was added slowly and stirred for 30 minutes. N-chlorosuccinimide (0.120 g, 0.889 mmol) was added in one portion and stirred at −78 ° C. for 30 minutes. The reaction was warmed to room temperature and stirred for 5 hours and the progress was checked using LC / MS. Dilute with ethyl acetate (100 mL), wash with saturated ammonium chloride (50 mL), and back-extract the aqueous layer with dichloromethane (50 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. This was generated using flash chromatography eluting with 100% hexane / 0% (25% THF / hexane) to 0% hexane / 100% (25% THF / hexane) with a step gradient in 10% increments. The residue was purified to give a white solid (0.087 g, 48%). $^{ES\ /\ MS\ m/z\ (35}$ Cl) 406.0 (M + 1) +.

The following examples were prepared essentially as described in Example 13, using the appropriate bromothiazole prepared above.

(Preparation Example 18)
A mixture of thiazolidine-2,4-dione (50 g, 0.43 mol) in 2,4-dichlorothiazole phosphorus oxychloride (240 mL) was cooled to 5 ° C. and pyridine (34 mL, 0.43 mol) was added over 15 minutes. added. The mixture was heated to 125 ° C. for 4 hours and cooled to 22 ° C. Excess phosphorus oxychloride was removed by vacuum distillation and the residue was added to water (1 L) cooled to 5 ° C. This mixture was extracted with methylene chloride (3 × 400 mL). The organic portions were combined and the solvent was evaporated to give the title compound (50 g, 76%). $^{ES\ /\ MS\ m/z\ (35}$ Cl 35 Cl / 35 Cl 37 Cl / 37 Cl 37 Cl) 153/155/157 (M + 1) +

(Preparation Example 19)
4-Chloro-2-morpholino-thiazole To a mixture of 2,4-dichlorothiazole (34 g, 0.22 mol) in acetonitrile (425 mL) was added potassium carbonate (60.9 g, 0.44 mol), followed by morpholine (21.2 mL, 0.225 mol) was added dropwise over 30 minutes. The mixture was refluxed at 40 ° C. and then cooled to 22 ° C. The mixture was filtered and the filtrate was evaporated. The residue was triturated with i-propyl alcohol (60 mL) at 22 ° C. for 1 hour. The solid was filtered and dried under vacuum to constant weight to give 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
Under a nitrogen atmosphere, 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) was dissolved in THF (1.5 mL) and cooled to -78 ° C. n-Butyllithium (0.1 mL, 2.5 M hexane solution, 0.25 mmol) was added, and the mixture was stirred at −78 ° C. for 30 minutes. N-chlorosuccinimide (33.4 mg, 0.25 mmol) was added, stirred for an additional 30 minutes and slowly warmed to room temperature. After stirring overnight, the reaction was quenched by adding a solution of saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to give a residue. The crude product was purified by flash chromatography eluting with hexane: dichloromethane: ethyl acetate (5: 5: 2) to give the title compound (54 mg). $^{MS\ (NH3)\ m/z\ (}$ 35 Cl) 420.6 (M + 1) +; 1 H NMR (400MHz, CDCl 3): 6.44 (s, 1H), 3.79 (t, 4H, J = 4. 8Hz), 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).

(Alternative preparation example from Preparation Example 6)
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) was mixed in dimethylformamide (90 mL) that had previously been degassed with nitrogen. 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) were added. The mixture was heated to 125 ° C. for 16 hours and cooled to 22 ° C. Water (900 mL) was added and extracted with methyl-t-butyl ether (3 × 200 mL). The organic portions were combined and the solvent was evaporated. Purification by silica gel chromatography eluting with hexane / ethyl acetate (4/1) gave 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- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine, hydrochloride 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) was dissolved in acetone (10 mL) at 50 ° C. and cooled to room temperature. Hydrogen chloride (2M diethyl ether solution, 2.0 mL, 4.0 mmol) was added and stirred well in the sonicator. The solution was concentrated slightly and a minimum amount of diethyl ether was added to crystallize the HCl salt. The mixture was cooled in the refrigerator overnight. Additional hydrogen chloride (2M diethyl ether solution, 2.0 mL, 4.0 mmol) was added and cooled in the refrigerator. The crystalline material was filtered and dried to give the title compound (1.15 g, 75%). $^{ES\ /\ MS\ m/z\ (35}$ Cl) 420 (M + 1) +; 1 H NMR (CDCl 3): 9.18 (br, 1H), 6.86 (s, 1H), 3.72 (m, 4H) , 3.49 (m, 1H), 3.39 (m, 4H), 2.48 (s, 3H), 2.38 (s, 3H), 1 79 (m, 4H), 0.79 (m, 6H).

(Example 17)
3- (4-Bromo-2-butyl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine n- Butyl lithium (2.5 M hexane solution, 0.2 mL, 0.5 mmol) was added to 3-

(2,4-dibromo-thiazol-5-yl) -7- (1-ethyl-propyl) in THF (3 mL). To a solution of −2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (230 mg, 0.5 mmol) was added at -78 ° C. After 30 minutes, 1-iodobutane (138 mg, 0.75 mmol) was added and stirring was continued for 1 hour. Warmed to room temperature and stirred for 1 hour. The reaction was quenched by adding saturated ammonium chloride solution and extracted with ethyl acetate. The organic portion was dried over sodium sulfate, filtered and concentrated to give a residue. The crude product was purified by flash chromatography eluting with hexane / ethyl acetate (10 / 1.5) to give the title compound as an orange foam (78 mg). $^{ES / MS\ m / z\ (^{81}}$ Br) 437.4 (M + 1) +.

The following examples were prepared essentially as described in Example 17.

(Example 19)
7- (1-Ethyl-propyl) -3- (2-methoxymethyl-thiazol-5-yl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine Under nitrogen atmosphere, n-butyllithium (2.5M hexane solution, 0.4 mL, 1.0 mmol) was added to 7- (1-ethyl-propyl) -2,5-dimethyl-3-thiazol-5-yl-pyrazolo [1, in THF (3 mL). To a solution of 5-a] pyrimidine (300 mg, 1.0 mmol) was added at -78 ° C. Stir for 30 minutes and add 1-iodomethyl methyl ether (205 mg, 1.2 mmol). Stirring was continued for 1 hour, then slowly cooled to room temperature and stirred overnight. The reaction was quenched by adding saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to give a residue. The crude product was purified by flash chromatography eluting with hexane / 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 n-butyllithium (2 0.5M hexane solution, 174 mL, 0.43 mmol) was added to 7- (1-ethyl-propyl) -3- (2-methoxymethyl-thiazol-5-yl) -2,5-dimethyl- in THF (3 mL). To a stirred solution of pyrazolo [1,5-a] pyrimidine (150 mg, 0.43 mmol) was added at −78 ° C. Stir for 30 minutes and add N-chlorosuccinimide (87 mg, 0.653 mmol). Stir for 30 minutes, then warm the reaction slowly to room temperature and allow the reaction to continue overnight. The reaction was quenched by adding saturated ammonium chloride solution, extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated to give a residue. Purification by flash chromatography eluting with hexane / ethyl acetate (10/2) gave 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 3- (4-bromo-2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl) -7- (1- Ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (175 mg, 0 38 mmol) and copper (I) chloride (132 mg, 1.33 mmol) were mixed in DMF (5 mL), Heated at 120 ° C. for 24 hours. Cool to room temperature, dilute with ethyl acetate and wash with brine. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum to a residue. Purification by flash chromatography eluting with hexane then hexane / EtOAc (10 / 1.8) gave a yellow to orange solid (45 mg). ES / MS m / z 382.0 (M + 1) $^{+}$.

(Alternative preparation example)
n-Butyllithium (2.5M hexane solution, 57.6 mL, 144 mmol) was added to a solution of N-methylitriazole (11.95 g, 144 mmol) in THF (600 mL) at -78 ° C. under a nitrogen atmosphere. The temperature was kept below -74 ° C during the addition. Zinc chloride dry powder (26 g, 192 mmol) was added in one portion and the mixture was warmed to 22 ° C. over 1 hour. 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 (tri Phenyl) phosphine palladium catalyst (1.15 g, 0.01 mol) was added in one portion and the mixture was heated at reflux under nitrogen for 8 hours. The mixture was cooled to 22 ° C. and water (300 mL) was added. The organic layer was separated and the aqueous layer was extracted with methyl-t-butyl ether (2 × 200 mL). The organic portions were combined, dried over sodium sulfate, filtered and the solvent was evaporated. Purification using hexane / ethyl acetate (4/1) eluting through a silica gel pad afforded 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 7- (1-ethyl-propyl) -2,5-dimethyl-3- [in dichloromethane (0.5 mL) and acetonitrile (0.5 mL) in a vial. 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-chloro A mixture of succinimide (7.6 mg, 0.0569 mmol) was stirred at room temperature overnight. Concentration gave a residue. Purification by flash chromatography eluting with hexane then hexane / ethyl acetate (10 / 1.5) gave 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 Sealed 3- (4-Bromo-2-morpholin-4-yl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl- in methanol (3 mL) in a 4 mL vial A mixture of 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) was stirred at 120 ° C. for 15 hours. did. Cool to room temperature, remove the solid by filtration, and concentrate the filtrate in vacuo. The residue was purified by flash chromatography eluting with hexane / THF (10/2). The product was recrystallized from methanol to give the title compound (20 mg). ES / MS m / z 416.9 (M + 1) $^{+}$.

(Preparation Example 20)
4-Bromo-5- [7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidin-3-yl] -thiazole-2-carbaldehyde under nitrogen atmosphere, n -Butyllithium (1.6 M in hexane, 0.312 mL, 0.50 mmol) was added to 3- (2,4-dibromo-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl -A solution of pyrazolo [1,5-a] pyrimidine (230 mg, 0.50 mmol) in THF (2.5 mL) was added at -78 ° C and stirred for 30 minutes. A solution of N-formylmorpholine (58 mg, 0.50 mmol) in THF (0.5 mL) was added. Stir for 1 hour and store the reaction at −20 ° C. overnight. The reaction was warmed to room temperature, diluted with ether and quenched by the addition of 4N HCl (4 mL). The layers were separated and the organic phase was extracted with 4N HCl (2 × 4 mL). The aqueous layers were combined, treated with solid sodium bicarbonate to pH = 8-9 and extracted with diethyl ether. All organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated to a residue. The crude product was purified by flash chromatography eluting with hexane / 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 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) were mixed in dichloromethane (3 mL) and methanol (0.5 mL). Stir overnight and add additional morpholine (35 mg, 0.405 mmol) and sodium triacetoxyborohydride (97 mg, 0.46 mmol) and stir for an additional 4 hours. The solvent was removed under vacuum, diluted with dichloromethane and washed with brine. The organic phase was dried over sodium sulfate, filtered and concentrated under vacuum. The resulting material was purified using flash chromatography eluting with dichloromethane: 2M ammonia in methanol (10: 1) to give a mixture. The mixture was purified 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 under nitrogen atmosphere N-butyllithium (1.6M hexane solution, 0.312 mL, 0.5 mmol) was added to 3- (2,4-dibromo-thiazol-5-yl) -7- (1- Ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (229 mg, 0.5 mmol) was added at −78 ° C. After stirring for 30 minutes, anhydrous zinc chloride (264 mg, 1.5 mmol) was added and stirring was continued for 30 minutes. The reaction was warmed to room temperature

and stirred for 1 hour. 4-Iodopyridine (103 mg, 0.5 mmol) was added, followed by 1,1'-bis (diphenylphosphino) ferrocenepalladium (II) chloride (dichloromethane adduct) (0.40.8 mg, 0.05 mmol). It was. The reaction was heated at reflux overnight. Cool to room temperature, dilute with ethyl acetate and wash with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated to give a residue. The crude product was purified by flash chromatography eluting with 2N ammonia in dichloromethane: methanol (10: 0.75) to give a mixture. The mixture was purified 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) 456.9 (M + 1) +.

(Preparation Example 21)
4-trifluoromethyl-thiazol-2-ylamine thiourea (4.0 g, 52.3 mmol) and 3-bromo-1,1,1-trifluoropropan-2-one (5.5 mL, 10 g, 52.3 mmol)) Was added to ethanol (100 mL) and heated at 50 ° C. for 2 hours. Cool to room temperature and concentrate to dryness. This residue was dissolved in water and the pH was adjusted to greater than 12 using 2M NaOH. Extracted with diethyl ether (4x). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under vacuum. The resulting material was purified by silica gel chromatography (CH_2Cl_2) to give the title compound (6.9 g, 79%). ES / MS m / z 169 (M + 1) $^{<+>}$.

(Preparation Example 22)
5-Bromo-4-trifluoromethyl-thiazol-2-ylamine, hydrobromide Bromine (2.0 mL, 6.28 g, 39.3 mmol) was added to 4-trifluoromethyl- in diethyl ether (60 mL). Thiazol-2-ylamine (6.0 g, 35.7 mmol) was added dropwise to the solution cooled in an ice bath. Stir for 1 hour after the end of the addition and then warm to room temperature. The solid was collected by filtration and washed with diethyl ether to give the title compound (10.5 g, 90%). ES / MS m / z (^{79} Br / ^{81} Br) 247/249 (M + 1) +.

(Preparation Example 23)
5-Bromo-2- (2,5-dimethyl-pyrrol-1-yl) -4-trifluoromethyl-thiazole hexane-2,5-dione (3.5 mL, 3.4 g, 30.2 mmol) was added to methanol. To a solution of 5-bromo-4-trifluoromethyl-thiazol-2-ylamine hydrobromide (9.0 g, 27.4 mmol) in (60 mL). Stir overnight at room temperature. Phosphate buffer (50 mL, pH = 7) was added. The resulting precipitate was collected by filtration and washed with water. The filter cake was dissolved in CH_2Cl_2 and dried over sodium sulfate. Filtration and concentration in vacuo gave 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
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) was placed in a dry ice bath. Cooled down. t-Butyllithium (1.7 M pentane solution, 8.5 mL, 14.5 mmol) was added dropwise. Stir for 45 minutes, then add zinc chloride (0.5 M in THF, 14.6 mL, 7.3 mmol) dropwise. Stir for 5 minutes and remove the cooling bath. Stir for 30 minutes, then 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) was added. Refluxed for 24 hours. The reaction was cooled and the mixture was poured into diethyl ether and washed with water (2 ×). The combined aqueous layer was extracted with diethyl ether. The combined organic portions were dried over sodium sulfate, filtered and concentrated under vacuum until dryness. The resulting residue was purified by silica gel chromatography (75-100% CH_2Cl_2 in hexanes) to give the title compound (1.47 g, 72%). $_{HR-ToF-MS\ m/z}$ C 23 H 26 F 3 N 5 S + H calcd for $^{+}$ 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 hydroxylamine (2 mL, 50% aqueous solution) in 3- [2- (2,5-dimethyl-pyrrol-1-yl) -4-trifluoromethyl-thiazol-5-yl] -7- (1-ethyl) in acetic acid (10 mL). -Propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (1.1 g, 2.3 mmol) was added. The reaction was heated to 80 ° C. for 6 hours. Cooled to room temperature. Pour into diethyl ether and wash once with 2M NaOH (2 ×) then water. The organic portion was dried over sodium sulfate, filtered and concentrated under vacuum until dryness. The resulting residue was purified by silica gel chromatography (40% ethyl acetate in hexane) to give the title compound (0.76 g, 87%). ES / MS m / z 384 (M + 1) $^{+}$.

(Preparation Example 24)
3- (2-Bromo-4-trifluoromethyl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine In acetonitrile (20 mL) Of copper (II) bromide (540 mg, 2.4 mmol) and t-butyl nitrite (0.36 mL, 310 mg, 3.0 mmol) were heated to 60 ° C. 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) was added as a solid. The reaction was heated to 80 ° C. for 2 hours. The reaction was cooled, poured into diethyl ether and extracted with water (3x). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo until dryness. The resulting residue was purified by silica gel chromatography with 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 3- (2-Bromo-4-trifluoromethyl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a in methanol (4 mL) The sealed reaction tube containing pyrimidine (313 mg, 0.7 mmol) and dimethylamine (2M THF solution, 4 mL, 8 mmol) was heated to 80 ° C. for 2 hours. The reaction was cooled and concentrated under vacuum. The residue produced by silica gel chromatography eluting with CH_2Cl_2 containing 0-30% ethyl acetate was purified to give the title compound (0.28 g, 97%). $_{HR-ToF-MS\ m/z}$ C 19 H 24 F 3 N 5 calcd 412.1770 for S + $^{H+}$, Found: 412.1783.

The following examples were prepared essentially as described for Example 28 except that the reaction was refluxed for 8 hours.

(Example 30)
N- (5- [7- (1-Ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidin-3-yl] -4-trifluoromethyl-thiazol-2-yl)- Acetamide hydroxylamine (50% aqueous solution, 5 mL) was added 3- [2- (2,5-dimethyl-pyrrol-1-yl) -4-trifluoromethyl-thiazol-5-yl]-in acetic acid (25 mL). 7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (2.4 g, 5.2 mmol) was added to the solution. The reaction was heated to 80 ° C. for 72 hours. The reaction was cooled to room temperature, poured into diethyl ether, washed once with 2M NaOH (2 ×) and then water. The organic portion was dried over sodium sulfate, filtered and concentrated to dryness. The resulting residue was purified by column chromatography eluting with 40% ethyl acetate in hexanes to give the title compound (0.28 g, 13%). $_{HR-ToF-MS\ m/z}$ C 19 H 22 F 3 N 5 O^{S} + H calcd for $^{+}$ 426.1575, Found: 426.1565.

(Example 31)
(2- (5- [7- (1-Ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidin-3-yl] -4-trifluoromethyl-thiazol-2-ylamino) -Ethyl) -carbamic acid tert-butyl ester
(2-Amino-ethyl) -carbamic acid tert-butyl ester (0.5 mL, 506 mg, 3.2 mmol) was added to 3- (2-bromo-4-trifluoromethyl-thiazole-5- 5 in methanol (1 mL). 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) Added to. Methanol was evaporated and heated to 80 ° C. overnight. The reaction was cooled to room temperature and concentrated under vacuum. The residue produced by column chromatography eluting with CH_2Cl_2 containing 10-50% ethyl acetate was purified to give the title compound (0.11 g, 97%). ES / MS m / z 527.2 (M + 1) $^{+}$

The following compounds were prepared essentially as described in Example 31, using the appropriate amine.

* Heated at reflux overnight in EtOH. EtOH was evaporated and heated at 110 ° C. for 24 hours.

** Heated at 80 ° C. overnight in EtOH.

*** Prepared HCl salt and recrystallized from EtOAc / hexane.

(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 (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) was added to 1 M HCl in methanol (1 mL). The reaction was heated at 70 ° C. overnight. The reaction was cooled and concentrated in vacuo from methanol / ethyl acetate. The resulting residue was triturated with ethyl acetate to give the title compound (64 mg, 78%). ES / MS m / z 427.0 (M + 1) +++ .

The following examples were prepared essentially as described for Example 33.

(Example A)

In Vivo Efficacy Assessment Using in Vitro Binding In order to assess in vivo efficacy, the compounds of the invention were evaluated using in vitro binding. D. R. The compounds were administered to rats by the oral route using the procedure provided in Gehert et al., EJP 509, 145-153 (2005). The binding of ^{125} I-sorbazine to the cerebellum was evaluated in vitro as described by Gehert et al. For example, Example 15 resulted in 65% inhibition at 10 mg / kg.

(Example B)

CRF1 filter binding method The limitation of plasmid-based human CRF1 expression in generating recombinant cell lines with sufficient receptor density to develop binding studies is the Phoenix retrovirus expression system licensed from Stanford. Overcame with Membranes were prepared using the stable HEK-hCRF1 cell line and the binding reaction (200 µL) was set up as follows: 50 µL ^{125} I-sorbazine (0.2 nM final concentration), 50 µL compound and 100 µL. CRF1 membrane (25 µg / reaction). The reaction was incubated at room temperature for 2 hours and stopped by filtering through pretreated FB Millipore glass fiber filter plates (96 wells). The plate was washed twice with ice-cold test buffer (50 mM Tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried overnight, and in a MicroBeta counter. Counting was performed using 100 µL Microscint40. Non-specific binding (NSB) was measured in the presence of 0.5 µM unlabeled sorvazine. Usually three measurements were taken and the average data points were plotted by Graph Pad Prism.

Using this test, the exemplified compounds of the invention inhibited the binding of ^{125} I-sorbazine (4 nM) with a Ki (inhibition constant) of less than 1 µM in roller / adherent cells. For example, Example 15 showed a Ki of 6.2 nM.

(Example C)

CRF2 filter binding method The limitation of plasmid-based human CRF2 expression in generating recombinant cell lines with sufficient receptor density to develop binding studies is the Phoenix retrovirus expression system licensed from Stanford. Overcame with Membranes were prepared using a stable HEK-hCRF2 cell line and the binding reaction (200 µL) was set up as follows: 50 µL ^{125} I-sorbazine (0.2 nM final concentration), 50 µL compound and 100 µL. CRF2 membrane (25 µg / reaction). The reaction was incubated at room temperature for 2 hours and stopped by filtering through pretreated FB Millipore glass fiber filter plates (96 wells). The plate was washed twice with ice-cold test buffer (50 mM Tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried overnight, and in a MicroBeta counter. Counting was performed using 100 µL Microscint40. Non-specific binding (NSB) was measured in the presence of 0.5 µM unlabeled sorvazine. Alternatively, compounds were evaluated using a scintillation proximity assay. The test procedure was set up as follows: 50 µL of ^{125} I-sorbazine (0.2 nM final concentration), 50 µL of compound or unlabeled sorvazine (NSB), and 250 µg of wheat germ agglutinin (WGA) SPA beads and 100 µL containing CRF2 membrane (1.5 µg / reaction). Plates were incubated for 4-5 hours at room temperature and centrifuged at 200 xg for 10 minutes. Bound radioactivity was assessed using a Wallac Trilux scintillation counter. Usually, three measurements were taken to assess binding and the average data points were plotted by Graph Pad Prism. Compounds were screened at the initially fixed concentration and when sufficient activity was observed, a concentration-response curve was subsequently generated.

Particularly exemplified compounds of the invention were tested in the CRF2 binding test and showed weak affinity for the CRF2 receptor. For example, Example 15 showed 11% inhibition at a concentration of 50 µM. This result suggests that the compounds of the invention are selective for the CRF1 receptor (rather than CRF2).

(Example D)

Bioavailability and pharmacokinetic properties The volume of distribution (Vdist) relates the amount of drug in the body to the drug concentration in blood or plasma. The volume of distribution refers to the volume of fluid that would be required to contain the entire amount of drug in the body at the same concentration as in blood or plasma. Vdist = amount of drug in the body / drug in blood or plasma Concentration (Goodman and Gilman literature). For a 10 mg dose and a plasma concentration of 10 mg / L, the distribution volume would be 1 liter. The volume of distribution reflects the extent to which the drug is present in extravascular tissue. A large volume of distribution reflects that certain compounds tend to bind to tissue components rather than plasma protein binding. In the clinical setting, Vdist can be used to determine the loading dose to achieve a steady state concentration.

To test for volume of distribution, male Sprague Dawley rats (N = 3) were dosed with a single intravenous dose of 1 mg / kg. Multiple plasma samples were collected at 0.08-24 hours after administration. The plasma sample was analyzed by LC / MS / MS to determine plasma concentration. Pharmacokinetic calculations in plasma were performed to determine pharmacokinetic parameters including Vdist and plasma clearance (Clp).

The compounds of the present invention preferably have a suitable bioavailability profile. For example, most commercially available CNS drugs and cardiovascular drugs exhibit a Vdist of less than 10 L / Kg for humans. Compared to 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)) When analyzed separately, the rat Vdist of 114 L / Kg and 76 L / Kg, respectively, is shown. Example 15 of the present invention, when analyzed separately, shows only 7.2 L / Kg rat Vdist after a single intravenous dose of 1 mg / kg.

In addition, plasma clearance (CLp) is a measure of the rate of drug removal from the body. According to intravenous administration and first order rate equations, plasma clearance can be determined using the following formula: CLp = dose / AUC, where AUC is plasma as a function of time from zero to infinity. The total area under the curve representing the drug concentration in the medium). The referenced CRF antagonists CP154526 and NBI27582, when analyzed separately, show rat clearance (CLp) of 83 mL / min / kg and 306 mL / min / kg, respectively, after a single intravenous administration, whereas Example 15 shows only 23.6 mL / min / kg of rat CLp when analyzed separately.

Patent Citations (10)

Publication number	Priority date	Publication date	Assignee	Title
JP2000503661A *	1996-02-07	2000-03-28	ジャンセン・ファーマシューチカ・ナームローゼ・フェンノートシャップ	Pyrazolopyrimidines as CRF receptor antagonists
WO2000059908A2 *	1999-04-06	2000-10-12	Du Pont Pharmaceuticals Company	Pyrazolopyrimidines as crf antagonists
JP2000302693A *	1999-04-02	2000-10-31	Pfizer Prod Inc	Corticotropin releasing factor antagonist for preventing sudden death
JP2002513382A *	1996-07-24	2002-05-08	デュポン ファーマシューティカルズ カンパニー	Azolotriazines and azolopyrimidines
WO2005063755A1 *	2003-12-22	2005-07-14	Sb Pharmco Puerto Rico Inc	Crf receptor antagonists and methods relating thereto
Family To Family Citations				
CZ286892B6	1992-12-17	2000-07-12	Pfizer	Pyrrolopyrimidine compounds, intermediates for their preparation and pharmaceutical preparations based thereon
EP0915888B1	1996-07-24	2007-10-10	Bristol-Myers Squibb Pharma Company	Azolo triazines and pyrimidines
JP3621706B2	1996-08-28	2005-02-16	ファイザー・インク	Substituted 6,5-hetero-bicyclic derivatives
DE60032249T2 *	1999-09-30	2007-07-19	Neurogen Corp., Branford	Amino-substituted pyrazolo [1,5-a] -1,5-pyrimidines and pyrazolo [1,5-a] -1,3,5-triazines
GEP20053608B *	2001-03-13	2005-09-12	Squibb Bristol Myers Co	4-(2-Butylamino)-2,7-Dimethyl-8-(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

* Cited by examiner, † Cited by third party

Non-Patent Citations (1)

Title
JPN6012062715, CHEN, C. et al.:'Design of 2,5-dimethyl-3-(6-dimethyl-4-methylpyridin-3-yl)-7-dipropylaminopyrazolo[1,5-a]pyrimidine' J. Med. Chem. Vol. 47, No. 19, 2004, p. 4787-4798 *

* Cited by examiner, † Cited by third party

Cited By (14)

Publication number	Priority date	Publication date	Assignee	Title
JP2017503030A *	2014-01-21	2017-01-26	ニューロクライン バイオサイエンシーズ, インコーポレイテッド	CRF1 receptor antagonist for the treatment of congenital adrenocortical hyperplasia
JP2020530831A *	2017-08-14	2020-10-29	スプルース バイオサイエンシズ インコーポレイテッド	Corticotropin-releasing factor receptor antagonist
JP2020530832A *	2017-08-14	2020-10-29	スプルース バイオサイエンシズ インコーポレイテッド	Corticotropin-releasing factor receptor antagonist
Family To Family Citations				
EP2025674A1	2007-08-15	2009-02-18	sanofi-aventis	Substituted tetra hydro naphthalines, method for their manufacture and their use as drugs
AU2009298757B2 *	2008-10-02	2013-08-01	Eli Lilly And Company	Thiazolyl-pyrazolopyrimidine compounds as synthetic intermediates and related synthetic processes
EP2567959B1	2011-09-12	2014-04-16	Sanofi	6-(4-hydroxy-phenyl)-3-styryl-1h-pyrazolo[3,4-b]pyridine-4-carboxylic acid amide derivatives as kinase inhibitors
PL238385B1 *	2015-04-02	2021-01-11	Celon Pharma Spolka Akcyjna	Derivatives of 7-(morpholin-4-yl)pyrazolo[1,5-a]pyrimidine as inhibitors of kinase PI3
CA3039026A1	2016-09-07	2018-03-15	The Regents Of The University Of California	Allosteric corticotropin-releasing factor receptor 1 (crfr1) antagonists that decrease p-tau and improve cognition

JP2021522340A *	2018-04-27	2021-08-30	スプルース バイオサイエンシーズ，インク．	Methods for Treating Testicular Adrenal Residual Tumors and Ovarian Adrenal Residual Tumors
CN109134483B *	2018-08-07	2021-05-14	中山大学	Substituted pyrrole chromone compound or pharmaceutically acceptable salt thereof, and preparation method and application thereof
AP120649A1 *	2019-12-04	2022-03-09	Neurocrine Biosciences Inc	CRF RECEPTOR ANTAGONISTS AND METHODS OF USE
GR10100968 *	2020-07-02	2021-10-08	Uni-Pharma Κλεων Τσετης Φαρμακευτικα Εργαστηρια Αβεε,	Pyrazolo[1,5-a]pyrimidines as autotaxin inhibitors
WO2022036123A1 *	2020-08-12	2022-02-17	Spruce Biosciences, Inc.	Methods and compositions for treating polycystic ovary syndrome
WO2022046905A1	2020-08-26	2022-03-03	Neurocrine Biosciences, Inc	Crf receptor antagonists and methods of use

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

Similar Documents

Publication	Publication Date	Title
JP5161226B2	2013-03-13	Thiazolepyrazolopyrimidines as CRF1 receptor antagonists
JP5184586B2	2013-04-17	Thiophenepyrazolopyrimidine compounds
US6734185B2	2004-05-11	Pyrrolo[3,4-d]pyrimidines as corticotropin releasing factor (CRF) antagonists
KR101432316B1	2014-08-29	4,5-dihydro-[1,2,4]triazolo[4,3-f]pteridines as protein kinase plk1 inhibitors for the treatment of proliferative disorders
MX2012010610A	2012-10-03	Pyrrolopyrazine derivatives and their use as jak and syk inhibitors.
US20190263828A1	2019-08-29	Heteroaromatic compounds as vanin inhibitors
AU2006334364B2	2011-09-29	Imidazo (1,2-a)pyridin-3-yl-acetic acid hydrazides, processes for their preparation and pharmaceutical uses thereof
CA2631034A1	2007-06-21	Tricyclic lactam derivatives, their manufacture and use as pharmaceutical agents

Priority And Related Applications

Priority Applications (3)

Application	Priority date	Filing date	Title
US82626406P	2006-09-20	2006-09-20	*US Provisional Application*
US60/826,264		2006-09-20	
PCT/US2007/078605	2006-09-20	2007-09-17	Thiazole pyrazolopyrimidines as crf1 receptor antagonists

Legal Events

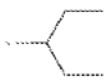
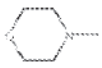
Date	Code	Title	Description
2010-09-10	A521	Written amendment	**Free format text:** JAPANESE INTERMEDIATE CODE: A523 **Effective date:** 20100909
2010-09-10	A621	Written request for application examination	**Free format text:** JAPANESE INTERMEDIATE CODE: A621 **Effective date:** 20100909
2012-11-27	TRDD	Decision of grant or rejection written	
2012-12-05	A01	Written decision to grant a patent or to grant a registration (utility model)	**Free format text:** JAPANESE INTERMEDIATE CODE: A01 **Effective date:** 20121204
2012-12-20	A61	First payment of annual fees (during grant procedure)	**Free format text:** JAPANESE INTERMEDIATE CODE: A61 **Effective date:** 20121213
2012-12-21	R150	Certificate of patent or registration of utility model	**Ref document number:** 5161226 **Country of ref document:** JP **Free format text:** JAPANESE INTERMEDIATE CODE: R150

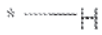
			Free format text: JAPANESE INTERMEDIATE CODE: R150
2012-12-27	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20151221 Year of fee payment: 3
2015-12-08	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2016-12-06	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2017-12-12	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2018-12-18	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2019-12-17	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2020-12-09	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250

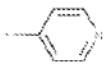
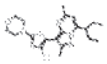
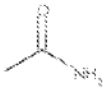
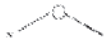
Concepts

machine-extracted

Download Filter table

Name	Image	Sections	Count	Query match
receptor antagonist		title,abstract,description	4	0.000
CRHR1		title,description	33	0.000
CRHR1		title,description	33	0.000
compounds		claims,abstract,description	147	0.000
Metabolic Syndrome		claims,abstract,description	10	0.000
pharmaceutical composition		claims,abstract,description	8	0.000
2-methyl-2H-[1,2,4] triazol-3-yl		claims,description	46	0.000
sodium chloride		claims,description	44	0.000
salts		claims,description	42	0.000
penten-3-yl group		claims,description	12	0.000
Alcohol abuse		claims,description	10	0.000
Drug abuse		claims,description	10	0.000
alcohol use disease		claims,description	10	0.000
morpholin-4-yl group		claims,description	10	0.000
Obesity		claims,description	8	0.000
obesity		claims,description	8	0.000
Anxiety		claims,description	7	0.000
Anxiety disease		claims,description	7	0.000
Chronic fatigue syndrome		claims,description	7	0.000
Hypersensitivity		claims,description	7	0.000
Hypertension		claims,description	7	0.000

Irritable Bowel Syndrome	claims,description	7	0.000
Pituitary Neoplasms	claims,description	7	0.000
Pituitary-dependent Cushing's syndrome	claims,description	7	0.000
Premature Birth	claims,description	7	0.000
Premenstrual syndrome	claims,description	7	0.000
Sleep disease	claims,description	7	0.000
Stomach Ulcer	claims,description	7	0.000
Visceral Pain	claims,description	7	0.000
anxiety	claims,description	7	0.000
ethyl group	claims,description	7	0.000
			
gastric ulcer	claims,description	7	0.000
inflammatory disease	claims,description	7	0.000
multiple sclerosis	claims,description	7	0.000
sexual dysfunction	claims,description	7	0.000
sexual dysfunction	claims,description	7	0.000
Adrenogenital Syndrome	claims,description	6	0.000
Congenital Adrenal Hyperplasia	claims,description	6	0.000
Convulsion	claims,description	6	0.000
Epilepsy	claims,description	6	0.000
Fibromyalgia	claims,description	6	0.000
Infertility	claims,description	6	0.000
Migraine	claims,description	6	0.000
Migraine Disorders	claims,description	6	0.000
Premature baby	claims,description	6	0.000
Seizure	claims,description	6	0.000
alkyl group	claims,description	6	0.000
hydrogen	claims,description	6	0.000
hydrogen	claims,description	6	0.000
hydrogen atoms	claims,description	6	0.000
			
infertility	claims,description	6	0.000
infertility	claims,description	6	0.000
n-propyl group	claims,description	6	0.000
			
pituitary	claims,description	6	0.000
4-pyridyl group	claims,description	4	0.000

				
trifluoromethyl group		claims,description	4	0.000
methyl group		claims,description	3	0.000
tildacerfont		claims,description	3	0.000
Cyclic olefin copolymer		claims,description	2	0.000
acetamide		claims,description	2	0.000
methoxy group		claims,description	2	0.000
methoxymethyl group		claims,description	2	0.000
n-butyl group		claims,description	2	0.000
Congenital anomaly		claims	1	0.000
Hyperplasia		claims	1	0.000
N1=CC=CN2N=C(CCCC)C=C21		claims	1	0.000
Neoplasm		claims	1	0.000
Tetraethylammonium bromide		claims	1	0.000
adrenal		claims	1	0.000
pharmacologic effect		claims	1	0.000
therapeutic procedure		claims	1	0.000
crf1		abstract,description	25	0.000
disease		abstract,description	9	0.000
Nervous System Disease		abstract,description	6	0.000
neuroendocrine		abstract,description	3	0.000

Show all concepts from the description section

Data provided by IFI CLAIMS Patent Services

About Send Feedback Public Datasets Terms Privacy Policy

Bibliographic data

Title:	No title available
Pub/Pat no:	JP2010504344A
Pub/Issue Date:	2010-02-12
Inventor(s):	
Applicant(s):	
Classification:	A61K31/519AI; A61K31/5377AI; A61P1/00AI; A61P1/04AI; A61P3/04AI; A61P9/12AI; A61P13/12AI; A61P15/06AI; A61P15/08AI; A61P15/10AI; A61P21/00AI; A61P25/00AI; A61P25/06AI; A61P25/08AI; A61P25/20AI; A61P25/22AI; A61P25/24AI; A61P25/32AI; A61P25/36AI; A61P29/00AI; A61P35/00AI; A61P37/08AI; C07D487/04AI
Application number:	JP20090529316 2007-09-17
Priority number:	US20060826264P 20060920; WO2007US78605 20070917;

Abstract of JP2010504344A

No abstract

(19)日本国特許庁(JP)　(12)公表特許公報(A)　(11)特許出願公表番号
特表2010-504344
(P2010-504344A)
(43)公表日　平成22年2月12日(2010.2.12)

(51)Int.Cl.		F I		テーマコード（参考）
C07D 487/04	(2006.01)	C07D 487/04	142	4C050
A61K 31/519	(2006.01)	C07D 487/04	CSP	4C086
A61K 31/5377	(2006.01)	A61K 31/519		
A61P 25/24	(2006.01)	A61K 31/5377		
A61P 25/22	(2006.01)	A61P 25/24		

審査請求 未請求　予備審査請求 未請求　（全 52 頁）　最終頁に続く

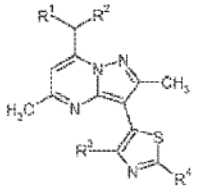
(21)出願番号　特願2009-529316 (P2009-529316)
(86)(22)出願日　平成19年9月17日 (2007.9.17)
(85)翻訳文提出日　平成21年3月23日 (2009.3.23)
(86)国際出願番号　PCT/US2007/078605
(87)国際公開番号　WO2008/036579
(87)国際公開日　平成20年3月27日 (2008.3.27)
(31)優先権主張番号　60/826,264
(32)優先日　平成18年9月20日 (2006.9.20)
(33)優先権主張国　米国 (US)

(71)出願人　594197872
イーライ　リリー　アンド　カンパニー
アメリカ合衆国　インディアナ州　４６２８５　インディアナポリス　リリー　コーポレイト　センター　（番地なし）
(74)代理人　100068526
弁理士　田村　恭生
(74)代理人　100100158
弁理士　鮫島　睦
(74)代理人　100138900
弁理士　新田　昌宏
(74)代理人　100076521
弁理士　坪井　有四郎

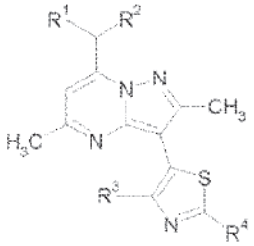
最終頁に続く

(54)【発明の名称】ＣＲＦ１受容体アンタゴニストとしてのチアゾールピラゾロピリミジン

(57)【要約】
本発明は、式Ｉの化合物、その医薬組成物、ならびに精神障害および神経内分泌系障害、神経系疾患およびメタボリックシンドロームの治療における副腎皮質刺激ホルモン放出因子１（ＣＲＦ１）受容体アンタゴニストとしてのその使用に関する。

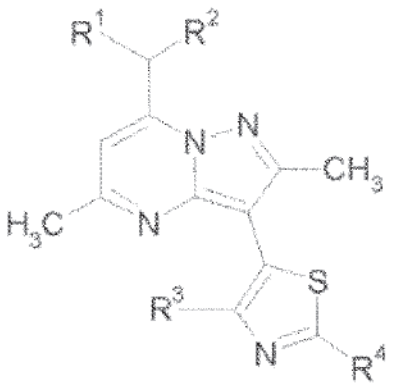


I



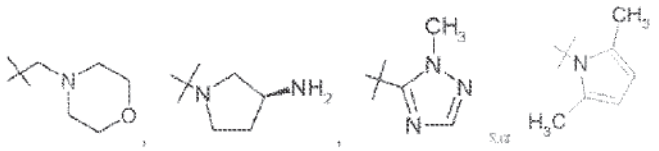
式Ｉ

【特許請求の範囲】
【請求項1】
式Ｉの化合物
【化1】



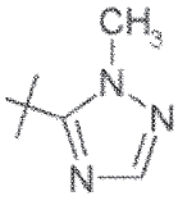
式Ｉ

（式中、
R^1 およびR^2 は独立に、エチルまたはｎ－プロピルであり、
R^3 は水素、Ｃｌ、Ｂｒ、メチル、トリフルオロメチルまたはメトキシであり、
R^4 は水素、Ｂｒ、$R^a R^b N$－、メトキシメチル、ｎ－ブチル、アセトアミド、ピリジン－４－イル、モルホリン－４－イル、
【化2】



であり、
R^a およびR^b は独立に、水素、C_1－C_3 アルキル、$H_2NCH_2CH_2$－、$(CH_3)_3COC(O)NHCH_2CH_2$－、または$CH_3CH_2CH_2NHCH_2CH_2$－である）
またはその薬理学的に許容できる塩。
【請求項2】
R^3 がＣｌ、Ｂｒ、メチルまたはトリフルオロメチルである、請求項１に記載の化合物またはその薬理学的に許容できる塩。
【請求項3】
R^3 がＣｌまたはＢｒである、請求項１または請求項２に記載の化合物またはその薬理学的に許容できる塩。
【請求項4】
R^4 が$R^a R^b N$－、ピリジン－４－イル、モルホリン－４－イル、または

【化3】

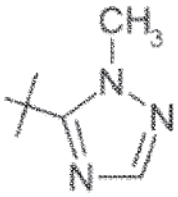


である、請求項１から請求項３のいずれか１項に記載の化合物またはその薬理学的に許容できる塩。

【請求項5】

R^4 がモルホリン－４－イルまたは

【化4】



である、請求項１から請求項４のいずれか１項に記載の化合物またはその薬理学的に許容できる塩。

【請求項6】

R^4 がR^a R^b Ｎ－であり、R^a およびR^b が独立にC_1－C_3 アルキルである、請求項１から請求項４のいずれか１項に記載の化合物またはその薬理学的に許容できる塩。

【請求項7】

３－［４－ブロモ－２－（２－メチル－２Ｈ－［１，２，４］トリアゾール－３－イル）－チアゾール－５－イル］－２，５－ジメチル－７－（１－プロピル－ブチル）－ピラゾロ［１，５－ａ］ピリミジンである、請求項１に記載の化合物またはその薬理学的に許容できる塩。

【請求項8】

３－（４－ブロモ－２－（２－メチル－２Ｈ－［１，２，４］トリアゾール－３－イル）－チアゾール－５－イル）－７－（１－エチル－プロピル）－２，５－ジメチル－ピラゾロ［１，５－ａ］ピリミジンである、請求項１に記載の化合物またはその薬理学的に許容できる塩。

【請求項9】

３－（４－クロロ－２－モルホリン－４－イル－チアゾール－５－イル）－７－（１－エチル－プロピル）－２，５－ジメチル－ピラゾロ［１，５－ａ］ピリミジンである、請求項１に記載の化合物またはその薬理学的に許容できる塩。

【請求項10】

請求項１から請求項９のいずれか１項に記載の化合物またはその薬理学的に許容できる塩と、薬理学的に許容できる賦形剤とを含む、医薬組成物。

【請求項11】

患者のうつ病、不安症、アルコール濫用または薬物濫用、肥満、高血圧、メタボリックシンドローム、過敏性大腸症候群、癲癇、発作、睡眠障害、アレルギー、片頭痛、月経前症候群、不妊性、性的機能不全、先天性副腎過形成、クッシング病、早産、ストレスにより誘発される胃潰瘍、炎症性障害、下垂体または異所性下垂体由来の腫瘍、慢性疲労症候群、線維筋痛、内膜痛または多発性硬化症を治療する方法であって、それを必要とする患者に治療上有効量の請求項１から請求項９のいずれか１項に記載の化合物またはその薬理

学的に許容できる塩を投与することを含む、方法。
【請求項12】
患者の不安症またはうつ病を治療する方法であって、それを必要とする患者に治療上有効量の請求項１から請求項９のいずれか１項に記載の化合物またはその薬理学的に許容できる塩を投与することを含む、方法。
【請求項13】
患者のアルコール濫用または薬物濫用を治療する方法であって、それを必要とする患者に治療上有効量の請求項１から請求項９のいずれか１項に記載の化合物またはその薬理学的に許容できる塩を投与することを含む、方法。
【請求項14】
治療における使用のための、請求項１から請求項９のいずれか１項に記載の化合物またはその薬理学的に許容できる塩。
【請求項15】
うつ病、不安症、アルコール濫用または薬物濫用、肥満、高血圧、メタボリックシンドローム、過敏性大腸症候群、癲癇、発作、睡眠障害、アレルギー、片頭痛、月経前症候群、不妊性、性的機能不全、先天性副腎過形成、クッシング病、早産、ストレスにより誘発される胃潰瘍、炎症性障害、下垂体または異所性下垂体由来の腫瘍、慢性疲労症候群、線維筋痛、内臓痛または多発性硬化症の治療において使用するための、請求項１から請求項９のいずれか１項に記載の化合物またはその薬理学的に許容できる塩。
【請求項16】
不安症またはうつ病の治療において使用するための、請求項１から請求項９のいずれか１項に記載の化合物またはその薬理学的に許容できる塩。
【請求項17】
アルコール濫用または薬物濫用の治療において使用するための、請求項１から請求項９のいずれか１項に記載の化合物またはその薬理学的に許容できる塩。

【発明の詳細な説明】
【技術分野】
【0001】
本発明は、精神障害および神経内分泌系障害、神経系疾患およびメタボリックシンドロームの治療におけるＣＲＦ１受容体アンタゴニストとしての新規なチアゾールピラゾロピリミジン化合物、その医薬組成物およびそれらの使用に関する。
【背景技術】
【0002】
副腎皮質刺激ホルモン放出因子（ＣＲＦ）は、脳下垂体前葉からのプロオピオメラノコルチン（ＰＯＭＣ）由来のペプチド分泌の主要な生理的調節因子である４１アミノ酸のペプチドである。下垂体でのその内分泌の役割に加えて、ＣＲＦの免疫組織化学的局在から、このホルモンが中枢神経系の幅広い視床下部外分布を有し、脳での神経伝達物質または神経修飾物質としての役割と整合した広い範囲の自律神経的効果、電子生理的効果および行為への効果を生じることが証明された。免疫系における生理的、心理的、および免疫学的ストレス因子に対する反応を統合する面でＣＲＦが重要な役割を果たすという証拠もある。
【0003】
ＣＲＦは、うつ病および神経不安症を含めた精神障害および神経系疾患、ならびにアルツハイマー病、ハンチントン病、進行性核上麻痺、筋萎縮性側索硬化症、パーキンソン病、癲癇、片頭痛、アルコール濫用および薬物濫用および関連する禁断症状、肥満、メタボリックシンドローム、先天性副腎過形成、クッシング病、高血圧、発作、過敏性大腸症候群、ストレスにより誘発される胃潰瘍、月経前症候群、性的機能不全、早産、炎症性障害、アレルギー、多発性硬化症、内臓痛、睡眠障害、下垂体部腫瘍または異所性下垂体由来の腫瘍、慢性疲労症候群および線維筋痛に関連付けられてきた。

【0004】
ＣＲＦ受容体亜型（ＣＲＦ１およびＣＲＦ２）が確認されており、これらは脳内に不均一に分布しており、これは機能的多様性の可能性を示唆している。例えば、広く分布した脳ＣＲＦ１受容体は、環境ストレス因子への曝露に付随する情動性に強く関係する。重要なことは、ＣＲＦ２受容体ではなくＣＲＦ１受容体が、不安惹起様行動の選択を媒介するように見えることである。より離散的な中隔／視床下部分布および別の内在性リガンドの入手可能性は、ＣＲＦ２受容体の異なる機能的な役割を示唆する。例えば、ＣＲＦ１受容体よりもＣＲＦ２受容体に対して優先的な親和性を有する新規なＣＲＦ族の神経ペプチドが、選択的なＣＲＦ１アゴニズムで観察される行動活性化の外観を生成することのなく食欲を抑制することが報告されている。他の場合には、ＣＲＦ２アゴニズムは、ＣＲＦ１アンタゴニストまたはＣＲＦ１遺伝子欠失について報告されている効果に類似の効果をもたらす。例えば、ＣＲＦ２アゴニストが抗肥満薬として提唱されてきたが、ＣＲＦ１アンタゴニストも同様に肥満に対する重要な治療法であるかも知れない。
【0005】
ＣＲＦアンタゴニストとして有用な特定のピロロ［２，３－ｄ］ピリミジン、ピロロ［３，２－ｄ］ピリミジン、ピラゾロ［１，５－ａ］ピリミジン、１，２，３－トリアゾロ［４，５－ｂ］ピリジン、およびピラゾロ［１，５－ａ］－１，３，５－トリアジンが特許文献１、特許文献２、特許文献３、および特許文献４に記載されている。

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/078605

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/505 A61P29/00 A61P25/22 A61P25/24
A61P25/30

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	GEHLERT ET AL: "3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine: a novel brain-penetrant, orally available corticotropin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism." THE JOURNAL OF NEUROSCIENCE, vol. 27, no. 10, 7 March 2007 (2007-03-07), pages 2718-2726, XP002465426 figure 1; table 1	1-17
Y	WO 01/23388 A (NEUROGEN CORP [US]; PFIZER [US]; DARROW JAMES W [US]; LOMBAERT STEPHAN) 5 April 2001 (2001-04-05) page 69; example 95 page 13, line 3	1-17

-/---

[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
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2008	31/01/2008

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	Gettins, Marc

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/078605

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/072202 A (BRISTOL MYERS SQUIBB PHARMA CO [US]) 19 September 2002 (2002-09-19) claims 1,16	1-17
A	HE LIQI ET AL: "4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine: A Potent, Orally Bioavailable CRF1 Receptor Antagonist" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, 2000, pages 449-456, XP002196777 ISSN: 0022-2623 table 1	1-17
A	WO 2005/063755 A (SB PHARMCO INC [US]; NEUROCRINE BIOSCIENCES INC [US]; LUO ZHIYONG [US]) 14 July 2005 (2005-07-14) claims 1,24	1-17
A	WO 00/59908 A (DU PONT PHARM CO [US]) 12 October 2000 (2000-10-12) page 21, line 15; claims 1,11	1-17
A	WO 97/29109 A (JANSSEN PHARMACEUTICA NV [BE]; NEUROCRINE BIOSCIENCES INC [US]; CHEN C) 14 August 1997 (1997-08-14) cited in the application page 1, line 5 - line 9; claim 1	1-17
Y	WO 98/03510 A (DU PONT MERCK PHARMA [US]) 29 January 1998 (1998-01-29) cited in the application page 162, line 20 - page 164, line 6; claim 1	1-17
Y	CHEN C ET AL: "DESIGN OF 2,5-DIMETHYL-3-(6-DIMETHYL-4-METHYLPYRIDIN-3-YL)-7-DIPROPYL AMINOPYRAZOLO[1,5-ALPHA]PYRIMIDINE (NBI 30775/R121919) AND STRUCTURE-ACTIVITY RELATIONSHIPS OF A SERIES OF POTENT AND ORALLY ACTIVE CORTICOTROPIN-RELEASING FACTOR RECEPTOR ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 47, no. 19, 9 September 2004 (2004-09-09), pages 4787-4798, XP001206057 ISSN: 0022-2623 figure 1	1-17

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

International application No.
PCT/US2007/078605

INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 3 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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

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

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

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

Remark on Protest

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

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

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

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/078605

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0123388 A	05-04-2001	AT	347553 T	15-12-2006
		AU	7737900 A	30-04-2001
		BG	106507 A	29-12-2002
		CA	2379633 A1	05-04-2001
		CN	1377355 A	30-10-2002
		CZ	20021089 A3	13-11-2002
		DE	60032249 T2	19-07-2007
		EP	1218381 A2	03-07-2002
		ES	2277855 T3	01-08-2007
		HU	0203131 A2	28-01-2003
		JP	2003510326 T	18-03-2003
		JP	2007077144 A	29-03-2007
		NO	20021357 A	23-05-2002
		OA	12049 A	02-05-2006
		PL	354982 A1	22-03-2004
		ZA	200202517 A	28-03-2003
WO 02072202 A	19-09-2002	AR	032986 A1	03-12-2003
		AT	355102 T	15-03-2006
		BG	108189 A	30-09-2004
		BR	0208357 A	29-06-2004
		CA	2440553 A1	19-09-2002
		CN	1509196 A	30-06-2004
		DE	60218434 T2	08-11-2007
		DK	1368094 T3	02-07-2007
		EE	200300435 A	15-12-2003
		EP	1368094 A1	10-12-2003
		ES	2282401 T3	16-10-2007
		HK	1057182 A1	06-07-2007
		HR	20030822 A2	30-04-2004
		HU	0303480 A2	28-01-2004
		IS	6947 A	10-09-2003
		JP	2004530662 T	07-10-2004
		MX	PA03008185 A	29-01-2004
		NO	20034023 A	11-09-2003
		NZ	528207 A	24-02-2006
		RU	2292347 C2	27-01-2007
		SK	11572003 A3	03-02-2004
		TW	257388 B	01-07-2006
		UA	74634 C2	15-12-2003
		US	2007054913 A1	08-03-2007
		YU	71503 A	25-05-2006
		ZA	200306995 A	08-09-2004
WO 2005063755 A	14-07-2005	AR	046967 A1	04-01-2006
		AU	2004309168 A1	14-07-2005
		BR	PI0417943 A	17-04-2007
		CA	2550948 A1	14-07-2005
		CN	1938309 A	28-03-2007
		EP	1697374 A1	06-09-2006
		JP	2007515472 T	14-06-2007
		KR	20070009537 A	18-01-2007
		US	2007287705 A1	13-12-2007
WO 0059908 A	12-10-2000	AU	4203500 A	23-10-2000
WO 9729109 A	14-08-1997	AT	336495 T	15-09-2006
		AU	713673 B2	09-12-1999

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/078605

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9729109 A		AU	1599197 A	28-08-1997
		BG	102349 A	26-02-1999
		BR	9707391 A	20-07-1999
		CN	1205009 A	13-01-1999
		CZ	9802445 A3	14-10-1998
		DE	69736513 T2	05-04-2007
		DE	880523 T1	04-07-2002
		DK	0880523 T3	26-03-2007
		EA	980394 A1	29-10-1998
		EE	9800124 A	15-10-1998
		EP	0880523 A1	02-12-1998
		ES	2168237 T1	16-06-2002
		HU	9900575 A2	28-06-1999
		ID	15905 A	14-08-1997
		JP	3356291 B2	16-12-2002
		JP	2000503661 T	28-03-2000
		JP	2002121194 A	23-04-2002
		NO	981357 A	03-08-1998
		NZ	330119 A	28-02-2000
		SK	106398 A3	02-12-1998
		TR	9800792 T2	21-07-1998
		TW	449599 B	11-08-2001
WO 9803510 A	29-01-1998	AT	375344 T	15-10-2007
		AU	3894297 A	10-02-1998
		EP	0915880 A1	19-05-1999
		HU	0102187 A2	28-11-2001
		LV	12292 A	20-06-1999
		RO	121272 B1	28-02-2007
		TW	542827 B	21-07-2003
		TW	238164 B	21-08-2005

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

(51)Int.Cl.			F I		テーマコード（参考）
Ａ６１Ｐ	25/32	(2006.01)	Ａ６１Ｐ	25/22	
Ａ６１Ｐ	25/36	(2006.01)	Ａ６１Ｐ	25/32	
Ａ６１Ｐ	3/04	(2006.01)	Ａ６１Ｐ	25/36	
Ａ６１Ｐ	9/12	(2006.01)	Ａ６１Ｐ	3/04	
Ａ６１Ｐ	1/00	(2006.01)	Ａ６１Ｐ	9/12	
Ａ６１Ｐ	25/08	(2006.01)	Ａ６１Ｐ	1/00	
Ａ６１Ｐ	25/20	(2006.01)	Ａ６１Ｐ	25/08	
Ａ６１Ｐ	37/08	(2006.01)	Ａ６１Ｐ	25/20	
Ａ６１Ｐ	25/06	(2006.01)	Ａ６１Ｐ	37/08	
Ａ６１Ｐ	25/00	(2006.01)	Ａ６１Ｐ	25/06	
Ａ６１Ｐ	15/08	(2006.01)	Ａ６１Ｐ	25/00	
Ａ６１Ｐ	15/10	(2006.01)	Ａ６１Ｐ	15/08	
Ａ６１Ｐ	13/12	(2006.01)	Ａ６１Ｐ	15/10	
Ａ６１Ｐ	15/06	(2006.01)	Ａ６１Ｐ	13/12	
Ａ６１Ｐ	1/04	(2006.01)	Ａ６１Ｐ	15/06	
Ａ６１Ｐ	29/00	(2006.01)	Ａ６１Ｐ	1/04	
Ａ６１Ｐ	35/00	(2006.01)	Ａ６１Ｐ	29/00	
Ａ６１Ｐ	21/00	(2006.01)	Ａ６１Ｐ	35/00	
			Ａ６１Ｐ	21/00	

(81)指定国　AP(BW,GH,GM,KE,LS,MW,MZ,NA,SD,SL,SZ,TZ,UG,ZM,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IS,IT,LT,LU,LV,MC,MT,NL,PL,PT,RO,SE,SI,SK,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BH,BR,BW,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DO,DZ,EC,EE,EG,ES,FI,GB,GD,GE,GH,GM,GT,HN,HR,HU,ID,IL,IN,IS,JP,KE,KG,KM,KN,KP,KR,KZ,LA,LC,LK,LR,LS,LT,LU,LY,MA,MD,ME,MG,MK,MN,MW,MX,MY,MZ,NA,NG,NI,NO,NZ,OM,PG,PH,PL,PT,RO,RS,RU,SC,SD,SE,SG,SK,SL,SM,SV,SY,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VC,VN,ZA,ZM,ZW

(72)発明者　チャオゲン・チェン
アメリカ合衆国４６０３２インディアナ州カーメル、タイタン・ラン１０５３２番
(72)発明者　チャフィク・アムドウチ・アムドウチ
アメリカ合衆国４６０３２インディアナ州カーメル、ツイン・オークス・ドライブ１４４６９番
(72)発明者　エリック・ジェイムズ・ヘンプル
アメリカ合衆国４６２０２インディアナ州インディアナポリス、ノース・ニュー・ジャージー・ストリート１３３２番
(72)発明者　フィリップ・アーサー・ヒップスカインド
アメリカ合衆国４６１６３インディアナ州ニュー・パレスタイン、キャビン・コート４２５５番
(72)発明者　ジェイソン・ケネス・マイヤーズ
アメリカ合衆国４６２５６インディアナ州インディアナポリス、スプリングウォーター・サークル８０２１番
(72)発明者　高▲桑▼　貴子
アメリカ合衆国４６２３７インディアナ州インディアナポリス、ジャーマンダー・レイン７６５３番
(72)発明者　ジェイムズ・リー・トス
アメリカ合衆国４６１４８インディアナ州ナイツタウン、サウス６２５ウエスト４６４２番

Ｆターム(参考)　4C050 AA01 BB05 CC08 DD10 EE03 FF02 GG01 HH04
4C086 AA01 AA02 AA03 CB06 MA01 MA04 NA14 ZA02 ZA05 ZA06
ZA08 ZA12 ZA42 ZA66 ZA68 ZA70 ZA81 ZA94 ZB11 ZB13
ZB26 ZC39

Patents JP2002501922A

Azolotriazines and azolopyrimidines

Abstract

translated from Japanese

(57) Abstract: Adrenocorticotropin-releasing factor (CRF) antagonists of formula (I) or (II) and associated with immunological, cardiovascular or cardiac diseases and psychopathological disorders and stress Its use in the treatment of anxiety, depression, and other psychiatric and neurological disorders as well as in the treatment of colon hypersensitivity. Embedded image (I) (II)

Classifications

C07D487/04 Ortho-condensed systems

View 19 more classifications

JP2002501922A

Japan

Find Prior Art Similar

Other languages: Japanese

Inventor: リチャ, ポール ポリガン, ロバート チョーバット, アルリオス ゲオルジオス アーバニティス

Worldwide applications

1999 AU NZ DK BR AT ES PT CN DK DE PL CA PT JP WO IL CN ES NZ SI EP CA DE SG KR EP AT SI TW 2004 HK

Application JP2000529335A events

1999-01-28 Application filed by ザ ジョンズ ホプキンス ユニバーシティ スクール オブ メディシン

2002-01-22 Publication of JP2002501922A

2006-03-16 Publication of JP2002501922A5

2009-02-25 Application granted

2009-02-25 Publication of JP4228332B2

2019-01-28 Anticipated expiration

Status Expired - Fee Related

Show all events

Info: Patent citations (5), Cited by (29), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

Claims (7)

Hide Dependent

translated from Japanese

[Claims] 1. A compound represented by the following formula (50): Formula (50) and its isomers, its stereoisomers, or its mixture of stereoisomers, and

A pharmaceutically acceptable salt of ^{Three}Is -NHCH ($CH_{Two}CH_{Two}$OMe) (CH_{Two}OMe), R^{4a}Is Me, R^{4b}Is H

, R^{4c}Is Me, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is -NHCH (Et)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes R^{4e}R is a compound of formula (50),^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Et) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Pr) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Bu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Me, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes $R^{4e}R$ is a compound of formula (50), ^{Three}is 2-ethylpiperid-1-yl, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is cyclobutylamino, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) $CH_{Two}CH = CH_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Et) $CH_{Two}CH = CH_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) $CH_{Two}cPr$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is M

e and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Et) $CH_{Two}cPr$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is M

e and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Pr) $CH_{Two}cPr$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is M

e and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) Pr, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) Et, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) Bu, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) propargyl, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Et) propargyl, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is O

Me, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, R^{4c} is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Me, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Et, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Pr, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OM

e, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is ·NHCH $(Et)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me

And $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH $(cPr)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me

And $R^{4e}R$ is a compound of formula (50), ^{Three}is ·NHCH $(Et)_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H

And $R^{4e}R$ is a compound of formula (50), ^{Three}is 2-ethylpiperid-1-yl, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is cyclobutylamino, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) $CH_{Two}CH = CH_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Et) $CH_{Two}CH = CH_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) $CH_{Two}cPr$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d}But

H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Et) $CH_{Two}cPr$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d}But

H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Pr) $CH_{Two}cPr$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d}But

H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) Pr, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) Et, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) Bu, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) propargyl, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Et) propargyl, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, $R^{4a}$is OMe, $R^{4b}$is H, R^{4c}But

OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{Four\ c}$ is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Me, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Et, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Pr, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is O

Me, $R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe,

$R^{4d}$is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH $(cPr)_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H

And $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH $(Et)_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me

And $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(Et)_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me

$R^{4e}R$ is a compound of formula (50), ^{Three}is 2-ethylpiperid-1-yl, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is cyclobutylamino, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) $CH_{Two}CH = CH_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Et) $CH_{Two}CH = CH_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) $CH_{Two}cPr$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d}But

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Et) $CH_{Two}cPr$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d}But

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Pr) $CH_{Two}cPr$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d}But

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) Pr, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) Et, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) Bu, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Me) propargyl, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N (Et) propargyl, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, $R^{4a}$is OMe, $R^{4b}$is H, R^{4c}But

OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{Four\ c}$ is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Me, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Et, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Pr, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is O

Me, $R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe,

$R^{4d}$is Me and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH $(cPr)_{Two}$, $R^{4a}$is OMe, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is M

e and R^{4e}R is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is Me and R^{4e}R is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me

And R^{4e}R is a compound of formula (50), ^{Three}Is N $(Et)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me

R^{4e}R is a compound of formula (50), ^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50), ^{Three}Is N (Me) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50), ^{Three}Is N (Et) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50), ^{Three}Is N (Pr) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50), ^{Three}Is N (Me) Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N (Me) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N (Me) Bu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N (Me) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N (Et) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}R is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is H and R^{4e}R is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is H and R^{4e}R is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}R is a compound of formula (50), ^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes R^{4e}R is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Et) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Pr) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) Bu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Et) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e} Wherein R is OMe, a compound of formula (50) ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is cyclobutylamino, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Et) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Pr) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) Bu, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Me) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N (Et) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50) ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe,

a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) Me, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}Wherein R is OMe, a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50),^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is H and R^{4e}Wherein R is OMe, a compound of formula (50),^{Three}Is NHCH ($cPr)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes R^{4e}Wherein R is OMe, a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

H and R^{4e}Wherein R is OMe, a compound of formula (50),^{Three}Is NHCH ($Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}Wherein R is OMe, a compound of formula (50),^{Three}Is N ($Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e} Wherein R is OMe, a compound of formula (50),^{Three}Is NHCH ($Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}R is a compound of formula (50),^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is cyclobutylamino, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Bu, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) Me, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH ($cPr)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH ($Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}R is a compound of formula (50),^{Three}Is N ($Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e} R is a compound of formula (50),^{Three}Is NHCH ($Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

R^{4e}R is a compound of formula (50),^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and R^{4e}R is a compound of formula (50),^{Three}Is cyclobutylamino, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is F and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is F and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

And R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

And R^{4e}R is a compound of formula (50),^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

And R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Bu, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is F and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is F and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) Me, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is F and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is F and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is F and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe$) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is F and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Cl, R^{4b}Is F, R^{4c}Is OMe, R^{4d} Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH ($cPr)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

Yes R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

F and R^{4e}R is a compound of formula (50),^{Three}Is NHCH ($Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

R^{4e}R is a compound of formula (50),^{Three}Is N ($Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and R^{4e} R is a compound of formula (50),^{Three}Is NHCH ($Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And R^{4e}R is a compound of formula (50),^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and R^{4e}R is a compound of formula (50),^{Three}Is cyclobutylamino, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM e and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

And R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Bu, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM

e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

$R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is cyclobutylamino, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and $R^{4c}R$ is a compound of formula (50), ^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Pr, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Et, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Bu, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) propargyl, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM

e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

$R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Bu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM

e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And ^{3e}A compound of formula (50) wherein R is H; ^{Three}Is N $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

R^{4c}Is selected from the group consisting of compounds of the formula (59) wherein

isomers, or mixtures of stereoisomers thereof, and pharmaceutically acceptable salts thereof. 2. A compound represented by the following formula (60): A compound of the formula (60) and its isomers, its stereoisomers, or a mixture of its stereoisomers, and a pharmaceutically acceptable salt thereof, wherein R^3 is NHCH $(Et)_2$ and Ar is 6 A compound of formula (60) which is -dimethylamino-4-methylpyrid-3-yl, a formula wherein R^3 is 2-ethylpiperid-1-yl and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of the formula (60), wherein R^3 is cyclobutylamino and Ar is 6-dimethylamino-4-methylpyrid-3-yl, wherein R^3 is N (Me) CH_2 CH = A compound of formula (60) wherein CH_2 is Ar and 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N (Et) CH_2 cPr and Ar is 6-dimethylamino-4 -Methylpyrid-3-yl Certain compounds of Formula (60), R^3 is $_{N\ (Pr)\ CH\ 2\ cPr,}$ Ar is 6-dimethylamino-4-methylpyrid-3-yl compound of formula (60) is, R^3 is N (Me) A compound of formula (60) wherein Pr is Ar and 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N (Me) Et and Ar is 6-dimethylamino-4-methylpyrid- 3-yl compound of formula (60), R^3 is N (Me) Bu, Ar is 6-dimethylamino-4-methylpyrid - 3-yl compound of formula (60) is, R^3 is N (Me) propargyl, a compound of formula (60) wherein Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 is N (Et) propargyl and Ar is 6-dimethylamino-4 -Methylpyrid-3-yl Compounds of formula (60), R^3 is $_{NHCH\ (CH\ 3)\ CH\ (CH}$ 3) CH 3, compounds of formula (60) Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 There are $_{N\ (CH\ 2\ CH\ 2\ OMe)}$ CH 2 CH = CH 2, Ar is 6-dimechirua amino-4-methylpyrid-3-yl compound of formula (60) is, R^3 is N (CH_2 CH_2 OMe) Me, a compound of formula (60) wherein Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 is N (CH_2 CH_2 OMe) Et and Ar is 6-dimethyl compounds of formula (60) is amino-4- main Chirupiridо-3-yl, R^3 is $_{N\ (CH\ 2\ CH\ 2\ OMe)}$ Pr, in which Ar is 6-dimethylamino-4-menu Chirupiridо 3-yl A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) a CH_2 cPr, Ar is 6-dimethylamino -

A compound of formula (60) that is 4-methylpyrid-3-yl; a compound of formula (60) wherein R^3 is NHCH (CH_3) CH_2 CH_3 and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of formula (60) wherein R^3 is NHCH $(cPr)_2$ and Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) $_2$ Wherein Ar is 6-dimethylamino-4-methylpyrid-3-yl; R ^{3} is NHCH $(Et)_2$, and Ar is 6-dimethylamino-4-methylpyrid-3-yl. A compound of formula (60), wherein R^3 is N $(Et)_2$ and Ar is 6-dimethylamino-4-methylpyrido-3-

Yl compound of formula (60) is, R^3 is 2-Echirupiperido-1-yl, the compounds of formula (60) Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 is cyclo Butylamino, Ar is 6-dimethylamino-4-methylpyrid-3-yl, a compound of formula (60), wherein R^3 is N (Me) CH_2 CH = CH_2 and Ar is 6-dimethyl A compound of formula (60) that is amino-4-methylpyrid-3-yl, wherein R ^{3} is N (Et) CH_2 cPr and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of formula (60) wherein R^3 is N (Pr) CH_2 cPr and Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N (Me) Pr, Yes, Ar is 6-dimethylamino-4 Methylpyrid - 3-yl compound of formula (60) is, R^3 is N (Me) Et, Ar is 6-dimethylamino-4-methylpyrid - 3-yl compound of formula (60) is, R^3 is N (Me) Bu, Ar is 6-dimethylamino-4-methylpyrid-3-yl, a compound of formula (60), R^3 is N (Me) propargyl, and Ar is 6-dimethylamino- A compound of formula (60) which is 4-methylpyrid-3-yl, wherein R^3 is NHCH (CH_3) CH (CH_3) CH_3 and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) CH_2 CH = CH_2 and Ar is 6-dimethylamino-4-methylpyrid-3-yl R^3 is N (CH_2 CH_2 OM) e) a compound of formula (60) wherein Me is and Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 is N (CH_2 CH_2 OMe) Et and Ar is 6-dimethyl A compound of formula (60) which is amino-4-methylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) Pr and Ar is 6-dimethylamino-4-methylpyrid-3-yl; A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) CH_2 cPr and Ar is 6-dimethylamino-

A compound of formula (60) that is 4-methylpyrid-3-yl; a compound of formula (60) wherein R^3 is NHCH (CH_3) CH_2 CH_3 and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of formula (60) wherein R^3 is NHCH $(cPr)_2$ and Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) $_2$ Wherein Ar is 6-dimethylamino-4-methylpyrid-3-yl; R ^{3} is NHCH $(Et)_2$, and Ar is 6-dimethylamino-4-methylpyrid-3-yl. A compound of formula (60), wherein R^3 is N $(Et)_2$ and Ar is 6-dimethylamino-4-methylpyrido-3-

Yl compound of formula (60) is, R^3 is 2-Echirupiperido-1-yl, the compounds of formula (60) Ar is 6-methoxy-4-methyl-pyrid-3-yl, R^3 is cyclo butyl amino, Ar is 6-methoxy-4-methylpyrido -3 - compound of formula (60) is yl, R^3 is $_{N\ (Me)\ CH\ 2\ CH\ =}$ CH 2, Ar is 6-methoxy-4 A compound of formula (60) which is -methylpyrid-3-yl, wherein R^3 is N (Et) CH_2 cPr and Ar is 6-methoxy-4-methylpyrido-

A compound of formula (60) that is 3-yl, wherein R^3 is N (Pr) CH_2 cPr and Ar is 6-methoxy-4-methylpyrido-

A compound of formula (60) wherein R^3 is N (Me) Pr and Ar is 6-methoxy-4-methylpyrid-3-yl; R^3 is N; (Me) Et, a compound of formula (60) wherein Ar is 6-methoxy-4-methylpyrid-3-yl, R^3 is N (Me) Bu and Ar is 6-methoxy-4-methylpyrido 3 compound Lee Le a is formula (60), R^3 is N (Me) propargyl, compound of formula (60) Ar is 6-methoxy-4-methylpyrid-3-yl, R^3 is N (Et) propargyl; a compound of formula (60) wherein Ar is 6-methoxy-4-methylpyrid-3-yl; R^3 is NHCH (CH_3) CH (CH_3) CH_3 ; and Ar is 6-methoxy-4-

Methylpyrid-3-yl compound of formula (60) is, R^3 is $_{N\ (CH\ 2\ CH\ 2\ OMe)}$ CH 2 CH = CH 2, Ar is 6-methoxy - 4-methylpyrid-3-yl and is formula A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) Me and Ar is 6-methoxy-4-methylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) Et, a compound of formula (60) wherein Ar is 6-methoxy-4-methylpyrid-3-yl, R^3 is N (CH_2 CH_2 OMe) Pr and Ar is 6 A compound of formula (60) which is -methoxy-4-methylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) CH_2 cPr and Ar is 6-methoxy 4-methylpyrid-3-yl compounds of formula (60) is, R^3 is NHCH (CH_3) An H_2 CH_3, Ar is a compound of formula (60) is 6-methoxy-4-methylpyrid-3-yl, R^3 is NHCH $(cPr)_2$, Ar is 6-methoxy-4-methylpyrido - 3

- yl, compound of formula (60), R^3 is $_{N\ (CH\ 2\ CH\ 2\ OMe)}$ 2, the compound of formula (60) Ar is 6-methoxy-4-methylpyrid-3-yl, R^3 is NHCH $(Et)_2$ and Ar is 6-methoxy-4-methylpyrido-3-

A compound of formula (60) wherein R^3 is N $(Et)_2$ and Ar is 6-methoxy-4-methylpyrid-3-yl, R^3 is 2-ethylpiperid- 1 is yl, compounds of formula (60) Ar is 4-methoxy-6-methyl-pyrid-3-yl, R^3 is cyclobutylamino, Ar is 4-methoxy-6-methylpyrid -3 - A compound of formula (60) wherein R^3 is N (Me) CH_2 CH CH_2 and Ar is 4-methoxy-6-methylpyrid-3-yl; ^{3} is N (Et) CH_2 cPr, and Ar is 4-methoxy-6-methylpyrido-

A compound of formula (60) that is 3-yl, wherein R^3 is N (Pr) CH_2 cPr and Ar is 4-methoxy-6-methylpyrido-

3-yl compound of formula (60), R^3 is N (Me) Pr, the compound of formula (60) Ar is 4-methoxy-6-methylpyrid-3-y le, R^3 is N (Me) is Et, compound of formula (60) Ar is 4-methoxy-6-methylpyrid-3-y le, R^3 is N (Me) Bu, Ar is 4-methoxy-6-methylpyrid 3 compound Lee Le a is formula (60), R^3 is N (Me) propargyl, compound of formula (60) Ar is 4-methoxy-6-methylpyrid-3-yl, R^3 is NHCH (CH_3) CH (CH_3) CH_3 , wherein Ar is 4-methoxy-6-

Methylpyrid-3-yl compound of formula (60) is, R^3 is $_{N\ (CH\ 2\ CH\ 2\ OMe)}$ CH 2 CH = CH 2, Ar is 4-methoxy - 6-methylpyrid-3-yl and is formula A compound of formula (60), wherein R^3 is N (CH_2 CH_2 OMe) Me and Ar is 4-methoxy-6-methylpyrid-3-yl, R^3 is N (CH a $_2$ CH_2 OMe) Et, Ar is 4-methoxy-6-methylpiperazin chloride 3-yl compound of formula (60) is, R^3 is $_{N\ (CH\ 2\ CH\ 2\ OMe)}$ Pr, Ar is 4 -Methoxy-6-methylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) CH_2 cPr and Ar is 4-methoxy-6-methylpyrid-3-yl compounds of formula (60) is, R^3 is NHCH (CH_3) An H_2 CH_3, Ar is 4-methoxy-6-methylpyrid-3-yl compound of formula (60) is, R^3 is NHCH $(cPr)_2$, Ar is 4-methoxy-6-methylpyrid - 3

- yl, compound of formula (60), R^3 is $_{N\ (CH\ 2\ CH\ 2\ OMe)}$ 2, the compound of formula (60) Ar is 4-methoxy-6-methylpyrid-3-yl, R^3 is NHCH $(Et)_2$ and Ar is 4-methoxy-6-methylpyrido-3-

A compound of formula (60) wherein R^3 is N $(Et)_2$ and Ar is 4-methoxy-6-methylpyrid-3-yl, R^3 is 2-ethylpiperido- A compound of the formula (60) wherein R 1 is 1-yl and Ar is 4,6-

dimethylpyrid-3-yl; a compound of the formula (60) wherein R^3 is cyclobutylamino and Ar is 4,6-dimethylpyrid-3-yl A compound of formula (60) wherein R^3 is N (Me) CH_2 CH = CH_2 and Ar is 4,6-dimethylpyrid-3-yl; R^3 is N (Et) CH_2 a compound of formula (60) wherein cPr is Ar and 4,6-dimethylpyrid-3-yl; R^3 is N (Pr) CH_2 cPr and Ar is 4,6-dimethylpyrid-3-yl A compound of the formula (60): wherein R^3 is N (Me) Pr, a compound of formula (60) wherein r is 4,6-dimethylpyrid-3-yl; a compound of formula (60) wherein R^3 is N (Me) Et and Ar is 4,6-dimethylpyrid-3-yl R^3 is N (Me) Bu and Ar is 4,6-dimethylpyrid-3-yl A compound of formula (60), wherein R^3 is N (Me) propargyl and Ar is 4,6-dimethylpyrido A compound of formula (60) wherein R^3 is N (Et) propargyl and Ar is 4,6-dimethylpyrid-3-yl; R^3 is NHCH A compound of formula (60) wherein (CH_3) CH (CH_3) CH_3 and Ar is 4,6-dimethylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) CH_2 CH = CH_2, wherein Ar is 4,6-dimethylpyrid-3-yl A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) Me and Ar is 4,6-dimethylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) Et, a compound of formula (60) wherein Ar is 4,6-dimethylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) Pr and Ar is 4,6-dimethylpyrid-3 - yl. compound of formula (60), R^3 is $_{N\ (CH\ 2\ CH\ 2\ OMe)}$ CH 2 cPr, compounds of formula (60) Ar is 4,6-dimethylpyrid-3-yl, R^3 Is NHCH (CH_3) CH_2 CH_3 and Ar is 4,6-dimethylpyrido-3

A compound of formula (60) wherein R^3 is NHCH (cPr) $_2$ and Ar is 4,6-dimethylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) is $_2$, Ar is a compound of formula (60) is 4,6-dimethylpyrid-3-yl, R ^{3} is NHCH (Et) $_2$, in which Ar is 4,6-dimethylpyrid-3-yl A compound of the formula (60), wherein R^3 is N (Et) $_2$ and Ar is 4,6-dimethylpyrid-3-yl

A compound of formula (60) wherein R^3 is 2-ethylpiperid-1-yl and Ar is 2,6-dimethylpyrid-3-yl; R^3 is cyclobutylamino and Ar is 2 A compound of formula (60) wherein R^3 is N (Me) CH_2 CH C HCH $_2$ and Ar is 2,6-dimethylpyrid-3-yl A compound of formula (60) wherein R^3 is N (Et) CH_2 cPr and Ar is 2,6-dimethylpyrid-3-yl; R^3 is N (Pr) CH_2 cPr, A compound of the formula (60) wherein R^3 is N (Me) Pr and Ar is 2,6-dimethylpyrid-3-yl; R^3 is N (Me) Et, Ar is 2,6-dimethylol Pyrid-3-yl compound of formula (60) is, R^3 is N (Me) Bu, compounds of formula (60) Ar is 2,6-dimethylpyrid-3-yi, R^3 is N (Me) a compound of formula (60) which is propargyl and Ar is 2,6-dimethylpyrid-3-yl, wherein R^3 is NHCH (CH_3) CH (CH_3) CH $_3$ and Ar is 2,6 A compound of formula (60) which is -dimethylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) CH_2 CH = CH_2 and Ar is 2,6-dimethylpyrid-3-yl A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) Me and Ar is 2,6-dimethylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) Et and Ar is 2,6-dimethylpyrid-3-yl Compound (60), R^3 is $_{N\ (CH\ 2\ CH\ 2\ OMe)}$ Pr, Ar is 2,6-dimethylpyrid-3 - compound of formula (60) is yl, R^3 is N (CH_2 CH_2 OMe) a compound of formula (60) wherein CH_2 cPr is Ar and 2,6-dimethylpyrid-3-yl; R^3 is NHCH (CH_3) CH_2 CH_3 and Ar is 2,6-dimethylpyrido -3

A compound of formula (60) wherein R^3 is NHCH (cPr) $_2$ and Ar is 2,6-dimethylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) is $_2$, Ar is a compound of formula (60) is 2,6-dimethylpyrid-3-yl, R ^{3} is NHCH (Et) $_2$, in which Ar is 2,6-dimethylpyrid-3-yl A compound of the formula (60) and a compound of the formula (^{3}) wherein R^3 is N (Et) $_2$ and Ar is 2,6-dimethylpyrid-3-yl 60) The compound selected from the group consisting of, and a isomer, a stereoisomer thereof, or a mixture of the stereoisomers, and a pharmaceutically acceptable salt thereof. 3. A compound selected from the group shown below, its isomer, its stereoisomer, or a mixture of its stereoisomers, and a pharmaceutically acceptable salt thereof. 4-((2-butyl) amino) -2,7-dimethyl-8- (2-methyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- ((2-butyl) amino) -2,7-dimethyl-8- (2,5-dimethyl-
4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4-((3-pentyl) amino) -2,7-dimethyl-8- (2,5-dimethyl-4 -Methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4-((3-pentyl) amino) -2,7-dimethyl-8- (2-methyl-4-
Methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- (N-cyclopropylmethyl-N-propylamino) -2,7-dimethyl-
8- (2-methyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,
3,5-triazine 4- (N-cyclopropylmethyl-N-propylamino) -2,7-dimethyl-
8- (2,5-dimethyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- (N-allyl-N- (2-methoxyethyl) amino)- 2,7-dimethyl-
8- (2-methyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,
3,5-triazine 4- (N-allyl-N- (2-methoxyethyl) amino) -2,7-dimethyl-
8- (2,5-dimethyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- (diallylamino) -2,7-dimethyl-8- (2- Methyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- (diallylamino) -2,7-dimethyl-8- (2,5-dimethyl-4-methoxy Phenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- (N-ethyl-N- (2-methoxyethyl) amino) -2,7-dimethyl-
8- (2-methyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,
3,5-triazine 4- (N-ethyl-N- (2-methoxyethyl) amino) -2,7-dimethyl-
8- (2,5-dimethyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- A compound represented by the following formula (70): Formula (70) and its isomers, its stereoisomers, or its mixture of stereoisomers,

A pharmaceutically acceptable salt of the compound, wherein R is Cl, R^{Three}Is -NHCH $(n\text{-}Pr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me

, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is M

e, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (cPr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is M

e, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d} Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H

And R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (n-Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (n-Bu) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH (n-Pr) $(CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}But

H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, $R^{4c}$is OMe,

R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, $R^{Three}$is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me,

R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me, R^{4b}But

H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is C

l, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NH (Et), $R^{4a}$is Me, $R^{4b}$is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(n\text{-}Pr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, $R^{4c}$is Cl

, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me,

R^{4b}Is H, R^{4c}Is Cl, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NH ($CH_{Two}CH_{Two}OMe$) $CH_{Two}OMe$, R^{4a}Is Me, R^{4b}But

H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (n-Pr) ($CH_{Two}CH_{Two}CN$), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is (S) -NH ($CH_{Two}CH_{Two}OMe$) $CH_{Two}OMe$, R^{4a}Is Cl,

R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NH ($CH_{Two}CH_{Two}OMe$) $CH_{Two}OMe$, R^{4a}Is Cl, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H

And R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (cPr) ($CH_{Two}CH_{Two}CN$), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (cPr) ($CH_{Two}CH_{Two}CN$), R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH (n-Pr) ($CH_{Two}OMe$), R^{4a}Is Me, R^{4b}But

H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH (n-Pr) ($CH_{Two}OMe$), R^{4a}Is Cl, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is OMe and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, $R^{4d}$is H

And R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

OMe and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, $R^{4a}$is Cl, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is OMe and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is C

l, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Pr) ($CH_{Two}CH_{Two}CN$), R^{4a}Is Cl, R^{4b}Is H, $R^{Four\ c}$ is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Bu) (Et), R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH (Et) $CH_{Two}OMe$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d} is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d} is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d} Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NEt$_{Two}$, R^{4a}Is Me, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is H

Yes R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Pr) ($CH_{Two}CH_{Two}CN$), $R^{4a}$is Me, $R^{4b}$is H, $R^{Four\ c}$ Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH (n-Pr)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me

, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, R^{4c}Is M

e, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (cPr) ($CH_{Two}CH_{Two}CN$), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is M

e, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, $R^{4a}$is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d} is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, $R^{4d}$is H

And R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (n-Pr) ($CH_{Two}CH_{Two}CN$), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (n-Bu) ($CH_{Two}CH_{Two}CN$), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH (n-Pr) ($CH_{Two}OMe$), R^{4a}Is Me, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is (S) -NH ($CH_{Two}CH_{Two}OMe$) $CH_{Two}OMe$, R^{4a}Is Me,

R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH ($CH_{Two}CH_{Two}OMe$) $CH_{Two}OMe$, R^{4a}Is Me, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is C

l, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH (Et), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH (n-Pr)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl

, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is (S) -NH ($CH_{Two}CH_{Two}OMe$) $CH_{Two}OMe$, R^{4a}Is Me,

R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH ($CH_{Two}CH_{Two}OMe$) $CH_{Two}OMe$, R^{4a}Is Me, R^{4b}But

H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (n-Pr) ($CH_{Two}CH_{Two}CN$), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Et)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is (S) -NH ($CH_{Two}CH_{Two}OMe$) $CH_{Two}OMe$, R^{4a}Is Cl,

R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH ($CH_{Two}CH_{Two}OMe$) $CH_{Two}OMe$, R^{4a}Is Cl, R^{4b}But

H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N $(Et)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Me, $R^{4d}$is H

And R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N (cPr) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N (cPr) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH (n-Pr) $(CH_{Two}OMe)$, $R^{4a}$is Me, R^{4b}But

H, $R^{4c}$is OMe, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH (n-Pr) $(CH_{Two}OMe)$, $R^{4a}$is Cl, R^{4b}But

H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Br, $R^{4b}$is H, $R^{4c}$is OMe,

$R^{4d}$is OMe and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Br, $R^{4b}$is H, $R^{4c}$is OMe,

$R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is Br, $R^{4b}$is H, $R^{4c}$is O

Me, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH $(CH_{Two}OMe)_{Two}$, $R^{4a}$is Br, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N $(Et)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Cl, $R^{4d}$is H

And R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N $(Et)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d}But

OMe and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is OMe,

$R^{4d}$is OMe and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is C

l, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH $(CH_{Two}OMe)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Cl, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N (Pr) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{Four\ c}$ is Cl, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N (Bu) (Et), $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Cl, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH (Et) $CH_{Two}OMe$, $R^{4a}$is Cl, $R^{4b}$is H, R^{4c} is Cl, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Cl, R^{4d} is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Me, R^{4d} is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Me, R^{4d} is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Cl, R^{4d} is H and R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -NEt$_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H

Yes R^{4e}A compound of the formula (70) wherein R is Me, $R^{Three}$is -N (Pr) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Me, $R^{4b}$is H, $R^{Four\ c}$ is OMe, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH (n-Pr)$_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Me,

$R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH $(CH_{Two}OMe)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Me

, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N (cPr) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Me, $R^{4b}$is H, $R^{Four\ c}$ is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Me

, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH $(CH_{Two}OMe)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Me, R^{4d} is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N $(Et)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Me, $R^{4d}$is H

Yes R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N (n-Pr) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N (n-Bu) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH (n-Pr) $(CH_{Two}OMe)$, $R^{4a}$is Me, $R^{4b}$is H

, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d} is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH $(CH_{Two}OMe)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is O Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, $R^{4a}$is Me, R^{4b} is H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, $R^{4a}$is Me, $R^{4b}$is H

, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Cl

, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NH (Et), $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH (n-Pr)$_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Cl,

$R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH $(CH_{Two}OMe)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Cl, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, $R^{4a}$is Me, R^{4b} is H, $R^{4c}$is Cl, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, $R^{4a}$is Me, $R^{4b}$is H

, $R^{4c}$is Cl, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N (n-Pr) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N (Et)$_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{4d}$is H

And R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, $R^{4a}$is Cl, R^{4b} is H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, $R^{4a}$is Cl, $R^{4b}$is H

, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N $(Et)_{Two}$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{4c}$is Me, $R^{4d}$is H

Yes R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N (cPr) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Me, $R^{4b}$is H, $R^{Four\ c}$ is OMe, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N (cPr) $(CH_{Two}CH_{Two}CN)$, $R^{4a}$is Cl, $R^{4b}$is H, $R^{Four\ c}$ is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH (n-Pr) $(CH_{Two}OMe)$, $R^{4a}$is Me, $R^{4b}$is H

, $R^{4c}$is OMe, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH (n-Pr) $(CH_{Two}OMe)$, $R^{4a}$is Cl, $R^{4b}$is H

, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Br, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d} is OMe and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH $(Et)_{Two}$, $R^{4a}$is Br, $R^{4b}$is H, $R^{4c}$is OMe, R^{4d} is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is Br, $R^{4b}$is H, $R^{4c}$is OM

e, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -NHCH $(CH_{Two}OMe)_{Two}$, $R^{4a}$is Br, $R^{4b}$is H, $R^{4c}$is O Me, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, $R^{Three}$is -N $(Et)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Cl, $R^{4d}$is H

Yes R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is OMe and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl

, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is Cl, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N (Bu) (Et), R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, $R^{Four\ d}$ Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NHCH (Et) $CH_{Two}OMe$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}But

Cl, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d} is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d} Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d} Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d} is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NEt_{Two}, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H

R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c} is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Et) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Me) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, $R^{Three}$is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Et) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Me) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N (Et) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N (Me) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NMePr, R^{4a}Is Me, $R^{4b}$is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NH-2-butyl, R^{4a}Is Me, $R^{4b}$is H, $R^{4c}$is OMe, $R^{Four\ d}$ is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N (Et) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -N (Me) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is Me and R^{4e}A compound of formula (70) wherein R is F, ^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Et) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Me) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Et) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Me) $(CH_{Two}CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}Is selected from the group consisting of the compounds of the formula (70) wherein

isomers, or mixtures of stereoisomers thereof, and pharmaceutically acceptable salts thereof. 5. 7- (Diethylamino) -2,5-dimethyl-3- (2-methyl-4-methoxyphenyl- [1,5-a] -pyrazolopyrimidine and 7- (diethylamino) -2,5-dimethyl-3- (2-methyl-4-methoxyphenyl- [1,5-a] -pyrazolopyrimidine)

(N- (3-cyanopropyl) -N-propylamino) -2,5-dimethyl-3

A compound selected from (2,4-dimethylphenyl) [1,5-a] -pyrazolopyrimidine and its isomer, its stereoisomer, or a mixture of its stereoisomers, and its pharmaceutically acceptable salts. 6. A pharmaceutically acceptable carrier and a therapeutically effective amount of claim 1.

A pharmaceutical composition comprising the compound according to 2, 3, 4, and 5. 7. Affective disorder, anxiety, depression, headache, irritability comprising administering to a mammal a therapeutically effective amount of a compound according to claims 1, 2, 3, 4 and 5. Bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa or other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory disease, cardiovascular disease or Heart disease, fertility problems, human immunodeficiency virus (HIV) infection, hemorrhagic stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcer, amyotrophic lateral sclerosis, hypoglycemia Or a method of treating a mammal, such as, but not limited to, a disorder induced or promoted by CRF, wherein treatment of the disorder is achieved or facilitated by antagonism with CRF.

Description translated from Japanese

DETAILED DESCRIPTION OF THE INVENTION

TECHNICAL FIELD [0001] The present invention relates to certain [1,5-a] -pyrazolo-1,3,5-triazines,
[1,5-a] -1,2,3-triazolo-1,3,5-triazines, [1,
immunological, cardiovascular or heart disease, and psychopathological by administering 5-a] -pyrazolo-pyrimidines and [1,5-a] -1,2,3-triazolo-pyrimidines Treatment of psychiatric and neurological disorders, including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and eating disorders, as well as treatment of disability and stress-related colon hypersensitivity. Regarding treatment.

BACKGROUND OF THE INVENTION [0002] Adrenocorticotropic hormone-releasing factor (hereinafter referred to as CRF) is a peptide consisting of 41 amino acids and is derived from pro-opiomelanocortin (POM) from the anterior pituitary gland.
C) is a major physiological regulator of peptide secretion from J. Rivier et al., Proc.
Nat. Acad. Sci. (USA), 80, 4851, 1983; W. Vale et al., Science
213, 1394, 1981). In addition to the endocrine role in the pituitary gland, the immunohistochemical localization of CRF indicates that this hormone is widely distributed outside the hypothalamus of the central nervous system and is consistent with the role of neurotransmitters or neuromodulators in the brain. While producing a wide range of autonomic, electrophysiological and behavioral effects (W. Val
e, et al., Rec. Prog. Horm. Res. 39, 245, 1983; GF Koob, Persp. Be
hav. Med. 2, 39, 1985; EB De Souza et al., J. Neurosci. 5, 3189
Page, 1985). There is also evidence that CRF plays a key role in integrating the immune system response to physiological, psychological and immunological stressors (JE Bla
lock, Physiological Reviews, 69, 1 page, 1989; JE Morley, Life Sc
i. 41, 527, 1987).

[0003] Clinical data provide evidence that CRF has a role in psychiatric and neurological disorders, including depression, anxiety-related disorders and eating disorders. CRF also plays a role in the pathogenesis and pathophysiology of diseases associated with CRF neuron dysfunction in the central nervous system, such as Alzheimer's disease, Parkinson's disease, Huntington's chorea, progressive supranuclear palsy and amyotrophic lateral sclerosis. Has been assumed (EB D
e Souza, Hosp. Practice, vol. 23, p. 59, 1988).

In emotional disorders or major depression, cerebrospinal fluid (C
CRF concentration in SF) is significantly increased (CB Nemeroff et al., Science, 226, 1
342, 1984; CM Banki et al., Am. J. Psychiatry, 144, 873, 198
7 years; RD France et al., Biol. Psychiatry, 23, 86, 1988; M. Arato et al., Biol Psychiatry, 25, 355, 1989). In addition, CRF receptor density in the suicide's frontal cortex was also significantly reduced, consistent with CRF hypersecretion (CB N
emeroff et al., Arch. Gen. Psychiatry, 45, 577, 1988). In depressed patients, corticotropin (ACT) against CRF (intravenously administered) was also observed.
H) is observed (PW Gold et al., Am. J. Psychiatry, 141, 61),
9, 1984, F. Holsboer et al., Psychoneuroendocrinology, 9, 147, 1984; PW Gold et al., New Eng. J. Med. 314, 1129, 1986). Preclinical studies in rats and non-human primates have also provided results supporting the hypothesis that CRF hypersecretion is involved in the symptoms seen in human depression (RM Sapolsky, Arch. Gen. Psychiatry, 46, 1047, 1989).
There is also preliminary evidence that tricyclic antidepressants alter CRF levels and modulate numerous CRF receptors in the brain (Grigoriadis et al., Neuropsychopharmacology, 2:53, 1989).

[0005] The role of CRF has also been postulated in the etiology of anxiety-related diseases. CRF produces anxiogenic effects in animals, and the interaction between benzodiazepine / non-benzodiazepine anxiolytics and CRF has been demonstrated in various behavioral anxiety models (DR Britton et al., Life Sci. 31). Vol. 363, 1982; C
.W. Berridge and AJ Dunn Regul. Peptides, 16, 83, 1986). Preliminary studies in various behavioral cases using α-helical sheep CRF (9-41), a putative CRF receptor antagonist, have shown that the antagonist is similar to benzodiazepines in "anxiolytic-like" Has been shown to produce an effect (CW Berridg
e and AJ Dunn Horm. Behav. 21, 393, 1987, Brain Research Re
views, vol. 15, p. 71, 1990). Neurochemical, endocrine and receptor binding studies all revealed the interaction between CRF and benzodiazepine anxiolytics and provided further evidence of the involvement of CRF in these diseases. Chlordiazepoxide has been tested in rat conflict tests (KT Britton et al., Psych
opharmacology, 86, 170, 1985; KT Britton et al., Psychopharmacolo
gy, 94, 306, 1988) and acoustic startle test (
NR Swerdlow et al., Psychopharmacology, 88, 147, 1986) alleviate the "anxiety-producing" effects of CRF. A benzodiazepine receptor antagonist (Ro15-1788) lacks behavioral activity only in the operant conflict test, but reverses the effect of CRF in a dose-dependent manner, whereas a benzodiazepine antagonist (FG7142) reverses the effect of CRF. (KT Britton et al., Psychopharmacology, 94, 306, 1988).

[0006] Elucidation of the mechanism and site of action by which ordinary anxiolytics and antidepressants produce therapeutic effects is awaited. However, it has been hypothesized that these drugs are involved in the suppression of CRF hypersecretion found in the disease. Of particular interest are CRF receptor antagonists (α-helix CRF $_{9-41}$) in various behavioral cases

in a preliminary study examining the effects of benzodiazepines, a CRF antagonist showed
(GF Koob and KT Britton, Corticotropin-Releasing Factor. Basic and Clinical Studie).
s of a Neuropeptide, edited by EBDe Souza and CB Nemeroff, CRC Press, p.221, 1990).

[0007] Several publications describe adrenocorticotropic hormone releasing factor antagonist compounds and their use in treating psychiatric disorders and neurological disorders. Such publications include, for example, DuPont Merck PCT application US94 / 11050.
, Pfizer WO95 / 33750, Pfizer WO95 / 34563, Pfizer W
O95 / 33727 and Pfizer EP 0778 277 A1.

To the best of knowledge, [1,5-a] -pyrazolo-1,3,5-triazines,
[1,5-a] -1,2,3-triazolo-1,3,5-triazines, [1,
5-a] -Pyrazolo-pyrimidines and [1,5-a] -1,2,3-triazolo-pyrimidines are useful for treating psychiatric disorders and neurological diseases Adrenocorticotropic hormone-releasing factor antagonists It has never been reported as a compound in the past. However, there were publications teaching the use of some of these compounds for other uses.

For example, EP 0 269 859 (Otsuka, 1988) is represented by the following equation

[0010]

Embedded image

A pyrazolotriazine compound, wherein 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, It is stated that these compounds have xanthine oxidase inhibitory activity and are useful for treating gout.

EP 0 594 149 (Otsuka, 1994) is represented by the following equation:

[0013]

Embedded image

Pyrazolotriazine and pyrazolopyrimidine compounds wherein 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 state that these compounds inhibit androgens and are useful in treating benign prostatic hyperplasia and prostate cancer.

US Pat. No. 3,910,907 (Oct, 1975) is represented by the following formula:

[0016]

Embedded image

In the above equation, R^1 is CH_{Three}, $C_{Two}H_{Five}$ Or C_6H_{Five}, X is H, C_6H_{Five}, M-$CH_{Three}C_6H_{Four}$, CN, COOEt, Cl, I or Br, Y is H, C_6H_{Five}, O-$CH_{Three}C_6H_{Four}$, Or p-$CH_{Three}C_6H_{Four}$And Z is OH, H, CH_{Three}, $C_{Two}H_{Five}$, C_6H_{Five}, N-$C_{Three}H_7$, I-$C_{Three}H_7$, SH, SCH_{Three}, $NHC_{Four}H_9$, Or N ($C_{Two}H_{Five}$)$_{Two}$Which disclose pyrazolotriazines which are useful as bronchodilator c-A.
It states that it is an MP phosphodiesterase inhibitor.

US Pat. No. 3,995,039 is represented by the following formula:

[0019]

Embedded image

In the above formula, 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 pyraziryl. Zolotriazines are disclosed and state that the compounds are useful as bronchodilators.

US Pat. No. 5,137,887 is represented by the following formula:

[0022]

Embedded image

Disclosed are pyrazolotriazines, where R is lower alkoxy, which teaches that these compounds are xanthine oxidase inhibitors and are useful in treating gout.

US Pat. No. 4,892,576 is represented by the following formula:

[0025]

Embedded image

In the above formula, pyrazolo wherein X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, $R_{6\text{-}10}$ R_8 are H, alkyl and the like, and R_9 is H, alkyl, phenyl and the like. Triazines are disclosed. The patent states that the compounds are useful as herbicides and plant growth regulators.

US Pat. No. 5,484,760 and WO 92/10098 are represented by the following formula:

[0028]

Embedded image

In the above formula, A can be N, B can be CR_3, R_3 can be phenyl or substituted phenyl, and R can be $-N(R_4)SO_2R_5$ or $-SO_2N(R_6)R_7$, wherein R_1 and R_2 together

[0030]

Embedded image

Wherein X, Y, and Z are H, alkyl, acyl, and the like, and the herbicidal composition contains a herbicidal compound in which D is O or S in another material. Disclosure.

US Pat. No. 3,910,907 and Senga et al. (J. Med. Chem. 25, 243-
249 pages, 1982) is expressed by the following formula,

[0033]

Embedded image

In the above formula, Z is H, OH, CH_{Three}, $C_{Two}H_{Five}$, C_6H_{Five}, N-$C_{Three}H_7$, Iso-$C_{Three}H_7$, SH, SCH_{Three}, NH (n-$C_{Four}H_9$) Or N ($C_{Two}H_{Five}$)$_{Two}$, R is H or CH_{Three}In $R_1$is OH_{Three}Or $C_{Two}H_{Five}$Which disclose a triazolotriazine cAMP phosphodiesterase inhibitor. This reference contains cAMP phosphodies
Asthma, diabetes mellitus, fertility control in women,
List eight treatment areas for male infertility, psoriasis, thrombosis, anxiety and hypertension
I have.

[0035] WO 95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that these compounds are useful as analgesics. The compound is represented by the following formula:

[0036]

Embedded image

in the above formula, Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R^1 is H, alkyl and the like, and R^2 is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or Phenoxy, R^3 is H, alkyl or phenyl, R^4 is H, alkyl, alkoxycarbonyl, phenylalkyl, phenyl optionally substituted with phenylthio, or halogen, R^5 and R^6 are H or alkyl.

EP 0 591 528 (Otsuka, 1991) is represented by the following formula:

[0039]

Embedded image

Wherein 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. Disclosed are pyrazolopyrimidines for use as anti-inflammatory agents wherein R_6 is pyridyl or an optionally substituted phenyl, and R_7 and R_8 are H or an optionally substituted phenyl.

Springer et al. (J. Med. Chem. 19, No. 2, pp. 291-296, 1976) and Spr.
inger US Patent Nos. 4021,556 and 3,920,652 are represented by the following formulas:

[0042]

Embedded image

In the above formula, pyrazolopyrimidines where R is phenyl, substituted phenyl or pyridyl, and their use for treating gout based on their ability to inhibit xanthine oxidase are disclosed.

Joshi et al. (J. Prakt. Chemie, Vol. 321, No. 2, pp. 341-344, 1979) is represented by the following formula:

[0045]

Embedded image

In the above formula, R^1 is CF_{Three}, $C_{Two}F_{Five}$ Or $C_6H_{Four}F$, R^{Two} is CH_{Three}, $C_{Two}H_{Five}$, CF_{Three} Or C_6H_{Four} Disclosed are compounds that are F.

Maquestiau et al. (Bull. Soc. Belg. 101, No. 2, pp. 131-136, 1992) disclose pyrazolo [1,5-a] pyrimidines of the formula

[0048]

Embedded image

Ibrahim et al. (Arch. Pharm. (Weinheim), Volume 320, pp. 487-491, 1987) are represented by the following formula:

[0050]

Embedded image

In the above formula, pyrazolo [1,5-a] pyrimidines in which R is NH_2 or OH and Ar is 4-phenyl-3-cyano-2-aminopyrid-2-yl are disclosed.

Other references disclosing azolopyrimidines include EP 0 511
528 (Otsuka, 1992), U.S. Pat. No. 4,997,940 (Dow, 1991); EP 0 374 448 (Nissan, 1990); U.S. Pat. No. 4,621,5.
No. 56 (ICN, 1997), EP 0 531 901 (Fujisawa, 1993), U.S. Pat. No. 4,567,263 (BASF, 1986), EP 0 662 477 (
Isagro, 1995), DE 4243 279 (Bayer, 1994), U.S. Patent No. 5,397,774 (Upjohn, 1995), EP 0 521 622 (Upjohn,
1993), WO 94/109017 (Upjohn, 1994), J. Med. Chem. 24
Vol., Pages 610-613, 1981 and J. Het. Chem. 22, page 601, 1985.

SUMMARY OF THE INVENTION In one aspect of the invention, novel compounds, pharmaceutical compositions and affective disorders, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immunosuppression, Alzheimer's disease, Treatment of gastrointestinal disorders, anorexia nervosa or other eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory diseases, fertility problems, etc.
Disorders, including but not limited to CRF-induced or promoted disorders, achieved or facilitated by antagonism to RF, or inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies General anxiety-related disease; panic, phobia, obsessive-compulsive disorder; post-traumatic stress disorder; stress sleep disorder; pain perception such as fibromyalgia; depression, including major depression; Mood disorders such as paroxysmal depression, recurrent depression, child abuse-induced depression, and postpartum depression; mood swings; bipolar disorders; circulatory temperament; fatigue syndrome; stress headaches; , Human immunodeficiency virus (HIV) infection, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's chorea;
Ulcers, irritable bowel syndrome, Crohn's disease, colon spasm, diarrhea, and postoperative ileus and colon irritability associated with psychopathological disorders or stress; eating disorders such as anorexia nervosa or bulimia nervosa; bleeding Sexual stress; stressful psychotic episodes; euthyroid sinus dysfunction syndrome; antidiuretic hormone (ADH) incompatibility syndrome; obesity; infertility, head trauma; spinal cord trauma, Cerebral ischemia, etc.); excitotoxic neuronal damage; epilepsy; cardiovascular and cardiac disorders including hypertension, tachycardia and congestive heart failure etc .; stroke; immune dysfunction including stress-induced immune dysfunction (eg, stressful Fever, pig stress syndrome, bovine shipping fever, paroxysmal fibrillation in horses, and housekeeping-induced dysfunction in chickens, sheep shaving Terres or dogs human - animal interaction stress);
Muscle spasm; urinary incontinence; senile dementia of the Alzheimer type; multi-infarct dementia; amyotrophic lateral sclerosis; chemical dependence or poisoning (eg, to alcohol, cocaine, heroin, benzodiazepines, or other drugs Drug and alcohol withdrawal symptoms; osteoporosis; sociopsychological dwarfism and hypoglycemia.

[0054] The present invention provides a CR by binding to the adrenocorticotropic hormone releasing factor receptor.
Novel compounds that alter the anxiogenic effects of F secretion are provided. The compounds of the present invention are useful for treating immunological, cardiovascular or cardiac diseases in mammals, as well as psychiatric disorders and stress-related colon hypersensitivity, as well as psychiatric and neurological disorders, anxiety-related disorders. It is useful for treating post-traumatic stress disorder, supranuclear palsy and eating disorders.

In another aspect, the present invention provides the novel compounds described below, which are useful as antagonists of corticotropin-releasing factor. Compounds of the present invention show activity as antagonists of corticotropin-releasing factor and appear to suppress CRF hypersecretion.
The present invention relates to a pharmaceutical composition comprising said compound of formulas (1) and (2), and a CR
Also included are methods of using the compounds to inhibit F hypersecretion and / or treat anxiety-producing diseases.

in another aspect of the present invention, the compounds provided by the present invention (and particularly the labeled compounds of the present invention) are used as standards and reagents in determining the potential of a potential drug to bind to the CRF receptor. Is also useful.

(Detailed Description of the Invention) [1] The present invention provides a compound represented by the following formula (50):

[0058]

Embedded image Equation (50)

And its isomers, its stereoisomers, or a mixture of its stereoisomers, and

A pharmaceutically acceptable salt thereof, wherein R^{Three} is -NHCH ($CH_{Two}CH_{Two}OMe$) ($CH_{Two}OMe$), R^{4a} is Me, R^{4b} is H

, R^{4c} is Me, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is -NHCH (Et)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H

Yes $R^{4e}R$ is a compound of formula (50), ^{Three} is 2-ethylpiperid-1-yl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) $CH_{Two}cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H

And $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Et) $CH_{Two}cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H

And $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Pr) $CH_{Two}cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H

And $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) Pr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) Et, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) Bu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) propargyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Et) propargyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a} is Me, R^{4b} is H, R^{4c} is O

Me, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) $CH_{Two}CH = CH_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) Me, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) Et, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) Pr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) $CH_{Two}cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OM

e, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is NHCH (cPr)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H

Yes $R^{4e}R$ is a compound of formula (50), ^{Three} is 2-ethylpiperid-1-yl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is cyclobutylamino, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) $CH_{Two}cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is M

e and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Et) $CH_{Two}cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is M

e and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Pr) $CH_{Two}cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is M

e and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) Pr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) Et, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) Bu, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) propargyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Et) propargyl, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a} is Me, R^{4b} is H, R^{4c} is O

Me, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) $CH_{Two}CH = CH_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) Me, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) Et, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) Pr, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, $R^{Four\ d}$ is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is N ($CH_{Two}CH_{Two}OMe$) $CH_{Two}cPr$, R^{4a} is Me, R^{4b} is H, R^{4c} is OM

e, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and $R^{4e}R$ is a compound of formula (50), ^{Three} is -NHCH (Et)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me

And $R^{4e}R$ is a compound of formula (50), ^{Three} is NHCH (cPr)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me

And $R^{4e}R$ is a compound of formula (50), ^{Three} is -NHCH (Et)$_{Two}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H

And $R^{4e}R$ is a compound of formula (50), ^{Three} is 2-ethylpiperid-1-yl, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is cyclobutylamino, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) $CH_{Two}cPr$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d}But

H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Et) $CH_{Two}cPr$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d}But

H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Pr) $CH_{Two}cPr$, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d}But

H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) Pr, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) Et, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) Bu, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Me) propargyl, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is N (Et) propargyl, R^{4a} is OMe, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and $R^{4e}R$ is a compound of formula (50), ^{Three} is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a} is OMe, R^{4b} is H, R^{4c}But

OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is OMe, R^{4b}Is H, $R^{Four\ c}$ is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4d}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me

And R^{4e}R is a compound of formula (50),^{Three}Is N $(Et)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me

R^{4e}R is a compound of formula (50),^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is cyclobutylamino, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $OH_{Two}OH = CH_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Pr, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Et, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Bu, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) propargyl, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) propargyl, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is Me and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is OMe, R^{4b}Is H, R^{4c}But

OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is OMe, R^{4b}Is H, $R^{Four\ c}$ Is OMe, R^{4b}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is Me and R^{4e}R is a compound of formula (50),^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is M

e and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is Me and R^{4e}R is a compound of formula (50),^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me

And R^{4e}R is a compound of formula (50),^{Three}Is N $(Et)_{Two}$, R^{4a}Is OMe, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me

R^{4e}R is a compound of formula (50),^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Bu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}R is a compound of formula (50),^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}R is a compound of formula (50),^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes R^{4e}R is a compound of formula (50),^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) Bu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Et) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Me, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) CH_{Two}cPr, R^{4a}Is Me, $R^{4b}$is H, $R^{4c}$is OM

e, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (cPr)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (Et)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Et)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e} Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is cyclobutylamino, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Et) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Pr) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) Bu, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Me) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Et) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Me, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (cPr)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N ($CH_{Two}CH_{Two}$OMe)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

H and R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}Wherein R is OMe, a compound of formula (50)^{Three}Is N (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e} Wherein R is OMe, a compound of formula (50)^{Three}Is NHCH (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}R is a compound of formula (50),^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, $R^{4d}$is H and R^{4e}R is a compound of formula (50),^{Three}Is cyclobutylamino, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Et) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Pr) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) Bu, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Me) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N (Et) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Me, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is N ($CH_{Two}CH_{Two}$OMe) CH_{Two}cPr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is H and R^{4e}R is a compound of formula (50),^{Three}Is NHCH (cPr)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is Cl, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}But

H and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, $R^{4a}$is Cl, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is H

$R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, $R^{4d}$is H and R^{4e} R is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, $R^{4a}$is Cl, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is F

$R^{4e}R$ is a compound of formula (50), ^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, $R^{4d}$is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is cyclobutylamino, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, $R^{4a}$is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, $R^{Four\ d}$ is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, $R^{4d}$is F

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, $R^{4d}$is F

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, $R^{4d}$is F

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Bu, $R^{4a}$is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) propargyl, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is O

Me, $R^{4d}$is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is OMe, $R^{4d}$is F and $R^{4e}R$ is a compound of formula (50), ^{Three}is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Cl, R^{4b}Is F, R^{4c}Is OMe, R^{4d} Is H and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

Yes $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

$R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is F and R^{4e} R is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is cyclobutylamino, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is OM e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Pr, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Bu, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) propargyl, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is O

Me, $R^{4d}$is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}CH = CH_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is OMe, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Me, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Et, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ Pr, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}cPr$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(cPr)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM

e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

$R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is 2-ethylpiperid-1-yl, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is cyclobutylamino, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}cPr$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is F

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}cPr$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Pr) $CH_{Two}cPr$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Pr, R^{4a}Is Br, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Et, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Bu, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) propargyl, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is O

Me, $R^{4d}$is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}is N ($CH_{Two}CH_{Two}$OMe) $CH_{Two}CH = CH_{Two}$, $R^{4a}$is Br, $R^{4b}$is H, R^{4c} is OMe, $R^{4d}$is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Me, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Et, R^{4a}Is Br, R^{4b}Is H, $R^{4c}$is OMe, $R^{Four\ d}$ is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Pr, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N ($CH_{Two}CH_{Two}$OMe) CH_{Two}cPr, $R^{4a}$is Br, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH $(cPr)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM

e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is OMe

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is OMe

$R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And $R^{4e}R$ is a compound of formula (50), ^{Three}is 2-ethylpiperid-1-yl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) $CH_{Two}CH = CH_{Two}$, $R^{4a}$is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is F

And $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Et) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, $R^{4c}$is OMe, R^{4d}Is O

Me and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Pr) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is O

Me and $R^{4c}R$ is a compound of formula (50), ^{Three}is N (Me) Pr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) Bu, R^{4a}Is Me, R^{4b}Is H, R^{3c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N (Me) propargyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is NHCH (CH_{Three}) CH (CH_{Three}) CH_{Three}, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is O

Me, $R^{4d}$is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}is N ($CH_{Two}CH_{Two}$OMe) $CH_{Two}CH = CH_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c} is OMe, R^{4d}Is F and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Me, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Et, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N ($CH_{Two}CH_{Two}$OMe) Pr, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{Four\ d}$ Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N ($CH_{Two}CH_{Two}$OMe) CH_{Two}cPr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH (CH_{Three}) $CH_{Two}CH_{Three}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d} is OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH $(cPr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OM

e and $R^{4e}R$ is a compound of formula (50), ^{Three}Is N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

OMe and $R^{4e}R$ is a compound of formula (50), ^{Three}is NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

And $R^{4e}A$ compound of formula (50) wherein R is H; ^{Three}Is N $(Et)_{TWO}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is OMe

$R^{4e}A$ compound of the formula (50) wherein is H, a compound selected from the group consisting of and isomers, stereoisomers or
And mixtures thereof, and pharmaceutically acceptable salts thereof.

[2] The present invention also relates to a compound represented by the following formula (60):

[0051]

Embedded image Equation (60)

And isomers thereof, stereoisomers thereof, or a mixture of stereoisomers thereof, and pharmaceutically acceptable salts thereof, wherein R^3 is NHCH $(Et)_2$, and Ar is 6- A compound of formula (60) which is dimethylamino-4-methylpyrid-3-yl, a compound of formula (60) wherein R^3 is 2-ethylpiperid-1-yl and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of formula (60) wherein R^3 is cyclobutylamino and Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 is N (Me) $CH_2CHCHCH_2$, a compound of formula (60) wherein Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N (Et) CH_2 cPr and Ar is 6-dimethylamino-4- Methylpyrid-3-i Compounds of formula (60) is, R^3 is N (Pr) CH_2 cPr, compounds of formula (60) Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 is N (Me) is Pr, Ar is 6-dimethylamino-4-methylpyrid - 3-yl compound of formula (60) is, R^3 is N (Me) Et, Ar is 6-dimethylamino-4-methylpyrido A compound of formula (60) wherein R^3 is N (Me) Bu and Ar is 6-dimethylamino-4-methylpyrid-3-yl, wherein R^3 is N (Me) propargyl, a compound of formula (60) wherein Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 is N (Et) propargyl and Ar is 6-dimethylamino- With 4-methylpyrid-3-yl Compounds of formula (60) that, R^3 is NHCH (CH_3) a CH (CH_3) CH_3, compounds of formula (60) Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 is N (CH_2CH_2OMe) $CH_2CH = CH_2$ and Ar is 6-dimethylamino-4-methylpyrid-3-yl, a compound of formula (60), wherein R^3 is N (CH_2CH_2OMe) Me, a compound of formula (60) wherein Ar is 6-dimethylamino-4-methylpyrid-3-yl, wherein R^3 is N (CH_2CH_2OMe) Et and Ar is 6- A compound of formula (60) which is dimethylamino-4-methylpyrid-3-yl, wherein R^3 is N (CH_2CH_2OMe) Pr and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of formula (60) wherein R^3 is N (CH_2CH_2OMe) a CH_2 cPr, Ar is 6-dimethylamino -

A compound of formula (60) that is 4-methylpyrid-3-yl, a compound of formula (60) wherein R^3 is NHCH (CH_3) CH_2CH_3 and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of formula (60) wherein R^3 is NHCH $(cPr)_2$ and Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N $(CH_2CH_2OMe)_2$ Wherein Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is NHCH $(Et)_2$, and Ar is 6-dimethylamino-4-methylpyrid-3-yl, A compound of formula (60), wherein R^3 is N $(Et)_2$ and Ar is 6-dimethylamino-4-methylpyrido-3-

Yl compound of formula (60) is, R^3 is 2-Echirupiperido-1-yl, the compounds of formula (60) Ar is 6-dimethylamino-4-methylpyrid-3-yl, R^3 is cyclo Butylamino, Ar is 6-dimethylamino-4-methylpyrid-3-yl, a compound of formula (60), wherein R^3 is N (Me) $CH_2CH = CH_2$ and Ar is 6-dimethyl A compound of formula (60) that is amino-4-

methylpyrid-3-yl, wherein R^3 is N (Et) CH_2 cPr and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of formula (60) wherein R^3 is N (Pr) CH_2 cPr and Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N (Me) Pr, Yes, Ar is 6-dimethylamino-4 Methylpyrid - 3-yl compound of formula (60) is, R^3 is N (Me) Et, Ar is 6-dimethylamino-4-methylpyrid - 3-yl compound of formula (60) is, R^3 is N (Me) Bu, Ar is 6-dimethylamino-4-methylpyrid-3-yl, a compound of formula (60), R^3 is N (Me) propargyl, and Ar is 6-dimethylamino- A compound of formula (60) which is 4-methylpyrid-3-yl, wherein R^3 is NHCH (CH_3) CH (CH_3) CH_3 and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) CH_2 CH = CH_2 and Ar is 6-dimethylamino-4-methylpyrid-3-yl R^3 is N (CH_2 CH_2 OM e) e) a compound of formula (60) wherein Me is and Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) Et and Ar is 6-dimethyl A compound of formula (60) which is amino-4-methylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) Pr and Ar is 6-dimethylamino-4-methylpyrid-3-yl; A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) CH $_2$ cPr and Ar is 6-dimethylamino-

A compound of formula (60) that is 4-methylpyrid-3-yl, a compound of formula (60) wherein R^3 is NHCH (CH_3) CH_2 CH_3 and Ar is 6-dimethylamino-4-methylpyrid-3-yl A compound of formula (60) wherein R^3 is NHCH (cPr) $_2$ and Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) $_2$ Wherein Ar is 6-dimethylamino-4-methylpyrid-3-yl; R^3 is NHCH (Et) $_2$, and Ar is 6-dimethylamino-4-methylpyrid-3-yl. A compound of formula (60), wherein R^3 is N (Et) $_2$ and Ar is 6-dimethylamino-4-methylpyrido-3-

Yl compound of formula (60) is, R^3 is 2-Echirupiperido-1-yl, the compounds of formula (60) Ar is 6-methoxy-4-methyl-pyrid-3-yl, R^3 is cyclo butyl amino, Ar is 6-methoxy-4-methylpyrido -3 - compound of formula (60) is yl, R^3 is $_{N (Me) CH 2 CH =}$ CH 2, Ar is 6-methoxy-4 A compound of formula (60) which is -methylpyrid-3-yl, wherein R^3 is N (Et) CH_2 cPr and Ar is 6-methoxy-4-methylpyrido-

A compound of formula (60) that is 3-yl, wherein R^3 is N (Pr) CH_2 cPr and Ar is 6-methoxy-4-methylpyrido-

A compound of formula (60) wherein R^3 is N (Me) Pr and Ar is 6-methoxy-4-methylpyrid-3-yl; R^3 is N, (Me) Et, a compound of formula (60) wherein Ar is 6-methoxy-4-methylpyrid-3-yl, R^3 is N (Me) Bu and Ar is 6-methoxy-4-methylpyrido 3 compound Lee Le a is formula (60), R^3 is N (Me) propargyl, compound of formula (60) Ar is 6-methoxy-4-methylpyrid-3-yl, R^3 is N (Et) propargyl, a compound of formula (60) wherein Ar is 6-methoxy-4-methylpyrid-3-yl; R^3 is NHCH (CH_3) CH (CH_3) CH_3 ; and Ar is 6-methoxy-4-

Methylpyrid-3-yl compound of formula (60) is, R^3 is $_{N (CH 2 CH 2 OMe)}$ CH 2 CH = CH 2, Ar is 6-methoxy - 4-methylpyrid-3-yl and is formula A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) Me and Ar is 6-methoxy-4-methylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) Et, a compound of formula (60) wherein Ar is 6-methoxy-4-methylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) Pr and Ar is 6 A compound of formula (60) which is -methoxy-4-methylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) CH_2 cPr and Ar is 6-methoxy-4-methylpyrid-3-yl compounds of formula (60) is, R^3 is NHCH (CH_3) An H_2 CH_3, Ar is a compound of formula (60) is 6-methoxy-4-methylpyrid-3-yl, R^3 is NHCH (cPr) $_2$, Ar is 6-methoxy-4-methylpyrido - 3

- yl, compound of formula (60), R^3 is $_{N (CH 2 CH 2 OMe)}$ 2, the compound of formula (60) Ar is 6-methoxy-4-methylpyrid-3-yl, R^3 is NHCH (Et) $_2$ and Ar is 6-methoxy-4-methylpyrido-3-

A compound of formula (60) wherein R^3 is N (Et) $_2$ and Ar is 6-methoxy-4-methylpyrid-3-yl; R^3 is 2-ethylpiperid- 1 is yl, compounds of formula (60) Ar is 4-methoxy-5-methyl-pyrid-3-yl, R^3 is cyclobutylamino, Ar is 4-methoxy-6-methylpyrid -3 - A compound of formula (60) wherein R^3 is N (Me) CH_2 CH CH_2 and Ar is 4-methoxy-6-methylpyrid-3-yl; ^{3} is N (Et) CH_2 cPr, and Ar is 4-methoxy-5-methylpyrido-

A compound of formula (60) that is 3-yl, wherein R^3 is N (Pr) CH_2 cPr and Ar is 4-methoxy-5-methylpyrido-

3-yl compound of formula (60), R^3 is N (Me) Pr, the compound of formula (60) Ar is 4-methoxy-6-methylpyrid-3-y le, R^3 is N (Me) is Et, compound of formula (60) Ar is 4-methoxy-6-methylpyrid-3-y le, R^3 is N (Me) Bu, Ar is 4-methoxy-6-methylpyrid 3 compound Lee Le a is formula (60), R^3 is N (Me) propargyl, compound of formula (60) Ar is 4-methoxy-6-methylpyrid 3-yl, R^3 is NHCH (CH_3) CH (CH_3) CH_3, wherein Ar is 4-methoxy-6-

Methylpyrid-3-yl compound of formula (60) is, R^3 is $_{N (CH 2 CH 2 OMe)}$ CH 2 CH = CH 2, Ar is 4-methoxy - 6-methylpyrid-3-yl and is formula A compound of formula (60), wherein R^3 is N (CH_2 CH_2 OMe) Me and Ar is 4-methoxy-6-methylpyrid-3-yl; R^3 is N (CH a $_2$ CH_2 OMe) Et, Ar is 4-methoxy-6-methylpiperazin chloride 3-yl compound of formula (60) is, R^3 is $_{N (CH 2 CH 2 OMe)}$ Pr, Ar is 4 -Methoxy-6-methylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) CH_2 cPr and Ar is 4-methoxy-6-methylpyrid-3-yl compounds of formula (60) is, R^3 is NHCH (CH_3) An H_2 CH_3, Ar is 4-methoxy-6-methylpyrid-3-yl compound of formula (60) is, R^3 is NHCH (cPr) $_2$, Ar is 4-methoxy-6-methylpyrid - 3 - yl, compound of formula (60), R^3 is $_{N (CH 2 CH 2 OMe)}$ 2, the compound of formula (60) Ar is 4-methoxy-6-methylpyrid-3-yl, R^3 is NHCH (Et) $_2$ and Ar is 4-methoxy-6-methylpyrido-3-

A compound of formula (60) wherein R^3 is N (Et) $_2$ and Ar is 4-methoxy-6-methylpyrid-3-yl; R^3 is 2-ethylpiperido- A compound of the formula (60) wherein R 1 is 1-yl and Ar is 4,6-dimethylpyrid-3-yl; a compound of the formula (60) wherein R^3 is cyclobutylamino and Ar is 4,6-dimethylpyrid-3-yl A compound of formula (60) wherein R^3 is N (Me) CH_2 CH = CH_2 and Ar is 4,6-dimethylpyrid-3-yl; R^3 is N (Et) CH_2 a compound of formula (60) wherein cPr is Ar and 4,6-dimethylpyrid-3-yl, R^3 is N (Pr) CH_2 cPr and Ar is 4,6-dimethylpyrid-3-yl A compound of the formula (60): wherein R^3 is N (Me) Pr; a compound of formula (60) wherein r is 4,6-dimethylpyrid-3-yl; a compound of formula (60) wherein R^3 is N (Me) Et and Ar is 4,6-dimethylpyrid-3-yl R^3 is N (Me) Bu and Ar is 4,6-dimethylpyrid-3-yl A compound of formula (60), wherein R^3 is N (Me) propargyl and Ar is 4,6-dimethylpyrido A compound of formula (60) wherein R^3 is N (Et) propargyl and Ar is 4,6-dimethylpyrid-3-yl, R^3 is NHCH A compound of formula (60) wherein (CH_3) CH (CH_3) CH_3 and Ar is 4,6-dimethylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) CH_2 CH = CH_2, wherein Ar is 4,6-dimethylpyrid-3-yl A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) Me and Ar is 4,6-dimethylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) Et, a compound of formula (60) wherein Ar is 4,6-dimethylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) Pr and Ar is 4,6-dimethylpyrid-3 - yl, compound of formula (60), R^3 is $_{N (CH 2 CH 2 OMe)}$ CH 2 cPr, compounds of formula (60) Ar is 4,6-dimethylpyrid-3-yl, R^3 is NHCH (CH_3) CH_2 CH_3 and Ar is 4,6-dimethylpyrido-3

A compound of formula (60) wherein R^3 is NHCH (cPr) $_2$ and Ar is 4,6-dimethylpyrid-3-yl; R^3 is N (CH_2 CH_2 OMe) is $_2$, Ar is a compound of formula (60) is 4,6-dimethylpyrid-3-yl, R^3 is NHCH (Et) $_2$, in which Ar is 4,6-dimethylpyrid-3-yl A compound of the formula (60), wherein R^3 is N (Et) $_2$ and Ar is 4,6-dimethylpyrid-3-yl

A compound of formula (60) wherein R^3 is 2-ethylpiperid-1-yl and Ar is 2,6-dimethylpyrid-3-yl, R^3 is cyclobutylamino and Ar is 2 A compound of formula (60) wherein R^3

is N (Me) CH_2 CH C H CH_2 and Ar is 2,6-dimethylpyrid-3-yl A compound of formula (60) wherein R^3 is N (Et) CH_2 cPr and Ar is 2,6-dimethylpyrid-3-yl; R^3 is N (Pr) CH_2 cPr, A compound of the formula (60) wherein R^3 is N (Me) Pr and Ar is 2,6-dimethylpyrid-3-yl; R^3 is N (Me) Et, Ar is 2,6-dimethylol Pyrid-3-yl compound of formula (60) is, R^3 is N (Me) Bu, compounds of formula (60) Ar is 2,6-dimethylpyrid-3-yl, R^3 is N (Me) a compound of formula (60) which is propargyl and Ar is 2,6-dimethylpyrid-3-yl, wherein R^3 is NHCH (CH_3) CH (CH_3) CH_3 and Ar is 2,6 A compound of formula (60) which is -dimethylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) CH_2 CH = CH_2 and Ar is 2,6-dimethylpyrid-3-yl A compound of the formula (60), wherein R^3 is N (CH_2 CH_2 OMe) Me and Ar is 2,6-dimethylpyrid-3-yl, wherein R^3 is N (CH_2 CH_2 OMe) Et and Ar is 2,6-dimethylpyrid-3-yl Compound (60), R^3 is $_{N (CH 2 CH 2 OMe)}$ Pr, Ar is 2,6-dimethylpyrid-3 - compound of formula (60) is yl; R^3 is N (CH_2 CH_2 OMe) a compound of formula (60) wherein CH_2 cPr is Ar and 2,6-dimethylpyrid-3-yl; R^3 is NHCH (CH_3) CH_2 CH_3 and Ar is 2,6-dimethylpyride -3

A compound of formula (60) wherein R^3 is NHCH (cPr) $_2$ and Ar is 2,6-dimethylpyrid-3-yl, R^3 is N (CH_2 CH_2 OMe) is $_2$, Ar is a compound of formula (60) is 2,6-dimethylpyrid-3-yl, R^3 is NHCH (Et) $_2$ in which Ar is 2,6-dimethylpyrid-3-yl A compound of the formula (60) and a compound of the formula (^{3}) wherein R^3 is N (Et) $_2$ and Ar is 2,6-dimethylpyrid-3-yl

60) A compound selected from the group consisting of: and isomers thereof, stereoisomers thereof, or a mixture of stereoisomers thereof, and a pharmaceutically acceptable salt thereof.

[3] Specific preferred compounds of the present invention include compounds selected from the following groups, and isomers thereof, stereoisomers thereof, or mixtures of the stereoisomers thereof, and pharmaceutically acceptable compounds thereof. Contains possible salts. 4-((2-butyl) amino) -2,7-dimethyl-8- (2-methyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- ((2-butyl) amino) -2,7-dimethyl-8- (2,5-dimethyl-
4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4-((3-pentyl) amino) -2,7-dimethyl-8- (2,5-dimethyl-4 -Methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4-((3-pentyl) amino) -2,7-dimethyl-8- (2-methyl-4-
Methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- (N-cyclopropylmethyl-N-propylamino) -2,7-dimethyl-
8- (2-methyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,
3,5-triazine 4- (N-cyclopropylmethyl-N-propylamino) -2,7-dimethyl-
8- (2,5-dimethyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- (N-allyl-N- (2-methoxyethyl) amino)- 2,7-dimethyl-
8- (2-methyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,
3,5-triazine 4- (N-allyl-N- (2-methoxyethyl) amino) -2,7-dimethyl-
8- (2,5-dimethyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- (diallylamino) -2,7-dimethyl-8- (2- Methyl-4-methoxyphenyl) [1,5-a] -pyrazolo-1,3,5-triazine 4-
(diallylamino) -2,7-dimethyl-8- (2,5-dimethyl-4-methoxy Phenyl)-[1,5-a] -pyrazolo-1,3,5-triazine 4- (N-ethyl-N- (2-methoxyethyl) amino) -2,7-dimethyl-
8- (2-methyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,
3,5-triazine 4- (N-ethyl-N- (2-methoxyethyl) amino) -2,7-dimethyl-
8- (2,5-dimethyl-4-methoxyphenyl)-[1,5-a] -pyrazolo-1,3,5-triazine

[4] The present invention provides a compound represented by the following formula (70):

[0065]

Embedded image Equation (70)

And its isomers, its stereoisomers, or a mixture of its stereoisomers, and
A pharmaceutically acceptable salt thereof, wherein R is Cl, R^{Three} is -NHCH (n-Pr)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me
, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NHCH (CH_{Two}OMe)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -N ($CH_{Two}CH_{Two}$OMe)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is M
e, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -N (cPr) ($CH_{Two}CH_{Two}$CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -N ($CH_{Two}CH_{Two}$OMe)$_{Two}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is M
e, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NHCH (CH_{Two}OMe)$_{Two}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NHCH (Et)$_{Two}$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -N (Et)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H
And R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -N (n-Pr) ($CH_{Two}CH_{Two}$CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -N (n-Bu) ($CH_{Two}CH_{Two}$CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NHCH (n-Pr) (CH_{Two}OMe), R^{4a} is Me, R^{4b} But
H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NHCH (Et)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NHCH (CH_{Two}OMe)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is (S) -NH ($CH_{Two}CH_{Two}$OMe) CH_{Two}OMe, R^{4a} is Me,
R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NH ($CH_{Two}CH_{Two}$OMe) CH_{Two}OMe, R^{4a} is Me, R^{4b} But
H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -N ($CH_{Two}CH_{Two}$OMe)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is C
l, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NH (Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NHCH (n-Pr)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{5c} is Cl
, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NHCH (CH_{Two}OMe)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is (S) -NH ($CH_{Two}CH_{Two}$OMe) CH_{Two}OMe, R^{4a} is Me,
R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -NH ($CH_{Two}CH_{Two}$OMe) CH_{Two}OMe, R^{4a} is Me, R^{4b} But
H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -N (n-Pr) ($CH_{Two}CH_{Two}$CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is -N (Et)$_{Two}$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} But
H and R^{4e} A compound of the formula (70) wherein R is Cl, R^{Three} is (S) -NH ($CH_{Two}CH_{Two}$OMe) CH_{Two}OMe, R^{4a} is Cl,

R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, $R^{Three}$is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, $R^{4a}$is Cl, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H

And R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (cPr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (cPr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH (n-Pr) $(CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}But

H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH (n-Pr) $(CH_{Two}OMe)$, R^{4a}Is Cl, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is OMe and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, $R^{Three}$is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, $R^{4a}$is Br, R^{4b}Is H, $R^{4c}$is O

Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(Et)_{Two}$, $R^{4a}$is Me, $R^{4b}$is H, $R^{4c}$is Cl, R^{4d}Is H

And R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

OMe and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, $R^{4a}$is Cl, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is OMe and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is C

l, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Cl, R^{4b}Is H, $R^{Four\ c}$ is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Bu) (Et), R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, $R^{Three}$is -NHCH (Et) $CH_{Two}OMe$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d} Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, $R^{4c}$is Me, R^{4d} is H and R^{4e}A compound of the formula (70) wherein R is Cl, $R^{Three}$is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is Me, R^{4d} Is H and R^{4e}A compound of the formula (70) wherein R is Cl, $R^{Three}$is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d} is H and R^{4e}A compound of the formula (70) wherein R is Cl, $R^{Three}$is -NEt$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H

Yes R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(n\text{-}Pr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me

, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is M

e, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (cPr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is M

e, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is Me, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is Me, R^{4d} Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H

And R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (n-Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (n-Bu) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH (n-Pr) $(CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me,

R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is C

l, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH (Et), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(n\text{-}Pr)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl

, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me,

R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me, R^{4b}But

H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (n-Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Cl,

R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Cl, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H

And R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (cPr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (cPr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH (n-Pr) $(CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}But

H, $R^{4c}$is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH (n-Pr) $(CH_{Two}OMe)$, R^{4a}Is Cl, R^{4b}But

H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is OMe and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is O

Me, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H

And R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, R^{4d}But

OMe and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe,

R^{4d}Is OMe and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is C

l, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Cl, R^{4b}Is H, $R^{Four\ c}$ Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Bu) (Et), R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH (Et) $CH_{Two}OMe$, R^{4a}Is Cl, R^{4b}Is H, R^{4c} Is Cl, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d} Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d} Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d} Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d} Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NEt$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

Yes R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH (n-Pr)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me,

R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me

, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N (cPr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me

, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d} Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N (Et)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H

Yes R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N (n-Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N (n-Bu) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH (n-Pr) $(CH_{Two}OMe)$, R^{4a}Is Me, R^{4b}Is H

, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is O Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me, R^{4b} Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me, R^{4b}Is H

, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4e}Is Me, R^{4b}Is H, R^{4c}Is Cl

, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NH (Et), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH (n-Pr)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl,

R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is C1, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me, R^{4b} is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Me, R^{4b}Is H

, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N (n-Pr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N (Et)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

And R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is (S) -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Cl, R^{4b} Is H, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NH $(CH_{Two}CH_{Two}OMe)$ $CH_{Two}OMe$, R^{4a}Is Cl, R^{4b}Is H

, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N $(Et)_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d}Is H

Yes R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N (cPr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Me, R^{4b}Is H, $R^{Four\ c}$ is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N (cPr) $(CH_{Two}CH_{Two}CN)$, R^{4a}Is Cl, R^{4b}Is H, $R^{Four\ c}$ Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH (n-Pr) $(CH_{Two}OMe)$, $R^{4a}$is Me, $R^{4b}$is H

, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH (n-Pr)$_{Two}$ $(CH_{Two}OMe)$, R^{4a}Is Cl, R^{4b}Is H

, R^{4c}Is Me, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH $(Et)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is OMe and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH (Et)$_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OMe, R^{4d} Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -N $(CH_{Two}CH_{Two}OMe)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is OM

e, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F, R^{Three}Is -NHCH $(CH_{Two}OMe)_{Two}$, R^{4a}Is Br, R^{4b}Is H, R^{4c}Is O Me, R^{4d}Is H and R^{4e}A compound of formula (70)

wherein R is F,^{Three}Is -N (Et)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H

Yes R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is O

Me and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NHCH (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, $R^{4c}$is OMe, R^{4d} is OMe and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (CH$_{Two}$CH$_{Two}$OMe)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl

, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NHCH (CH$_{Two}$OMe)$_{Two}$, $R^{4a}$is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Pr) (CH$_{Two}$CH$_{Two}$CN), R^{4a}Is Cl, R^{4b}Is H, R^{4c} is Cl, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Bu) (Et), R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R$^{Four\ d}$ Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NHCH (Et) CH$_{Two}$OMe, R^{4a}Is Cl, R^{4b}Is H, R^{4c}But

Cl, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NHCH (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Cl, R^{4d} is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NHCH (Et)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Me, R^{4d} Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NHCH (Et)$_{Two}$, R^{4a}Is Cl, R^{4b}Is H, R^{4c}Is Me, R^{4d} Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NHCH (Et)$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is Cl, R^{4d} Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NEt$_{Two}$, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H

R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Pr) (CH$_{Two}$CH$_{Two}$CN), R^{4a}Is Me, R^{4b}Is H, R^{4c} is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Pr) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Et) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Me) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Pr) (CH$_{Two}$CH$_{Two}$OMe), $R^{4a}$is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Et) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -N (Me) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is Me and R^{4e}A compound of the formula (70) wherein R is Cl, R^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Pr) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R$^{four\ c}$ Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Et) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R$^{Four\ c}$ Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Me) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R$^{Four\ c}$ Is OMe, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R$^{Four\ d}$ Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{5c}Is OMe, R$^{Four\ d}$ Is H and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Pr) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{6b}Is H, R$^{Four\ c}$ Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Et) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R$^{Four\ c}$ Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -N (Me) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R$^{Four\ c}$ Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is Me and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NMeBu. R^{4a}Is Me, $R^{4b}$is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R$^{Four\ d}$ Is Me and R^{4e}A compound of formula (70) wherein R is F,^{Three}Is cyclobutylamino, $R^{4a}$is Me, $R^{4b}$is H, R^{4c}Is OMe, R$^{Four\ d}$ Is Me and R^{5e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Pr) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Et) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{5d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Me) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMeEt, R^{4a}Is Me, $R^{4b}$is H, R^{4c}Is OMe, $R^{4d}$is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMeBu, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H and R^{4c}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH-2-butyl, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is H and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is H and R^{3e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Pr) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Et) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -N (Me) (CH$_{Two}$CH$_{Two}$OMe), R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{5e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMeEt, R^{4a}Is Me, R^{4b}Is H, R^{3c}Is OMe, R^{4d}Is Me and R^{5e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMePr, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, R^{4d}Is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NMeBu, R^{4a}Is Me, $R^{4b}$is H, R^{4c}Is OMe, $R^{4d}$is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is -NH-2-butyt, R^{4a}Is Me, R^{4b}Is H, R^{4c}Is OMe, $R^{4d}$is Me and R^{4e}A compound of the formula (70) wherein R is Me, R^{Three}Is cyclobutylamino, R^{4a}Is Me, R^{4b}Is H, R^{5c}Is OMe, R^{4d}Is Me and R^{5e}Further provided is a compound selected from the group consisting of: a compound of formula (70) wherein is H. [5] A particularly preferred compound of the present invention is 7- (diethylamino) -2,5-dimethyl

Tyl-3- (2-methyl-4-methoxyphenyl-) 1,5-a] -pyrazolopi

Limidine and 7- (N- (3-cyanopropyl) -N-propylamino) -2

, 5-Dimethyl-3- (2,4-dimethylphenyl) [1,5-a] -pyrazo

Compounds selected from Lopyrimidine and isomers thereof, stereoisomers thereof, or

It includes mixtures of its stereoisomers, and its pharmaceutically acceptable salts.

[6] The present invention provides a pharmaceutical composition comprising a therapeutically effective amount of the above compound and a pharmaceutically acceptable carrier.

[7] The present invention comprises administering to a mammal a therapeutically effective amount of the compound.
Affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa or other eating disorders, drug addiction, drugs or Alcohol withdrawal, inflammatory disease, cardiovascular or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, hemorrhagic stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcer Amyotrophic lateral sclerosis, hypoglycemia, or disorders including, but not limited to, disorders induced or promoted by CRF, wherein treatment of the disorder is achieved or facilitated by antagonism with CRF The invention further provides a method of treating mammals.

Many compounds of the present invention have one or more asymmetric centers or planes.
All chiral forms (enantiomers and diastereomers) unless otherwise indicated
And racemates are included in the present invention. Many geometric isomers, such as olefins, C = N double bonds, are also present in the compounds of the present invention, and all of these stable isomers are contemplated herein. The compounds of the present invention can be isolated in optically active or racemic forms. Methods for producing optically active forms, such as by resolution of a racemate or synthesis from optically active starting materials, are well known in the art. Unless the specific stereochemistry or isomers are specifically indicated, all chiral (enantiomers and diastereomers) and racemates, and all geometric isomers, are intended in structure.

The term "alkyl" includes both branched and straight-chain alkyls having the specified number of carbon atoms. Commonly used abbreviations have the following meanings. Me is methyl, Et
is ethyl, Pr is propyl, Bu is butyl. The prefix 'n' means straight chain alkyl. The prefix 'c' means cycloalkyl. The prefix "(S)" is S
The enantiomer, the prefix "(R)" means the R enantiomer. "Alkenyl"
is a hydrocarbon chain of either linear or branched structure, such as ethenyl, propenyl, etc., and one or more unsaturated carbon-carbon bonds which may be at any stable site along the carbon chain. including. "Alkynyl" refers to either straight or branched hydrocarbon chains, such as ethynyl, propynyl, and the like, and one or more carbon-carbon triplets which may be at any stable site along the carbon chain. Including binding. "Haloalkyl" is meant to include both branched and straight-chain alkyls having the specified number of carbon atoms, substituted with one or more halogen atoms. "Alkoxy"
Represents an alkyl group of the indicated number of carbon atoms attached through an oxygen bridge. "Cycloalkyl" is meant to include saturated cyclic groups, including mono-, bi- or polycyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. "Halo" and "halogen" are fluoro,
includes chloro, bromo, and iodo.

The term "substituted," as used herein, means that one or more hydrogen atoms on the specified atom is replaced with a selected group from the indicated group, with the proviso that Should not exceed the normal valency of the specified atom, and the substitution shall provide a stable compound. When the substitution is keto (ie, = 0), two hydrogen atoms 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 isolated from a reaction mixture in useful purity and that is sufficiently robust to withstand formulation into an effective therapeutic agent.

The term "suitable amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. These amine protecting groups are described in Greene and Wuts, Protective Groups in Organic Synthesis.
Organic Synthesis), John Wiley & Sons, New York, 1991, and "The Peptides: Analysis, Synthesis, Biology", Volume 3, Academic Press, New York, 1981. The disclosures of which are incorporated herein by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following. 1) acyl forms such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1- (p-Aromatic carbamate types such as biphenyl) -1-methylethoxycarbonyl and 9-fluorenylmethyloxycarbonyl (Fmoc), 3) t-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl 4) cyclic alkyl carbamates such as cyclopentyloxycarbonyl and adamantyloxycarbonyl, 5) alkyls such as triphenylmethyl and benzyl, 6) trialkylsilanes such as trimethylsilane, and 7) Forms containing thiols such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes salts of the compounds of Formulas (1) and (2) with acids or bases. Examples of pharmaceutically acceptable salts include, but are not limited to, salts of mineral or organic acids of basic residues such as amines, and alkali or organic salts of acidic residues such as carboxylic acids. It is not done.

Pharmaceutically acceptable salts of the compounds of the present invention can be prepared by combining the compound in free acid or base form with a stoichiometric amount of a suitable base or acid, water or organic solvent, or both. It can be prepared by reacting in a mixture. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. A list of suitable salts can be found in Remington's Phar
maceutical Sciences) ", 17th Edition, Mack Publishing Company, Easton, PA, 1418
1985, the disclosure of which is incorporated herein by reference.

A "prodrug" is a covalently bonded carrier that releases the active parent drug of Formulas (i) and (II) in vivo when the prodrug is administered to a mammalian subject. Conceivable. Prodrugs of the compounds of formulas (I) and (II) modify the functional groups present on the compounds of the present invention such that the modification is cleaved, either by normal operations or in vivo, to the original compound. It is prepared by Prodrugs include compounds in which a hydroxy, amine, or sulfhydryl group is linked to any group that, when administered to a mammalian subject, cleaves to give a free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include compounds of formula (I)
And acetate, formate and benzoate derivatives of the alcohol and amine functions in the compounds of (II) and the like, but are not limited thereto.

A "therapeutically effective amount" of a compound of the present invention is that which antagonizes abnormal levels of CRF,
An effective amount for treating a condition such as affective disorder, anxiety or depression in the host.

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

[0079]

Embedded image

The compound of formula (7) wherein Y is O can be prepared at a reaction temperature ranging from −80 ° C. to 250 ° C. with or without an inert solvent and with or without a base. Treatment with a halogenating or sulfonylating agent gives the product of formula (8), wherein X is halogen, alkanesulfonyloxy, arylsulfonyloxy, or haloalkane-sulfonyloxy. Halogenating agents include S

$_{OCl_2, POCl_3 PCl_5}$, PCl S, POBr 3, including but PBr_3 or PBr_5 but is not limited to them. Examples of the sulfonylating agent include halides or anhydrides of alkanesulfonic acid (such as methanesulfonyl chloride or methanesulfonic anhydride) and halides or anhydrides of arylsulfonic acid (p-toluenesulfonyl chloride or p-toluene). But not limited to, halides or anhydrides of haloalkylsulfonic acid (preferably trifluoromethanesulfonic anhydride). Examples of the base include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1 to C6) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, and alkali metal hydrides.

Dialkylamides (preferably lithium di-isopropylamide)
, Alkali metal bis (trialkylsilyl) amides (preferably sodium bis (trimethylsilyl) amide), trialkylamines (preferably N, N
-Di-isopropyl-N-ethylamine or triethylamine) or aromatic amines (preferably pyridine), but are not limited thereto. Examples of the inert solvent include lower alkanenitrile (C 1-6, preferably acetonitrile), dialkyl ether (preferably diethyl ether), cyclic ether (preferably tetrahydrofuran or 1,4-dioxane), N 2
, 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) Alternatively, haloalkanes having 1 to 10 carbon atoms and 1 to 10 halogen atoms (preferably dichloromethane) may be included, but the present invention is not limited thereto. Preferred reaction temperatures range from -20C to 100C.

The compound of formula (8) can be prepared by reacting a compound of formula R^3H (Wherein R^3 is as defined above, but not SH, COR^7, CO_2R^7, aryl or heteroaryl) to form a compound of formula (1)
Can be produced. Examples of the base include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1 to C6) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, and alkali metal hydrides. Dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis (trialkylsilyl) amides (preferably sodium bis (trimethylsilyl) amide), trialkylamines (preferably is N, N-di-isopropyl-N-ethylamine) or aromatic amines (preferably pyridine)
May be included, but is not limited thereto. Examples of the inert solvent include alkyl alcohols (1-8 carbon atoms, preferably methanol or ethanol),
Lower alkane nitriles (1-6 carbon atoms, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (preferably is dimethylformamide), N, N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (Preferably, benzene or toluene) or haloalkanes having 1 to 10 carbon atoms and 1 to 10 halogen atoms (preferably dichloromethane) may be included, but not limited thereto. Preferred reaction temperatures range from 0 ° C to 140 ° C.

Scheme 2 outlines a method for converting an intermediate compound of formula (7) where Y is S to some compounds of formula (1).

[0083]

Embedded image

The compound of formula (7) wherein Y is S is not reacted at a reaction temperature in the range of -80 ° C to 250 ° C.
With or without an active solvent and with or without a base, a compound of formula $R^{13}X$ (where $R^{13}$is as defined above, but aryl and heteroaryl
(But not any of the above). All bases
Potassium metal hydrides (preferably sodium hydride), alkali metal alkoxy
(C1-C6) (preferably sodium methoxide or sodium ethoxide)
Oxides), alkaline earth metal hydrides, alkali metal dialkylamides (preferably
Preferably lithium di-isopropylamide), alkali metal carbonates, alkali
Metal hydroxides, alkali metal bis (trialkylsilyl) amides (preferably
Are sodium bis (trimethylsilyl) amide) and trialkylamines (preferably
Or N, N-di-isopropyl-N-ethylamine or triethylamine
) Or aromatic amines (preferably pyridine).
It is not specified. As the inert solvent, alkyl alcohols (C1 to C8)
, Preferably methanol or ethanol), lower alkane nitriles (carbon
Formulas 1 to 6, preferably acetonitrile), dialkyl ethers (preferably
Ethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,
4-dioxane), N, N-dialkylformamides (preferably
Lumamide), N, N-dialkylacetamides (preferably dimethylacetamide)
Amide), cyclic amides (preferably N-methylpyrrolidin-2-one), dia
Alkyl sulfoxides (preferably dimethyl sulfoxide), aromatic hydrocarbons
(Preferably benzene or toluene) or a halogen having 1 to 10 carbon atoms
Haloalkanes having 1 to 10 atoms (preferably dichloromethane) may be included
However, it is not limited to them. Preferred reaction temperature is -80 ° C to 100 ° C
Range.

A compound of formula (12) (where $R^{3\,in}$ formula (1) is SR^{13}) is converted from a compound of formula (8) as outlined in Scheme 1 above to a compound of formula (1) The compound of the formula (1) can be obtained by reacting with the compound of the formula R^3H using the same conditions and reagents as those used in this case. Alternatively, formula (12) (R^3 of formula (1) is SR^{13}) treating a compound of the the presence of an inert solvent at temperatures ranging from -80 ° C. to 250 DEG ° C. oxidant Thus, the compound can be oxidized to a compound of the formula (13) ($R^{3\,in\,the}$ formula (1) is $S(O)_nR^{13}$ and n is 1, 2). Oxidizing agents include, but are not limited to, hydrogen peroxide, alkanes or aryl peracids (preferably peracetic acid or m-chloro-perbenzoic acid), dioxirane, oxone or sodium periodate. Absent. As the inert solvent, alkanones (3 to 10 carbon atoms) are used.
, Preferably, acetone), water, alkyl alcohols (1-6 carbon atoms), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes having 1-10 carbon atoms and having 1-10 halogen atoms. (Preferably dichloromethane) or a combination thereof, but is not limited thereto. The choice of oxidizing agents and solvents is known to those skilled in the art (Uemura, S., 'Oxidation of Sulfur, Selenium and Tellurium', Comprehensive Organic Synthesis). , Trost, BM, (Elmsford
, NY: Pergamon Press, 1991), Vol. 7, pp. 762-769). Preferred reaction temperatures range from -20C to 100C. Then, a compound of formula (13) (wherein $R^{3\,in}$ formula (1) is $S(O)_nR^{13}$ and n is 1 or 2) is converted to a compound of formula (8) as outlined in Scheme 1 above. The compound of the formula (1) can be reacted with the compound of the formula R^3H using the same conditions and reagents as those used when converting the compound of the formula (1) to the compound of the formula (1).

Formula (1) (where $R^{Three}$is $-NR^8COR^7$, $-N(COR^7)_{Two}$, $-NR^8CONR^6R^7$, $-NR^8CO_{Two}R^{13}$, $-NR^6R^7$, $-NR^8SO_{Two}R^7$is obtained from a compound of formula (7), wherein Y is NH, by the method shown in Scheme 3.
Can be manufactured.

[0087]

Embedded image

A compound of the formula (7) (where Y is NH) and an alkylating agent, a sulfonylating agent
Or a continuous reaction with an acylating agent, or a combination thereof, at -80 ° C to 25 ° C.
The reaction is carried out in an inert solvent at a reaction temperature in the range of 0 ° C, with or without the presence of a base.
By the formula (1) (where R^{Three} is -NR^8COR^7, -N $(COR^7)_{Two}$, -NR^8 $CONR^6R^7$, -$NR^8CO_{Two}R^{13}$, -NR^6R^7, -$NR^8SO_{Two}R^7$) Can be obtained. Alkylating agents include C_1 ~ C_{Ten}Alkyl halides, tosylates, mesylates or triflates; C_1 ~ C_{Ten}Haloalkyl (has 1 to 10 halogen atoms) halides, tosylate, mesylate
Or triflates; C_{Two} ~ C_8Alkoxyalkyl halides, Toshi
Rates, mesylates or triflates; C_{Three} ~ C_6Cycloalkyl halo
Genides, tosylate, mesylate or triflate; C_{Four} ~ C_{12}Halides, tosylates, mesylates or cycloalkylalkyl cycloalkyls
Reflates; aryl (C_1 ~ C_{Four}Alkyl) halides and tosylate
, Mesylate or triflate, heteroaryl (C_1 ~ C_{Four}Alkyl)
Halides, tosylate, mesylate or triflate; or
Prime ring (C_1 ~ C_{Four}Alkyl) halides, tosylate, mesylate and
May include, but is not limited to, triflates. Acyl
The agent is C_1 ~ C_{Ten}Halides or anhydrides of alkanoic acids, C 1-10 halogen atoms $_1$ ~ C_{Ten}Haloalkanoic acid halides or anhydrides, C_{Two} ~ C_8Halides or anhydrides of alkoxyalkanoic acids, C_{Three} ~ C_8Halides or anhydrides of cycloalkanoic acid, C_{Four} ~ C_{12}Halides or anhydrides of cycloalkylalkanoic acids, aromatic carboxylic acid halides or
Anhydrides, aryl (C_1 ~ C_{Four}) Halides or anhydrides of alkanoic acids,
Aromatic heterocyclic carboxylic acid halides or anhydrides, heteroaryl (C_1 ~ C_{Four}) Alkanoic acid halides or anhydrides, heterocyclic carboxylic acid halides or anhydrides, or heterocyclic (C_1 ~ C_{Four}) Halides of alkanoic acids
Or anhydrides, but is not limited thereto. Sulfo
Nylating agents include C_1 ~ C_{Ten}Halides or anhydrides of alkylsulfonic acids, C 1-10 halogen atoms $_1$ ~ C_{Ten}Haloalkylsulfonic acid halides or anhydrides, C_{Two} ~ C_8Halides of alkoxyalkyl sulfonic acids
Or anhydrides, C_{Three} ~ C_6Halides of cycloalkylsulfonic acid or anhydrous
Things, C_{Four} ~ C_{12}Halides or anhydrides of cycloalkylalkylsulfonic acids, halides or anhydrides of arylsulfonic acids, aryl (C_1 ~ C_{Four}Alkyl)-, heteroaryl sulfonic acid halides or anhydrides, heteroaryl (C_1 ~ C_{Four}Alkyl) sulfonic acid halides or none
Hydrates, halides or anhydrides of heterocyclic sulfonic acids, or heterocyclic (C_1 ~ C_{Four}Alkyl) sulfonic acid halides or anhydrides.
It is not limited to these. Bases include alkali metal hydrides (preferably
Is sodium hydride), alkali metal alkoxides (C1-6) (preferred)
Or sodium methoxide or sodium ethoxide), alkaline earth metal water
Iodides, alkali metal dialkylamides (preferably lithium di-isopro
Pyramide), alkali metal carbonates, alkali metal bis (trialkylsilyl)
) Amides (preferably sodium bis (trimethylsilyl) amide), tria
Alkylamines (preferably -di-isopropylethylamine) or aromatic
Amines (preferably pyridine) may be included, but are not limited thereto.
There is no. As the inert solvent, alkyl alcohols (1 to 8 carbon atoms, preferably
Methanol or ethanol), lower alkanenitrile (C1-6, preferably
Or 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), dialkyl sulfoxy
Sids (preferably dimethyl sulfoxide) or aromatic hydrocarbons (preferably
May include benzene or toluene), but are not limited to
Absent. Preferred reaction temperatures range from 0 ° C to 100 ° C.

Scheme 4 outlines a method that can be used to produce an intermediate compound of formula (7), where Y is O, S and Z is CR^2.

[0099]

Embedded image

The compound of formula $ArCH_2CN$ is prepared by converting a compound of formula R^2COR^b, wherein R^2 is as defined above, and R^b is halogen, cyano, lower alkoxy (1-6 carbon atoms) or lower alkanoyl. Oxy (having 1 to 6 carbon atoms)) and -78 ° C to 200 ° C
By reacting in an inert solvent in the presence of a base at a reaction temperature in the range of the above, a compound of the formula (3) is obtained. Examples of the base include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1 to C6) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, and alkali metal hydrides. Dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis (trialkylsilyl) amides (preferably sodium bis (trimethylsilyl) amide), trialkylamines (Preferably, N, N-diisopropyl-N-ethylamine) or aromatic amines (preferably pyridine) may be included, but is not limited thereto. Examples of the inert solvent include alkyl alcohols (1-8 carbon atoms, preferably methanol or ethanol), lower alkane nitriles (1-6 carbon atoms, preferably acetonitrile), water, and 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 May include, but are not limited to, N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures are between 0 ° C and 100 ° C.
It is in the range of ° C.

The compound of formula (3) is prepared at a temperature ranging from 0 ° C. to 200 ° C., preferably from 70 ° C. to 15 ° C.
The compound of formula (4) is obtained by reacting with hydrazine hydrate in the presence of an inert solvent at a temperature of 0 ° C. Inactive solvents include water, alkyl alcohols (
C1-C8, preferably methanol or ethanol), lower alkanenitrile (C1-C6, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkyl Formamides (preferably dimethylformamide), N, N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic Group hydrocarbons (preferably benzene or toluene) may be included, but are not limited thereto. A

compound of formula (4)

Reacting with a compound of formula (5) (where R^{b} is alkyl having 1 to 6 carbon atoms) at a temperature in the range of 0 ° C. to 200 ° C. in the presence of an inert solvent, with or without an acid; Thereby, the compound of the formula (6) can be produced. Acids have 2 to 2 carbon atoms
10 alkanoic acids (preferably acetic acid), haloalkanoic acids (such as trifluoroacetic acid having 2 to 10 carbon atoms and 1 to 10 halogen atoms), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), It may include, but is not limited to, alkanesulfonic acids having 1 to 10 carbon atoms (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of the acid can be used. Examples of the inert solvent include water, alkane nitriles (1 to 6 carbon atoms, preferably acetonitrile), 1 to 6 carbon atoms and 1 to 6 halogen atoms.
Halogenated carbons (preferably dichloromethane or chloroform), alkyl alcohols having 1 to 10 carbon atoms (preferably ethanol), dialkyl ethers (4 to 12 carbon atoms, preferably diethyl ether or di-isopropyl ether) or Cyclic ethers such as dioxane or tetrahydrofuran may be included, but are not limited thereto. Preferred temperatures are ambient to
It is in the range of 100 ° C.

The compound of formula (6) is prepared in an inert solvent at a reaction temperature ranging from -50 ° C. to 200 ° C.

With or without the presence of a base, the formula $Y = C(R^{d})_{2}$, wherein Y is O or S, and R^{d} is halogen (preferably chlorine), alkoxy (1-4 carbon atoms) or By treating with a compound of the formula (7)
Can be converted to the compound of Bases include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1-6) (preferably sodium methoxide or sodium ethoxide), alkali metal carbonates, alkali metal hydroxides , Trialkylamines (preferably N, N-di-isopropyl-N-ethylamine or triethylamine) or aromatic amines (preferably pyridine), but are not limited thereto. Examples of the inert solvent include alkyl alcohols (1 to 8 carbon atoms, preferably methanol or ethanol), lower alkanenitrile (1 to 6 carbon atoms, preferably acetonitrile), and cyclic ethers (preferably tetrahydrofuran or 1, 4-dioxane), N, N-dialkylformamides (preferably dimethylformamide), N, N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkyl Sulfoxides (preferably dimethyl sulfoxide) or aromatic hydrocarbons (
Preferably, benzene or toluene) may be included, but is not limited thereto. Preferred temperatures are between 0C and 150C.

The intermediate compound of formula (7) (where Z is N) can be synthesized according to the method outlined in Scheme 5.

[0095]

Embedded image

The compound of formula $ArCH_{2}CN$ is optionally substituted with a compound of formula $R^{g}CH_{2}N_{3}$, wherein R^{g} is H, alkyl (1-6 carbons) or alkoxy (1-6 carbons). A phenyl group) in an inert solvent at a temperature in the range of 0 ° C. to 200 ° C. with or without the presence of a base to produce a compound of formula (9). It can. Bases include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1-6) (preferably sodium methoxide, sodium ethoxide or potassium t-butoxide), alkaline earth metal hydrogen Compounds, alkali metal dialkylamides (preferably lithium di-
isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis (trialkylsilyl) amides (preferably sodium bis (trimethylsilyl) amide), and trialkylamines (preferably N, N-diamide). --
isopropyl-N-ethylamine or triethylamine) or aromatic amines (preferably pyridine), but are not limited thereto. Examples of the inert solvent include alkyl alcohols (1-8 carbon atoms, preferably methanol or ethanol), lower alkane nitriles (1-6 carbon atoms, 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) or aromatic hydrocarbons (preferably benzene or toluene) , But is not limited thereto.
Preferred reaction temperatures range from ambient to 100 ° C.

The compound of formula (10) is obtained by treating the compound of formula (9) with a reducing agent in an inert solvent at -100 ° C to 100 ° C. The reducing agent includes (a) Pd-carbon,
A combination of hydrogen gas with a noble metal catalyst such as PtO_{2}, Pt-carbon, Rh-alumina or Raney nickel, (b) a combination of liquid ammonia and alkali metals (preferably sodium), or (c) cerium ammonium nitrate. , But is not limited to them. Examples of the inert solvent include alkyl alcohols (1-8 carbon atoms, preferably methanol or ethanol), lower alkane nitriles (1-6 carbon atoms, preferably acetonitrile), water, and 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 May include, but are not limited to, N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures are between -50C and 60C.
The compound of formula (9) then converts the reagents and reaction conditions outlined in Scheme 4 when converting formula (4) to a compound of formula (7), wherein Z is CR^{2}. When used, it is converted to a compound of formula (7) (where Z is N) via an intermediate of formula (11).

The compound of formula (1) can be prepared by reacting a compound of formula (7) (where Y is O
, S, and Z is as defined above).

[0099]

Embedded image

The compound of formula (7) is dehydrated in an inert solvent at a reaction temperature in the range of 0 ° C. to 250 ° C.
In the presence of an agent, the formula $R^{Three}R^{Four}H$ compound. Dehydrating agents include $P_{Two}O_{Five}$, Molecular sieves, or inorganic or organic acids, but is not limited thereto. Acids include alkanoic acids having 2 to 10 carbon atoms (preferably vinegar).
Acid), arylsulfonic acid (preferably p-toluenesulfonic acid or benzene)
Sulfonic acid), an alkanesulfonic acid having 1 to 10 carbon atoms (preferably methanesulfonic acid)
Acid), hydrochloric acid, sulfuric acid or phosphoric acid, but is not limited thereto
There is no. As the inert solvent, alkyl alcohols (1 to 8 carbon atoms, preferably
Methanol or ethanol), lower alkanenitrile (C1-6, preferably
Or acetonitrile), dialkyl ethers (preferably glyme or jig)
Rim), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane)
Sun), N, N-dialkylformamides (preferably dimethylformamide)
), N, N-dialkylacetamides (preferably dimethylacetamide),
Cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfur

Oxides (preferably dimethyl sulfoxide), aromatic hydrocarbons (preferably
is benzene or toluene) or 1-10 carbon atoms and 1-halogen atoms.
10 halogenated carbons (preferably chloroform) may be included,
However, the present invention is not limited to this. Preferred reaction temperatures range from ambient to 150 ° C.
You.

Certain compounds of formula (1) (where A is N) can also be prepared by the method shown in Scheme 7.

[0102]

Embedded image

An intermediate compound of formula (14), wherein Z is as defined above, is treated at 0 ° C.
Of the formula $R^3C(OR^6)_3$, in the presence or absence of an acid, in an inert solvent at a temperature in the range of 2 5 0 250 ° C. wherein R^6 is alkyl (C 1-6) It can be reacted with a compound. Examples of the acid include alkanoic acid having 2 to 10 carbon atoms (preferably acetic acid), arylsulfonic acid (preferably p-toluenesulfonic acid or benzenesulfonic acid), and alkanesulfonic acid having 1 to 10 carbon atoms (preferably methanesulfonic acid).), Hydrochloric acid, sulfuric acid or phosphoric acid, but is not limited thereto. Stoichiometric or catalytic amounts of these acids can be used. Examples of the inert solvent include lower alkane nitriles (1-6 carbon atoms, preferably acetonitrile),
Dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (preferably dimethylformamide), N, N-dialkylacetamides (preferably dimethyl Acetamide), cyclic amides (preferably N-
Methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene)
Alternatively, haloalkanes having 1 to 10 carbon atoms and 1 to 10 halogen atoms (preferably dichloromethane) may be included, but the present invention is not limited thereto. Preferred reaction temperatures range from 50C to 150C.

The intermediate compound of formula (7) can also be synthesized by the reaction shown in Scheme 8.

[0105]

Embedded image

Formula (15) wherein Y is OH, SH, NR^8R^7, Z is as defined above, and X is Br, Cl, I, O_3SCF_3 or B (OR "in) $_2$, R '" a "compound H or alkyl (the number 1-6) atoms), -100 ° C. to 200 DEG
in an inert solvent at a temperature in the range of ° C., with or without the presence of a base and with or without the presence of an organometallic catalyst, the formula ArM wherein M is a halogen, an alkali metal, ZnCl, ZnBr, ZnI , MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides). As will be appreciated by those skilled in the art, the reagent ArM can be generated in the reaction system. Examples of the organometallic catalyst include palladium phosphine complexes (such as $Pd(PPh_3)_4$), halides or alkanoates of palladium (such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$) or nickel complexes (such as $NiCl_2(PPh_3)_2$ etc., but is not limited thereto. The base may include, but is not limited to, alkali metal carbonates or trialkylamines (preferably, N, N-di-isopropyl-N-ethylamine or triethylamine). As the inert solvent, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (preferably dimethylformamide)
, N, N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), and aromatic hydrocarbons (preferably (Benzene or toluene) or water, but is not limited to such. Preferred reaction temperatures range from -80C to 100C.

The choice of M and X is known to those skilled in the art (Imamoto, T., "Organocerium Reagents", Comprehensive Organic Synthesis).
Synthesis), Trost, BM, (Elmsford, NY: Pergamon Press, 1991), 1
Vol., Pp. 231-250, Knochel, P., "Organozinc, Organocadmium, and Organomercury Reagents", Comprehensive Organic Synthesis, Trost, BM. (Elmsford, NY: Pergamon Press, 1991), 1
Vol. 211-230, Knight, DW. "Coupling reaction between sp^2 carbon centers (Cou
pling Reactions between sp^2 Carbon Centers), Comprehensive Organic Synthesis, Trost, B
M. Ed. (Elmsford, NY: Pergamon Press, 1991), vol 3, pages 481-520).

The compound of the formula (1) can also be produced using the method shown in Scheme 9.

[0109]

Embedded image

Formula (16) wherein A, Z, R^1 and R^3 are as defined above, and X is Br, Cl, I, O_3SCF_3 or B (OR " ")$_2$, R ' ' is H or alkyl having 1 to 6 carbons) in an inert solvent at a temperature in the range of - 100 ° C. to 200 ° C. in the presence or absence of a base; Exist,
Or without the formula ArM (where M is halogen, alkali metal, ZnCl, Zn
Br, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides). As will be appreciated by those skilled in the art, the reagent ArM can be generated in the reaction system.
(See the above references in "Comprehensive Organic Synthesis"). Palladium phosphine complexes (Pd
$(PPh_3)_4$), palladium halides or alkanoates (Pd
$Cl_2(PPh_3)_2$ or $Pd(OAc)_2$ or nickel complexes (NiC
$l_2(PPh_3)_2$, etc., but is not limited thereto. The base includes an alkali metal carbonate or a trialkylamine (preferably, N, N
-Di-isopropyl-N-ethylamine or triethylamine). Examples of the inert solvent include dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (preferably dimethylformamide), N, N-dialkyl Acetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidine-2-one), dialkyl sulfoxides (preferably dimethyl sulfoxide),
It may include, but is not limited to, aromatic hydrocarbons (preferably benzene or toluene) or water. The preferred reaction temperature is -80C to 100C.
It is in the range of 0 ° C.

An intermediate compound of formula (7) wherein Y is O, S, NH, Z is CR^2 and R^1, R^2 and Ar are as defined above, Produced as illustrated in Scheme 10.

[0112]

Embedded image

The compound of formula (3) is reacted with a base or an acid in an inert solvent at a temperature of 0 ° C. to 250 ° C.
With or without presence, the formula $H_{Two}NNH(C=Y)NH_{Two}$ (Where Y is O, S or
is NH) to produce a compound of formula (17)
Can be The acid includes alkanoic acid having 2 to 10 carbon atoms (preferably acetic acid),
Reel sulfonic acid (preferably p-toluene sulfonic acid or benzene sulfonic acid
Acid), an alkanesulfonic acid having 1 to 10 carbon atoms (preferably methanesulfonic acid),
It may include, but is not limited to, hydrochloric, sulfuric, or phosphoric acid.
Stoichiometric or catalytic amounts of these acids can be used. Bases include alka
Limetal hydrides (preferably sodium hydride), alkali metal alkoxides
(C1-C6) (preferably sodium methoxide or sodium ethoxy)
Sid), alkaline earth metal hydrides, alkali metal dialkylamides (preferred)
Or lithium di-isopropylamide), alkali metal bis (trialkyl
Lyl) amides (preferably sodium bis (trimethylsilyl) amide),
Lialkylamines (preferably N, N-di-isopropyl-N-ethylamido)
Or triethylamine) or aromatic amines (preferably pyridine).
May be, but is not limited to, inactive solvents include alkyl
Rucols (C1-6), lower alkanenitrile (C1-6, preferred
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), dialkylsulfoxy
(Preferably dimethyl sulfoxide), aromatic hydrocarbons (preferably
Benzene or toluene) or having 1 to 10 carbon atoms and 1 to 10 halogen atoms.
May include, but is not limited to, haloalkanes (preferably dichloromethane)
It is not something to be done.

Preferred reaction temperatures range from 0 ° C. to 150 ° C. The compound of formula (17) is then reacted with $R^3C(OR^8)_3$ in an inert solvent at a temperature

ranging from 0 ° C. to 250 ° C , with or without an acid, wherein R^8 is It can be reacted with a compound of alkyl (C1-6). Examples of the acid include alkanoic acid having 2 to 10 carbon atoms (preferably acetic acid), arylsulfonic acid (preferably p-toluenesulfonic acid or benzenesulfonic acid), and alkanesulfonic acid having 1 to 10 carbon atoms (preferably methanesulfonic acid).), Hydrochloric acid, sulfuric acid or phosphoric acid, but is not limited thereto. Stoichiometric or catalytic amounts of these acids can be used. Examples of the inert solvent include lower alkane nitriles (1-6 carbon atoms, preferably acetonitrile),
Dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (preferably dimethylformamide), N, N-
dialkylacetamides (preferably dimethyl Acetamide), cyclic amides (preferably N-
Methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene)
Alternatively, haloalkanes having 1 to 10 carbon atoms and 1 to 10 halogen atoms (preferably dichloromethane) may be included, but the present invention is not limited thereto. Preferred reaction temperatures range from 50C to 150C.

Scheme 11 includes compounds of formula (1) wherein R^3 is COR^7, CO_2R^7, NR^8COR^7 and $CONR^6R^7$ at a temperature of −80 ° C. to 250 ° C. Treatment with a reducing agent in an inert solvent at a temperature in the range of formula (1) wherein R^3 is $CH(OH)R^7$, CH_2OH, $NR^8CH_2R^7$ and $CH_2NR^6R^7$ Are methods that can be used to convert to other compounds.

[0116]

Embedded image

The reducing agents include alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane, dialkylboranes (
Di-isoamyl borane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy) aluminum hydrides or dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride). However, it is not limited to them. Examples of the inert solvent include alkyl alcohols (C1-6), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), and aromatic hydrocarbons (preferably , Benzene or toluene) may be included, but is not limited thereto.
Preferred reaction temperatures range from -80C to 100C.

Scheme 12 shows that a compound of formula (1), wherein R^3 is COR^7 or CO_2R^7, can be prepared by reacting a compound of formula (1) in an inert solvent at a temperature ranging from −80 ° C. to 250 ° C. Shown is a method that can be used to treat with the reagents of R^7M and convert to another compound of formula (1) where R^3 is $C(OH)(R^7)_2$.

[0119]

Embedded image

M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, Mg
Cl, MgI, $CeCl_2$, $CeBr_2$ or copper halides. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran) or aromatic hydrocarbons (preferably benzene or toluene). Not something. Preferred reaction temperatures range from -80C to 100C.

Formula (1) (wherein R^{Three} Is $-NR^8COR^7$, $-N(COR^7)_{Two}$, $-NR^8CONR^6R^7$, $-NR^8CO_{Two}R^{13}$, $-NR^6R^7$, $-NR^8SO_{Two}R^7$Can be synthesized as shown in Scheme 13.

[0122]

Embedded image

A compound of formula (18), wherein R and R^1 are as defined above, is reacted with a base in an inert solvent at a temperature in the range of −50 ° C. to 250 ° C., or Without this, the compound of formula (19) can be produced by reacting with the compound of formula (4) or (10). Examples of the base include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1 to C6) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, and alkali metal hydrides. Dialkylamides (preferably lithium di-isopropylamide)

, Alkali metal carbonates, alkali metal bis (trialkylsilyl) amides (
Preferably, sodium bis (trimethylsilyl) amide), trialkylamines (preferably di-isopropylethylamine) or aromatic amines (preferably pyridine) may be included, but are not limited thereto. Examples of the inert solvent include alkyl alcohols (1-8 carbon atoms, preferably methanol or ethanol), lower alkane nitriles (1-6 carbon atoms, 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) or aromatic hydrocarbons (preferably benzene or toluene), but are not limited thereto. Preferred reaction temperatures range from 0 ° C to 100 ° C.

Next, a compound of the formula (19) is added to an alkylating agent, a sulfonylating agent or an acylating agent.
The continuous reaction with the agent, or a combination thereof, is carried out in the range of -80 ° C to 250 ° C.
By carrying out in an inert solvent with or without a base at the reaction temperature
, Formula (1) (wherein, $R^{Three}$is -NR^8COR^7, -N $(COR^7)_{Two}$, -$NR^8CONR^6R^7$, -$NR^8CO_{Two}R^{13}$, -NR^6R^7, -$NR^8SO_{Two}R^7$) Can be obtained. Alkylating agents include C_1~ C_{Ten}Alkyl
halides, tosylate, mesylate or triflate; C_1~ C_{Ten}Haloalkyl (having 1 to 10 halogen atoms) halides, tosylate, mesylate or
Triflates; C_{Two}~ C_8Alkoxyalkyl halides and tosylate
, Mesylate or triflate; C_{Three}~ C_6Cycloalkyl halides
, Tosylate, mesylate or triflate; C_{Four}~ C_{12}Cycloalkylalkyl halides, tosylates, mesylates or triflaky
G; aryl (C_1~ C_{Four}Alkyl) halides, tosylates, mesile
Or triflates; heteroaryl (C_1 ~ C_{Four}Alkyl) halogen
Compounds, tosylate, mesylate or triflate; or heterocyclic (C_1 ~ C_{Four}Alkyl) halides, tosylate, mesylate or trif
Rates may be included, but are not limited to. Acylating agents include
, C_1~ C_{Ten}Halides or anhydrides of alkanoic acids, C 1-10 halogen atoms$_1$~ C_{Ten}Haloalkanoic acid halides or anhydrides, C_{Two}~ C_8Halides or anhydrides of alkoxy
alkanoic acids, C_{Three}~ C_6Cycloalkane
Acid halides or anhydrides, C_{Four}~ C_{12}Halogens or anhydrides of cycloalkylalkanoic acids, halides or anhydrides of aromatic carboxylic acids
, Aryl (C_1 ~ C_{Four}) Halides or anhydrides of alkanoic acids, aromatic
Heterocyclic carboxylic acid halides or anhydrides, heteroaryl (C_1~ C_{Four})
Alkanic acid halides or anhydrides, heterocyclic carboxylic acid halides
Or anhydrides, or heterocyclic (C_1 ~ C_{Four}) Halides of alkanoic acids or
May include, but are not limited to, anhydrides. Sulfonylation
The agent contains C_1~ C_{Ten}Halides or anhydrides of alkyl sulfonic acids, C 1 to C 10 halogen atoms$_1$~ C_{Ten}Haloalkylsulfonic acid halides or anhydrides, C_{Two}~
C_8Halides of alkoxyalkylsulfonic acids or none
Waters, C_{Three}~ C_6Halides or anhydrides of cycloalkylsulfonic acid,
C_{Four}~ C_{12}Halides or anhydrides of cycloalkylalkylsulfonic acids, halides or anhydrides of aromatic sulfonic acids, aryl (C_1~ C_{Four}Al
Kill)-, halides or anhydrides of heteroarylsulfonic acids, hetero
Aryl (C_1~ C_{Four}Alkyl) sulfonic acid halides or anhydrides,
Halides or anhydrides of elementary ring sulfonic acids or heterocyclic (C_1~ C_{Four}Al
Kill) sulfonic acid halides or anhydrides, including but not limited to
It is not something to be done. Bases include alkali metal hydrides (preferably hydrogenated
Thorium), alkali metal alkoxides (C1-6) (preferably sodium
Methoxide or sodium ethoxide), alkaline earth metal hydrides,
Alkali metal dialkylamides (preferably lithium di-isopropylamide
), Alkali metal carbonates, alkali metal bis (trialkylsilyl) amides
(Preferably sodium bis (trimethylsilyl) amide), trialkylamido
(Preferably di-isopropylethylamine) or aromatic amines (preferably
Preferably pyridine), but is not limited thereto. Inactivity
Examples of the aprotic solvent include alkyl alcohols (1-8 carbon atoms, preferably methanol and the like).
Or ethanol), lower alkanenitrile (having 1 to 6 carbon atoms, preferably
Nitriles), dialkyl ethers (preferably diethyl ether), cyclic ethers
Ters (preferably tetrahydrofuran or 1,4-dioxane), N, N-
Dialkylformamides (preferably dimethylformamide), N, N-dia
Alkylacetamides (preferably dimethylacetamide) and cyclic amides (preferably
N-methylpyrrolidin-2-one) and dialkyl sulfoxides (preferably
Or dimethyl sulfoxide) or aromatic hydrocarbons (preferably benzene
Or toluene) may be included, but is not limited thereto. Preferred
Reaction temperatures range from 0 ° C to 100 ° C.

Compounds of formula (1) wherein A is CR and R is as defined above can be synthesized by the method shown in Scheme 14.

[0126]

Embedded image

The compound of formula (4) or (19) can be prepared by reacting a compound of formula (20) (wherein R^1 and By treating with a compound of the formula (1) wherein R ^{3} is as defined above, a compound of formula (1) (where A is CR and R is as defined above) can be obtained. Bases include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1-6) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal hydrides Dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis (trialkylsilyl) amides (preferably sodium bis (
Trimethylsilyl) amide), trialkylamines (preferably di-isopropylethylamine) or aromatic amines (preferably pyridine), but are not limited thereto. Examples of the inert solvent include alkyl alcohols (1-8 carbon atoms, preferably methanol or ethanol), lower alkane nitriles (1-6 carbon atoms, 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)
Alternatively, aromatic hydrocarbons (preferably, benzene or toluene) may be included, but are not limited thereto. Preferred reaction temperatures range from 0 ° C to 100 ° C. Alternatively, a compound of formula (1) wherein A is CR and R is as defined above is synthesized via intermediates of formulas (22) and (23). Can be.

The compound of formula (4) or (10) can be prepared by reacting the compound of formula (21) in an inert solvent at a temperature ranging from 0 ° C. to 250 ° C. with or without the presence of a base, wherein R^1 is is as defined above, by the R^e of treating a compound of alkyl (1 to 6 carbon atoms), formula (1) (wherein, a is CR, R is as defined above The base includes alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1 to C6) (preferably sodium methoxide or sodium ethoxide).), Alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis (trialkylsilyl) amides (Preferably, sodium bis (trimethylsilyl) amide), trialkylamines (preferably di-isopropylethylamine) or aromatic amines (preferably pyridine) may be included, but are not limited thereto. Examples of the active solvent include alkyl alcohols (1-6 carbon atoms, preferably methanol or ethanol), lower alkane nitriles (1-6 carbon atoms, 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) or aromatic hydrocarbons (preferably benzene or toluene) , But is not limited thereto.
Preferred reaction temperatures range from 0 ° C to 100 ° C. A compound of the formula (22) is converted to -8
By treating with a halogenating agent or a sulfonylating agent at a reaction temperature in the range of 0 ° C. to 250 ° C. with or without an inert solvent and with or without a base, the compound of formula (23) (formula (23) Wherein X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkanesulfonyloxy). The halogenating $_{agent,}$ $_{SOCl\ 2,\ POCl\ 3,\ PCl}$ $_{3,}$ PCl 5, POBr 3, including but PBr_3 or PBr_5 but is not limited to them. Examples of the sulfonylating agent include halides or anhydrides of alkanesulfonic acid (such as methanesulfonyl chloride or methanesulfonic anhydride) and halides or anhydrides of arylsulfonic acid (p-toluenesulfonyl chloride or anhydride). Or haloalkylsulfonic acid halides or anhydrides (preferably trifluoromethanesulfonic anhydride),
It is not limited to them. Examples of the base include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1 to C5) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, and alkali metal hydrides Dialkylamides (preferably lithium di-isopropylamide), alkali metal bis (trialkylsilyl) amides (preferably sodium bis (trimethylsilyl) amide), trialkylamines (preferably N, N-di-isopropyl-N) -Ethylamine or triethylamine) or aromatic amines (preferably pyridine), but are not limited thereto. Inert solvents include lower alkane nitriles (C 1 -C 1)
6, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (preferably dimethylformamide), N, N- Dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or Haloalkanes having 1 to 10 carbon atoms and 1 to 10 halogen atoms (preferably dichloromethane) may be included, but are not limited thereto. Preferred reaction temperatures range from -20C to 100C.

The compound of formula (23) can be prepared by reacting a compound of formula R^3 H (with or without an inert solvent, with or without a base) at a reaction temperature ranging from −80 ° C. to 250 ° C., R^3 are as defined above, but are not SH, COR^7, CO_2R^7, aryl or heteroaryl) to produce a compound of formula (1). Bases include alkali metal hydrides (preferably sodium hydride),
Alkali metal alkoxides (C1-6) (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), trialkylamines (preferably N, N-di-isopropyl-N-ethylamine) or aromatics Amines (preferably pyridine) may be included, but are not limited thereto. As the inert solvent, alkyl alcohols (C 1 - C 1)
8, preferably methanol or ethanol), lower alkane nitriles (C1-6, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or , 4-dioxane), N, N-dialkylformamides (preferably dimethylformamide), N, N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), Dialkyl sulfoxides (preferably dimethyl sulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes having 1 to 10 carbon atoms and 1 to 10 halogen atoms (preferably dichloromethane) may be contained. However, it is not limited to them. Preferred reaction temperatures range from 0 ° C to 140 ° C.

Some compounds of formula (1) can also be prepared using the method shown in Scheme 15.

[0131]

Embedded image

Reaction of a compound of formula (24), wherein R_c is a lower alkyl group and Ar is as defined above, with hydrazine in the presence or absence of an inert solvent An intermediate of formula (25), wherein Ar is as defined above, can be obtained. The conditions are the same as those used for producing the intermediate of formula (4) from the compound of formula (3) in Scheme 4. A compound of the formula (25) (where A is N):
In an inert solvent, with or without the presence of an acid, a compound of the formula $R^1C(=NH)OR_e$,
R^1 is as defined above, and $_{Re}$ is a lower alkyl group), then reacting with a compound of the formula $Y=C(R_d)_{2\ in}$ an inert solvent, with or without the presence of a base. (Wherein Y is O or S, and R_d is halogen (preferably chlorine), alkoxy (1-4 carbons) or alkylthio (1-4 carbons). A compound of formula (27) is obtained, wherein A is N and Y is O, S. The conditions for these conversions are the same as those used to convert the compound of formula (4) into a compound of formula (7) in Scheme 4.

Alternatively, using the same conditions as used for converting the compound of formula (21) to the compound of formula (22) in Scheme 14, the compound of formula (25) (where A is CR is a compound of formula $R^1(COO)CHR(CYY)OR_c$, wherein R^1 and R are as defined above, and R_c is a lower alkyl group. When reacted with a compound, a compound of formula (27) (where A is CR) is obtained. The intermediate of formula (27), wherein Y is O, is treated with a halogenating or sulfonylating agent in an inert solvent, with or without the presence of a base, and then treated with a base in an inert solvent. By reacting with R^3 H or R^2 H with or without the presence of
Z is CR^2).

As will be appreciated by those skilled in the art, in order to obtain compounds of formula (1), in Scheme 15, the halogenating agent, sulfonylating agent, R^3 H or R^2 H Various combinations of can be used. For example, in some cases, a compound is reacted with a stoichiometric amount of a halogenating or sulfonylating agent to form R^2 H (or R^3 H
) And then repeating the reaction with a halogenating or sulfonylating agent,
It may be desirable to further react with R^3 H (or R^2 H) to obtain a compound of formula (1). The reaction conditions and reagents used for these transformations are shown in Scheme 14 (
When the intermediate compound of the formula (22) is converted to a compound of the formula (23) in the case of A is CR, and further to a compound of the formula (1), or in the scheme 1 (where A is N) The conditions are the same as those used when converting the intermediate compound (7) into the compound of the formula (8) and further into the compound of the formula (1).

Alternatively, a compound of formula (27) in which Y is S can be converted to a compound of formula (1) in Scheme 15. Alkylating the intermediate compound of formula (27) with a compound of R^f X, wherein R^f is lower alkyl, X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy, in an inert solvent,

(Then, optionally oxidized with an oxidizing agent in an inert solvent) and further reacting with R^3H in an inert solvent, with or without the presence of a base, to give the compound of formula (1) can get. The reaction conditions and reagents used are the same as those used to convert the intermediate compound of formula (7) into a compound of formula (12) (or formula (13)) and further to a compound of formula (1) in Scheme 2. It is.

Compounds of formula (1) can be prepared from compounds of formula (24) using the alternative route shown in Scheme 15. The compound of formula (24) is prepared by converting the compound of formula (3) into a compound of formula (17) and then a compound of formula (7) in Scheme 10 using an acid in an inert solvent. Reaction with a compound of formula $NH_2NH(C=NH)NH_2$, with or without presence, followed by a formula $R^1C(OR_c)_3$ where R_c is lower alkyl and R^1 is as defined above (As defined above), can be converted to a compound of formula (27).

Some compounds of formula (2) can be prepared by the method illustrated in Scheme 16.

[0138]

Embedded image

[0139] The compound of formula (27b), in an inert solvent, wherein $R^{14}X$ (where without a base in the presence of, or is, R^{14} is as defined above, X is halogen, alkanesulfonyloxy Treatment with various alkylating agents (which are oxy or haloalkanesulfonyloxy) gives the structure of formula (28). Treating a compound of formula (28), wherein Y is O, with a halogenating agent or a sulfonylating agent in an inert solvent, with or without the presence of a base, followed by the addition of the base in an inert solvent is reacted with R^3H with or without the presence of a compound of formula (2). The reaction conditions for these conversions are as follows: In Scheme 14 (when A is CR), the intermediate compound of the formula (22) is converted to the compound of the formula (2)
When the compound of formula (3) is further converted to the compound of formula (1), or in scheme 1 (where A is N), the intermediate compound of formula (7) is converted to a compound of formula (8) and further a compound of formula (8)
The conditions are the same as those used when converting into the compound of 1). Alternatively, the formula (2)
8) (in the formula, Y is in R^fX (wherein a compound of a S) in an inert solvent, R^f is lower alkyl, X is halogen, alkanesulfonyloxy or haloalkane sulfonyloxy) of By alkylating with a compound, and then optionally oxidizing with an oxidizing agent in an inert solvent, and further reacting with R^3H in an inert solvent, with or without the presence of a base, the formula (The compound of 1) is obtained. The reaction conditions and reagents used were the intermediate compound of formula (7) in scheme 2
(Or the conditions used to convert the compound of the formula (13) into the compound of the formula (1)).

Compounds of formula (1) where Z is COH can be converted to compounds of formula (2) as illustrated in Scheme 16. In an inert solvent, a compound of formula $R^{14}X$, with or without the presence of a base, wherein R^{14} is as defined above and X is a halogen,
Treatment with various alkylating agents of alkanesulfonyloxy or haloalkanesulfonyloxy) provides the structure of (2). As the skilled artisan will appreciate, the methods used in Scheme 16 Formula (1) (wherein, Z is COR^7 is) can also be used in the preparation of a compound of.

For Scheme 16, the terms "base" and "inert solvent" can have the following meanings. Examples of the base include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (C1 to C6) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, and alkali metal hydrides. Dialkylamides (preferably lithium diisopropylamide), alkali metal bis (trialkylsilyl) amides (preferably sodium bis (trimethylsilyl) amide), trialkylamines (preferably N
, N-di-isopropyl-N-ethylamine or triethylamine) or aromatic amines (preferably pyridine), but are not limited thereto. Examples of the inert solvent include lower alkane nitriles (1-6 carbon atoms, preferably acetonitrile) and 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 having 1 to 10 carbon atoms and having 1 to 10 halogen atoms (preferably dichloromethane) may be included, but are not limited thereto. Preferred reaction temperatures range from -20C to 100C.

[0142] EXAMPLES Analytical data using the following general procedure, were recorded for the compounds described below. Proton NMR spectra were recorded on an IBM-Bruker FT-NMR (300 MHz). Chemical shifts were recorded using ppm (δ) relative to the internal standard tetramethylsilane in deuterated chloroform or deuterated dimethyl sulfoxide specified below. Mass spectra (MS) or high-resolution mass spectra (HRMS) are available from Finnegan
MAT 8230 spectrometer (using chemical ionization (CI) or gas chromatography (GC) with ammonia as carrier gas, as specified below) or
Recorded on a Hewlett Packard Model 5988A spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH measurements during the reaction procedure were performed on pH test paper.

Reagents were purchased commercially and, if necessary, D. Perrin and W.L.F Armarego, Purification of Laboratory Chemicals, 3rd Edition, (New York: Pe
rgamon Press, 1988) and purified prior to use according to the general method outlined. Chromatography was performed on silica gel using the solvent system indicated below. In the case of a mixed solvent system, the volume ratio is shown. Otherwise, parts and percentages are based on mass.

The following examples describe the invention in more detail. These examples illustrate the best means currently contemplated for carrying out the invention and are provided by way of illustration only and not limitation.

Example 1 2,7-Dimethyl-8- (2,4-dimethylphenyl) [1,5-a] -pyrazolo- [1,3,5] -triazin-4 (3H) -one (Wherein Y is O, R^1 is CH_3, Z is $C-CH_3$, and Ar is 2,4-dimethylphenyl).

A. 1-cyano-1- (2,4-dimethylphenyl) propan-2-one sodium pellet (9.8 g, 0.43 mol) was added to 2,4-dimethylphenylacetonitrile (48 g, 0.33 mol) in ethyl acetate (150 mL).) Added in small portions to the solution at ambient temperature. The reaction mixture was heated to reflux and stirred for 16 hours. The resulting suspension was cooled to room temperature and filtered. The collected precipitate was washed with a large amount of ether and air-dried. Dissolve the solid in water and add 1N HCl solution to pH = 5
To 6. The mixture was extracted with ethyl acetate (3 × 200 mL). The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced pressure to obtain a white solid (45.7 g, yield: 74%). ^{1}NMR (CDCl 3, 300MHz) ; CI-MS: 188 (M + H).

B. 5-Amino-4- (2,4-dimethylphenyl) -3-methylpyrazole 1-cyano-1- (2,4-dimethylphenyl) propan-2-one (43.
8 g, 0.23 mol), hydrazine hydrate (22 mL, 0.46 mol),
A mixture of glacial acetic acid (45 mL, 0.78 mol) and toluene (500 mL) was stirred at reflux temperature in a device equipped with a Dean-Stark trap for 18 hours. The reaction mixture was cooled to ambient temperature and the solvent was distilled off under reduced pressure. The residue was washed with 6N HCl
The resulting solution was extracted three times with ether. Concentrated aqueous ammonia was added to the aqueous layer to adjust the pH to 11. The resulting half solution was extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced

pressure to obtain a pale brown viscous oil (34.6 g, yield: 75%). NMR ($CDCl_3$, 300 MHz): 7.10 (s, 1H), 7.05 (d, 2H, J = 1), 2.37 (s, 3H), 2.10 (s, 3H). CI-MS: 202 (M + H).

C. 5-acetamidino-4- (2,4-dimethylphenyl) -3-methylpyrazole, acetate of rapidly stirring potassium carbonate (69.5 g, 0.50 mol), dichloromethane (120 mL) and water (350 mL). To the mixture was added ethylacetimidate hydrochloride (60 g, 0.48 mol) quickly The two layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 120 mL). The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was distilled off by atmospheric distillation, and the residue (35.0 g) in the vessel, which was a clear pale yellow liquid, was used without further purification.

5-Amino-4- (2,4-dimethylphenyl) -3-methylpyrazole (3
4 g, 0.17 mol), ethyl acetimidate (22 g, 0.25 mol)
Acetic acid (9.7 g) while stirring a mixture of
mL, 0.17 mol) was added. The resulting reaction mixture was stirred at room temperature for 3 days.
After the stirring, the solution was concentrated under reduced pressure to about one third of the initial volume. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. The white solid was dried under reduced pressure (3
1.4 g, 61% yield). NMR (DMSO-d 6, 300MHz): 7.00 (s, 1H), 6.90 (dd, 2H, J = 7,1), 2.28 (s, 3H),
2.05 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.8
1 (s, 3H). CI-MS: 243 (M + H). D. 2,7-dimethyl-8- (2,4-dimethylphenyl) [1,5-a]-
Pyrazolo- [1,3,5] -triazin-4 (3H) -one Sodium pellet (23 g, 1 mol) was stirred vigorously and ethanol (500
mL). After all the sodium had reacted, 5-acetamidino-4- (2,4-dimethylphenyl) -3-methylpyrazole, acetate (31.
2 g, 0.1 mol) and diethyl carbonate (97 mL, 0.8 mol) were added. The resulting reaction mixture was heated to reflux and stirred for 18 hours. The mixture was cooled to room temperature and the solvent was distilled off under reduced pressure. The residue was dissolved in water and 1N HCl solution was added slowly to pH = 5-6. The aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced pressure to obtain a light tan solid (26 g, yield: 98%). NMR ($CDCl_3$, 300 MHz): 7. 15 (s, 1H), 7.09 (s, 2H), 2.45 (s, 3H), 2.39 (S, 3H), 2.30 (s, 3H). CI-MS: 269 (M + H).

Example 2 5-Methyl-3- (2,4,6-trimethylphenyl) [1,5-a]-[1,
Preparation of 2,3] triazolo- [1,3,5] -triazin-7 (6H) -one (Formula 7, where Y is O, R^1 is CH_3, Z is N, Ar is 2,4, 6-trimethylphenyl)

A. 1-phenylmethyl-4- (2,4,6-trimethylphenyl) -5
Aminotriazole 2,4,6-trimethylbenzyl cyanide (1.0 g, 6.3 mmol), benzyl azide (0.92 g, 6.9 mmol) and potassium t-butoxide (
(0.78 g, 6.9 mmol) in tetrahydrofuran (10 mL) was stirred at ambient temperature for 2.5 days. The resulting suspension was diluted with water and extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced pressure to obtain a brown oily substance. This was triturated with ether and filtered to give a yellow solid (1.12 g, 61% yield). NMR (CDCl 3, 300M Hz) : 7.60~7.30 (m, 5H), 7.30~7.20 (m, 2H),
5.50 (s, 2H), 3.16 (broad s, 2H), 2.30 (s, 3H)
, 2.10 (s, 6H). CI-MS: 293 (M + H).

B. 4- (2,4,6-trimethylphenyl) -5-aminotriazole Liquid ammonia (30 mL) and 1-phenylmethyl-4- (2,4,6-
Trimethylphenyl) -5-aminotriazole (1.1 g, 3.8 mmol)
To a mixture of was added sodium (500 mg, 22 mmol) with stirring.
The reaction mixture was stirred until a dark green color persisted. An ammonium chloride solution (mL) was added and stirred for 16 hours while warming to ambient temperature. The residue was treated with 1M HCl.
Filtered. The aqueous layer was made basic (pH = 9) with concentrated aqueous ammonia and extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced pressure to obtain a single yellow solid by thin layer chromatography (ethyl acetate) (520 mg). NMR (CDCl 3, 300MHz) 6.97 (s, 2H), 3.68~3.50 (broad s, 2H), 2.32 (s , 3H), 2.10 (S, 6H). CI-MS: 203 (M + H).

C. 4- (2,4,6-trimethylphenyl) -5-acetamidinotriazole, acetate 4- (2,4,6-trimethylphenyl) -5-aminotriazole (400
mg, 1.98 mmol), ethylacetimidate (261 mg, 3 mmol)
) And glacial acetic acid (0.1 mL, 1.98 mmol) in acetonitrile (5 mL)
The medium mixture was stirred at ambient temperature for 4 hours. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. Drying under reduced pressure gave a white solid (490 m
g, 82% yield). NMR (DMSO-d 6, 300MHz): 7.90~7. 70 (broad s, 0.5H), 7.50-7.20 (broad s, 0.5H)
, 6.90 (s, 2H), 6.90 (s, 2H), 3.50-3.10 (broad s, 3H), 2.30-2.20 (broad s, 3H), 2.05 (D, 1H
, J = ?), 1.96 (s, 6H), 1.87 (s, 6H). CI-MS: 24
4 (M + H).

D. 5-methyl-3- (2,4,6-trimethylphenyl) [1,5-a]
-[1,2,3] -Triazolo- [1,3,5] -triazin-7 (4H) -one Sodium (368 mg, 16.2 mmol) was added to ethanol (10 mL) with stirring at room temperature. After sodium had reacted, 4- (2,4,6-trimethylphenyl) -5-acetamidinotriazole, acetate (490 mg, 1.
6 mmol) and diethyl carbonate (1.6 mL, 13 mmol) were added. The reaction mixture was stirred at reflux for 5 hours, then cooled to room temperature. The reaction mixture was diluted with water, adjusted to pH = 5-6 by adding 1N HCl solution, and extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced pressure to obtain a yellow residue. Trituration with ether and filtration gave a yellow solid (300 mg, 69% yield). NMR (CDCl 3, 300MHz). 6.98 (s, 2H), 2.55 (s, 3H), 2.35 (s, 3H), 2.10 (s, 6H). CI-MS: 270 (
M + H).

Example 3 4- (Di (carbomethoxy) methyl) -2,7-dimethyl-8- (2,4-dimethylphenyl) [1,5-a] -pyrazolo- [1,3 Preparation of 5] -triazine (Formula 1, wherein R^3 is CH ($CHCO_2CH_3$) $_2$, R^1 is CH_3, Z is C--CH_3, and Ar is 2,4-dimethylphenyl)

A. 4-chloro-2,7-dimethyl-8- (2,4-dichlorophenyl) [1,5-a] -pyrazolotriazine 2,7-dimethyl-8- (2,4-dimethylphenyl) [1,5 -A] -Pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38 g, 4.5 mm
ol), N, N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) were stirred at reflux for 48 hours. Excess phosphorus oxychloride was distilled off under reduced pressure. The residue was poured into ice water, stirred for a short time, and quickly extracted three times with ethyl acetate. The organic layers were combined,

washed with ice water, then dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced pressure to obtain a brown oily substance. One fraction (Rf = 0.5) by flash column chromatography (ethyl acetate: hexane :: 1: 4)) Got. The solvent was distilled off under reduced pressure to obtain a yellow oil. (1.0 g, yield 68 %). NMR ($CDCl_3$, 300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7, 1), 7.30 (d, 1H, J = 7), 2.6 8 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

B. 4- (di (carbomethoxy) methyl) -2,7-dimethyl-8- (2 4-dimethylphenyl) [1,5-a] -pyrazolo-1,3,5-triazine Sodium hydride (80 mg in 60% oil) while discarding hexane for each wash , 2 mmol) was washed twice with hexane and dried in anhydrous tetrahydrofuran (THF, 1 mL). Diethyl malonate (0.32 g, 2 mmol) in THF (2 mL) solution was added dropwise over 5 minutes. During that time, vigorous gas evolution occurred. A solution of 4-chloro-2,7-dimethyl-8- (2,4-dichlorophenyl) [1,5-a] -pyrazolotriazine (0.5 g, 1.75 mmol) in THF (2 mL) was added and the reaction mixture was added. Was stirred for 48 hours under a nitrogen atmosphere. Pour the resulting suspension into water. Extracted three times with ethyl acetate. The organic layers were combined, washed once with brine, dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced pressure to obtain a brown oil. Column chromatography (ethyl acetate: hexane :: 1: 9) was performed, and the solvent was distilled off under reduced pressure to obtain a pale yellow solid (Rf = 0.2, 259 mg, yield 35%). Melting point 50-52 [deg.] C. $NMR_{(CDCl3, 300MHz)}$: 12.35 (broad s, 1H), 7.15~7.00 (m , 3H), 4.40 (q, 2H, J = 7), 4.30 (q, 3H, J = 7), 2.4, 2.35, 2.3, 2.2, 2.1 (5s, 12H), 1.4 (t, 3H, J = 7), 1.35 to 1.25 (m, 3H)), CI-HRMS: Calculated: 411.2023, Observed: 411.223.

Example 6 4- (1,3-dimethoxy-2-propylamino) -2,7-dimethyl-8- (

Production of 2,4-dichlorophenyl) [1,5-a] -pyrazolo-1,3,5-triazine (Formula 1, where R^3 is NHCH (CH_2OCH_3) $_2$, R^1 is CH_3, Z is C-CH_3, Ar is 2,4-dichlorophenyl)

A. 4-chloro-2,7-dimethyl-8- (2,4-dichlorophenyl) [1,5-a] -Pyrazolotriazine 2,7-dimethyl-8- (2,4-dimethylphenyl) [1,5-a] -pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38 g, 4.5 mm ol), N, N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) were stirred at reflux for 48 hours. Excess phosphorus oxychloride was distilled off under reduced pressure. The residue was poured into ice water, stirred for a short time, and quickly extracted three times with ethyl acetate. The organic layers were combined, washed with ice water, then dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced pressure to obtain a brown oil. One fraction (Rf = 0.5) by flash column chromatography (ethyl acetate: hexane :: 1: 4) I got The solvent was distilled off under reduced pressure to obtain a yellow oil. (1.0 g, yield 68%). NMR ($CDCl_3$, 300 MHz): 7.55 (d, 1H, J = 1); 38 (dd, 1H, J = 7, 1), 7.30 (d, 1H, J = 7), 2.68 (S, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

B. 4- (1,3-dimethoxy-2-propylamino) -2,7-dimethyl-8- (2,4-dichlorophenyl) [1,5-a] -pyrazolo-1,3,5- Triazine 4-chloro-2,7-dimethyl-8- (2,4-dichlorophenyl) [1,5 -A] -Pyrazolo-1,3,5-triazine (Part A, 570 mg, 1.74 mmol), 1,3-dimethoxypropyl-2-aminopropane (25 mg, 2 . 08 mmol) and ethanol (10 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was poured into water (25 mL) and extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was distilled off under reduced pressure. One fraction was obtained by column chromatography (CH_2Cl_2 : CH_3OH :: 50: 1). The solvent was distilled off under reduced pressure to obtain a solid (250 mg, yield: 35%). Melting point 118 ~ 120 ° C. NMR ($CDCl_3$, 300 MHz): 7.50 (s, 1H); 28 (dd, 2H, J = 8, 1), 6.75 (d, 1H, J = 8), 4.70 4.4.58 (m, 1H), 3.70 to 3.55 (m, 4H), 3.43 (s, 6 H), 2.50 (s, 3H), 2.35 (s, 3H). CI-HRMS: Calculated value: 409.1072, found value: 409.1085. Calcd ($C_{18}H_{25}Cl_2N_5O_2$): C, 52.69, H, 5.17, N, 17.07, Cl, 17. 26. Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17 . 50.

The following examples in Tables 1 to 4 can be prepared using the above preparation methods and modifications that are well known to those skilled in the art of organic synthesis.

The examples outlined in Table 1 can be manufactured by the methods outlined in Examples 1, 2, 3 or 6. Commonly used abbreviations are as follows: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, and Ex is an example.

Table 1

[0164]

Embedded image

[0165]

Notes for Table 1: a) Elemental analysis: Calculated: C, 52.69, H, 5.17, N, 17.07, Cl. , 17.26. Found: C, 52.82, H, 5.06, N, 16.77, Cl. , 17.50. bu) Elemental analysis: Calculated: C, 65.90, H, 7.72, N, 18.27. Found: C, 65.77, H, 7.62, N, 18.26. bv) Elemental analysis: Calculated: C, 65.02, H, 7.38, N, 18.96. Found: C, 65.01, H, 7.43, N, 18.68. bz) CI-HRMS: calculated: 430.2454, found: 430.2468 (M + H).

Example 431 2,4,7-Dimethyl-8- (4-methoxy-2-methylphenyl) [1,5-

Preparation of a] -Pyrazolo-1,3,5-triazine (Formula 1, wherein R^3 is CH_3, R^1 is CH_3, Z is C--CH_3, and Ar is 2,4-dimethylphenyl)) 5-acetamidino-4- (4-methoxy-2-methylphenyl) -3-methylpyrazole, acetic acid salt (602 mg, 2 mmol) was mixed with a saturated $NaHCO_3$ solution (10 mL). The aqueous mixture was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was added to toluene (10 mL) and trimethyl orthoacetate (0.36 g, 3 mmol) to form a suspension. The reaction mixture was heated to reflux under a nitrogen atmosphere and stirred for 16 hours. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure to give an oily solid. Column chromatography ($CHCl_3$: MeOH :: 9: 1) was performed, and the solvent was distilled off under reduced pressure to obtain a yellow viscous oil (Rf = 0.6, 210 mg, yield 37%). NMR ($CDCl_3$, 300 MHz): 7.15 (d, 1H, J =

1), 6.9 (d, 1H, J = 1), 6.85 (dd, 1H, J = 8, 1), 3.85 (s,
3H), 2.95 (s, 3H), 2.65 (s, 3H), 2.4 (s, 3H),
2.15 (s, 3H); CI-HRMS: calculated: 283.1559, found:
283.1554 (M + H).

Example 432 7-Hydroxy-5-methyl-3- (2-chloro-4-methylphenyl) pyrazo

B [1,5-a] pyrimidine (Formula 1, wherein A is CH, R^1 is Me, R^{Three} is OH, Z is C-Me, Ar is 2-
5-amino-4- (2-chloro-4-methylphenyl) -3-methylpyrazo
(1.86 g, 8.4 mmol) was dissolved in glacial acetic acid (30 mL) with stirring.
Was. Next, ethyl acetoacetate (1.18 mL, 9.2 mmol) was added to the obtained solution.
) Was added dropwise. Heat the reaction mixture to reflux temperature, stir for 16 hours, then cool to room temperature
Rejected. Ether (100 mL) was added and the resulting precipitate was collected by filtration. Decrease
Drying under pressure gave a white solid (1.0 g, 42%). NMR ($CDCl_{Three}$, 300 Hz): 8.70 (broad s, 1H), 7.29 (s, 1H), 7.21 to 7.09 (m, 2H), 5.62 (s, 1H), 2.35 (s, 6H)
, 2.29 (s, 3H); CI-MS: 288 (M + H).

Example 433 7-chloro-5-methyl-3- (2-chloro-4-methylphenyl) pyrazolo [
1,5-a] pyrimidine (Formula 1, wherein A is CH, R^1 is Me, R^3 is Cl, Z is C-Me, and Ar is 2-chloro-4-methylphenyl) 7-hydroxy-5-methyl-3- (2-chloro-4-methylphenyl) pyrazolo [1,5-a] pyrimidine (1.0 g, 3.5 mmol), phosphorus oxychloride (2.7 g, 1.64 mL, 17.4 mmol), N, N-diethylaniline (
A mixture of 0.63 g, 0.7 mL, 4.2 mmol) and toluene (20 mL) was stirred at reflux for 3 hours, then cooled to ambient temperature. The volatile components were distilled off under reduced pressure. Flash column chromatography of the residue (EtOAc: Hexane ::
1: 2) to give 7-chloro-5-methyl-3- (2-chloro-4-methylphenyl) pyrazolo [1,5-a] pyrimidine as a yellow oil (900 mg).
, 84% yield). NMR ($CDCl_3$, 300Hz): 7.35 (s, 1H), 7.28~7.26 (m, 1H), 7.16 (d, 1H, J = 7), 6.80 (
s, 1H), 2.55 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H)
H); CI-MS: 306 (M + H).

Example 434 7- (Pentyl-3-amino) -5-methyl-3- (2-chloro-4-methylphenyl) pyrazolo [1,5-a] pyrimidine (Formula 1, wherein A is CH, R^1 is Me, R^3 is pentyl-3-amino, Z is CM
e, Ar is 2-chloro-4-methylphenyl) 3-pentylamine (394 mg, 6.5 mmol) and 7-chloro-5-
Methyl-3- (2-chloro-4-methylphenyl) pyrazolo [1,5-a] pyrimidine (200 mg, 0.65 mmol) in dimethyl sulfoxide (DMSO,
(10 mL) The solution was stirred at 150 ° C. for 2 hours and then cooled to ambient temperature. Then, the reaction mixture was poured into water (100 mL) and mixed.
Extract three times with dichloromethane.
The combined organic layers were washed with brine. After drying over $MgSO_4$ and filtration, the solvent was distilled off under reduced pressure to obtain a yellow solid.
Flash chromatography (EtOAc: Hexane :: 1: 4) provided a white solid (140 mg, 60% yield).
). MP 139~141 ° C; NMR ($CDCl_3$, 300Hz): 7.32 (s, 1H), 7.27 (d, 1H, J = 8), 7.12 (d, 1H, J = 7), 6
. 02 (d, 1H, J = 9), 5.78 (s, 1H), 3.50-3.39 (m
, 1H), 2.45 (s, 3H), 2.35 (s, 6H), 1.82 to 1.60.
(M, 4H), 1.01 (t, 6H, J = 8); Elemental analysis: Calculated ($C_{26}H_{26}C$
$1N_4$): C, 67.31, H, 7.06, N, 15.70, Cl, 9.93. Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.

The examples outlined in Table 7 can be manufactured by the methods outlined in Examples 1, 2, 3 or 6. Commonly used abbreviations are as follows: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, and Ex is an example.

[0172]

[Table 7-1] Table 7

[0173]

Embedded image

[0174]

[0175]

[Table 7-2]

[0176]

[Table 7-3]

[0177]

[Table 7-4]

[0178]

[Table 7-5]

[0179]

[Table 7-6]

[0180]

[Table 7-7]

[0181]

[Table 7-8]

[0182]

[Table 7-9]

[0183]

[Table 7-10]

[0184]

[Table 7-11]

[0185]

[Table 7-12]

[0186]

[Table 7-13]

[0187]

[Table 7-14]

[0188]

[Table 7-15]

[0189]

[Table 7-16]

[0190]

[Table 7-17]

[0191]

[Table 7-18]

[0192]

[Table 7-19]

Notes for Table 7: a) CI-MS: 330 (M + H) $^{+}$; b) CI-MS: 338 (M + H) $^{+}$; c) CI-MS: 338 (M + H) $^{+}$; d) CI-MS : 400 (M + H) $^{+}$; f) CI-MS: 326 (M + H) $^{+}$; g) CI-MS: 354 (M + H) $^{+}$;

h) CI-MS: 336 (M + H) $^{+}$; i) CI-MS: 354 (M + H) $^{+}$; j) CI-MS: 378 (M + H) $^{+}$; k) CI-HRMS: Calculated: 356. 2087 (M + H) $^{+}$, found: 356. 2071; m) CI-MS: 340 (M + H) $^{+}$; n) CI-MS: 368 (M + H) $^{+}$, o) CI-MS: 326 (M + H) $^{+}$; p) CI-MS. 368 (M + H) $^{+}$; q) CI-MS: 394 (M + H) $^{+}$, r) CI-HRMS: calculated: 380.2087 (M + H) $^{+}$, found. 380. 2078; s) CI-HRMS: calc .: 356.2008 (M + H) $^{+}$, found: 356. 1997; t) CI-HRMS: Calculated: 416.2220 (M + H) $^{+}$, Found: 416. 2005; u) CI-HRMS: calc .: 370.2243 (M + H) $^{+}$, found: 370. 2246; v) CI-HRMS: calc .: 380.2400 (M + H) $^{+}$, found: 384. 2382; w) CI-HRMS: calc .: 429.2376 (M + H) $^{+}$, found: 429. 2358; x) CI-HRMS: Calculated: 397.2478 (M + H) $^{+}$, Found: 397. 2484; y) CI-HRMS: Calculated: 410.5438 (M + H) $^{+}$, Found. 410. 2558; z) CI-HRMS: calcd: 368.4625 (M + H) $^{+}$, found: 368. Aa) CI-HRMS: Calculated. 368.2090 (M + H) $^{+}$, Found: 368.4625; ab) CI-MS: 410 (M + H) $^{+}$; ac) CI-HRMS: Calculated: 370. 4785 (M + H) $^{+}$, Found: 37 0.2246; ad) CI-HRMS: Calculated: 356.4514 (M + H) $^{+}$, Found: 35 6.2606; ae) CI-MS: 384 (M + H) $^{+}$ Af) CI-MS: 400 (M + H) $^{+}$; ag) CI-MS: 426 (M + H) $^{+}$; ah) CI-HRMS: Calculated: 388.1553 (M + H) $^{+}$, Observed: 38 8.1554; ai) CI-HRMS: $^{calcd. 388.1549 (M + H) +}$, Found: 35 8.1546, aj) CI- HRMS: $^{calcd. 430.2005 (M + H) +}$, Found : 43 0.2006, ak) CI- HRMS: $^{calcd. 390.1683 (M + H) +}$, Found: 39 0.1682; al) CI- HRMS: $^{calcd. 376.1554 (M + H) +}$, Found Am) CI-HRMS: Calculated: 404.11853 (M + H) $^{+}$, Found: 40 4.1850; an) CI-HRMS: Calculated: 420.1810 (M + H) $^{+}$, Obtained : 42 0.1809;

Ao) CI-HRMS: Calculated: 446.1946 (M + H) $^{+}$, Found: 44 6.1949; ap) CI-HRMS: Calculated: 450.1917 (M + H) $^{+}$, Found: 450 .1913; aq) CI-HRMS: Calculated: 404.1839 (M + H) $^{+}$, Found: 40 4.1846; ar) CI-HRMS: Calculated: 390.1678 (M + H) $^{+}$, Found: 390 As) CI-HRMS: Calculated: 418.2010 (M + H) $^{+}$, Found: 41 8.22012; at) CI-HRMS: Calculated: 384.2512 (M + H) $^{+}$, Found: 384. .2506; au) CI-HRMS: $^{calcd. 414.2617 (M + H) +}$, Found: 41 4.2600; av) CI- HRMS: calculated: 367.24 4 (M $^{+}$ H) +, Found: 36 7.2477; aw) CI- HRMS: $^{calcd. 354.2406 (M + H) +}$, Found: 35 4.2388, ax) CI- MS: 370 (M + H) + Ay) CI-MS: 380 (M + H) $^{+}$; az) CI-MS: 340 (M + H) $^{+}$; ba) CI-HRMS: Calculated: 376.1340 (M + H) $^{+}$, Observed: 37 6.1347; bb) CI-HRMS: Calculated: 378.1497 (M + H) $^{+}$, Found: 37 8.1495; bc) CI-HRMS: Calculated: 364.1340 (M + H) $^{+}$, Found: 36 4.1333; bd) CI-HRMS: $^{calcd. 376.1553 (M + H) +}$, Found: 37 8.1498; be) CI- HRMS: $^{calcd. 392.1653 (M + H) +}$, Found: 9 2.1649; bf) CI-HRMS : $^{calcd. 378.1497 (M + H) +}$, Found: 37 8.1489; bg) CI- HRMS: $^{calcd. 406.1810 (M + H) +}$, Found: 40 6.1819;

The examples outlined in Table 8 can be manufactured by the methods outlined in Examples 1A, 1B, 432, 433, 434. Common abbreviations are as follows: Ph is phenyl, Pr is propyl. Me is methyl, Et is ethyl, Bu is butyl, cPr
is cyclopropyl, Ex is an example, and EtOAc is ethyl acetate.

[0197]

[Table 8-1] Table 8

[0198]

Embedded image

[0199]

[0200]

[Table 8-2]

[0201]

[Table 8-3]

[0202]

[Table 8-4]

[0203]

[Table 8-5]

[0204]

[Table 8-6]

[0205]

[Table 8-7]

[0206]

[Table 8-8]

[0207]

[Table 9-9]

[0208]

[Table 8-10]

[0209]

[Table 8-11]

[0210]

[Table 8-12]

[0211]

[Table 8-13]

[0212]

[Table 8-14]

[0213]

[Table 8-15]

[0214]

[Table 8-16]

[0215]

[Table 8-17]

[0216]

[Table 8-18]

A) CI-HRMS: Calculated: 367.2498, Found: 367.2468 (
M + H) + b) CI-HRMS: Calculated: 387.1952, Observed: 387.1939 (
M + H) +

[0218] The following CRF-R1 Receptor Binding Assay for utility physiological activity evaluation, describes the separation of human CRF-R1 receptor-containing cell membranes was cloned for use in the standard binding assay, also, assay it Describe itself.

[0219] Messenger RNA was isolated from the human hippocampus Oligo (dt) 12-18
Reverse transcribes the mRNA using
Amplified by R. The resulting PCR fragment was cloned into the EcoRV site of pGEMV and the insert was regenerated therefrom using XhoI + XbaI, and the vector pm3ar (which includes the CMV promoter, SV40t 'splice and early polyA signal, Epstein-Barr Virus origin of replication, as well as the hygromycin selectable marker). The expression vector called phchCRFR thus obtained was transfected into 293EBNA cells, and cells retaining episomes were selected in the presence of 400 μM hygromycin. Cells that survived the 4-week selection with hygromycin were pooled, adapted to growth in suspension, and used for membrane generation for binding assays described below. Each aliquot containing approximately 1 × 10 ^{8} suspended cells was then centrifuged into a pellet and frozen.

The frozen pellet containing 293EBNA cells transfected with the hCRFR1 receptor was combined with ice-cold tissue buffer (50 mM HEP) for binding assays. Homogenize in ES buffer, pH 7.0, containing $_{10}$ mM $MgCl_2$, 2 mM EGTA, 1 μg / l aprotinin, 1 μg / l leupeptin and 1 μg / ml pepstatin). The homogenate is centrifuged at 40,000 × g for 12 minutes, and the resulting pellet is re-homogenized in 10 ml of tissue buffer. After a further centrifugation at 40,000 × g for 12 minutes, the pellet is resuspended until the protein concentration is 360 μg / ml and used for the assay.

The binding assay was performed in a 96-well plate, and the volume of each well was 300

μl. To each well, 50 μl of the diluted test agent (final concentration of the drug is in the range of 10^{-10} to 10^{-5} M) and 100 μl of ^{125}I-sheep-CRF (^{125}I-o-CRF)
) (Final concentration 150 pM) and 150 μl of said cell homogenate.
The plate is then incubated at room temperature for 2 hours, after which the culture is filtered through a GF / F filter (prewetted with 0.3% polyethyleneimine) using a suitable cell harvester. After rinsing the filters twice with ice-cold assay buffer, each filter is removed and their radioactivity assessed with a gamma counter.

By varying the dilution of the test drug, the inhibition curve of ^{125}Io-CRF binding to the cell membrane was determined using the reciprocal curve fitting program LIGAND [PJ Munson and D. Rodbard, An.
al. Biochem. 107: 220 (1980)]. This gives Ki values representing the inhibition and these values are used for the evaluation of bioactivity

A compound is considered to be active if the Ki value representing inhibition of CRF is less than about 10,000 nM

Inhibition of CRF-stimulated adenylate cyclase activity Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described in G. Battaglia et al., Synapse 1: 572 (1987). . Briefly, Tris-HCl (pH 7.4 at 37 ° C.) 100 mM, $MgCl_2$ 10 mM, EGTA 0.4 mM, 0.1% BSA, isobutylmethylxanthine (IBMX) for 10 minutes at 37 ° C. 1
mM, 250 mM phosphocreatine kinase
Unit / ml, creatine phosphate 5 mM, guanosine 5'-triphosphate 100 n

M, assay performed in 100 ml of cCRF, 200 ml of buffer containing antagonist peptide (concentration range 10^{-9} to 10^{-6} m) and 0.8 mg tissue (about 40-60 mg protein) at the original wet mass. I do. The reaction was performed with 1 mM ATP

Start by adding / [^{32}P] ATP (about 2-4 mCi / tube) and terminate by adding 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. To monitor the cAMP recovery, add 1 μl of [^{3}H] cAMP (about 40,000 dpm) to each tube before separation. Separation of [^{32}P] cAMP from [^{32}P] ATP is performed by eluting sequentially with a Dowex and alumina column.

[0225] In vivo activity of the compounds in vivo bioassay present invention can also be evaluated using any as long as bioassay utilized can and accepted in the art. Examples of these tests include the sound startle test, the stair climb test and the chronic dosing test. For these and other models useful for testing compounds of the present invention, see CW Berridge and AJ Dunn
, Outlined in Brain Research Reviews 15:71 (1990). The compounds could be tested in any rodent or small mammal species.

The compounds of the present invention are useful for treating imbalance associated with abnormal levels of adrenocorticotropic hormone-releasing factor in patients suffering from depression, affective disorders and / or anxiety.

The compounds of the present invention can be administered to treat these disorders by means of contacting the active ingredient with the site of action of the active ingredient in the mammalian body.
These compounds can be administered by any conventional method, as long as they are available for use in conjunction with the formulation as individual therapeutic agents or a combination of therapeutic agents. These compounds may be administered alone, but will generally be administered together with a pharmaceutical carrier chosen on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage depends on the method of use and the pharmacodynamic properties of the individual drug, the mode and route of administration, the age, weight and health of the recipient, the nature and extent of the symptoms, the type of combination therapy, the number of treatments, It depends on known factors such as the desired effect. For use in the treatment of the aforementioned diseases or conditions, the compounds of the present invention contain 0.002 active ingredients per day.
It can also be administered orally at a dose of ~ 200 mg / kg body weight. To achieve the desired pharmacological effect, typically 0.01 to 4 divided doses per day or in sustained release formulations
-10 mg / kg body weight is effective.

Formulations (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. Generally, these pharmaceutical compositions will have from about 0.5% to 95% by weight of active ingredient based on the total weight of the composition.

The active ingredients can be administered orally in solid formulations such as capsules, tablets and powders, or in solutions such as elixirs, syrups and / or suspensions. The compounds of the present invention can also be administered parenterally in sterile solutions.

A gelatin capsule can also be used to contain the active ingredient and a suitable carrier such as, but not limited to, lactose, starch, magnesium stearate, stearic acid or a cellulose derivative. 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 may be sugar-coated or film-coated to prevent unpleasant taste, to protect the active ingredient from the air, or to selectively disintegrate the tablet in the gastrointestinal tract.

For ease of patient acceptance, coloring agents and flavoring agents can be included in the liquid preparation for oral administration.

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 administration solutions. It is. The solution for parenteral administration preferably contains a water-soluble salt of the active ingredient, suitable stabilizers, and if necessary, buffer substances. Antioxidants, such as sodium bisulfite, sodium sulfite or ascorbic acid, alone or in combination, are suitable stabilizers. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions may contain preservatives, such as benzalkonium chloride, methyl or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington Pharmaceutical Sciences, A. Osol, a standard reference in the art.

Pharmaceutical dosage forms useful for administering the compounds of the present invention can be described as follows.

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

Soft Gelatin Capsules A mixture of a digestible oil such as soybean oil, cottonseed oil or olive oil and the active ingredient is prepared and injected into gelatin with a positive displacement pump to form a soft gelatin capsule containing 100 mg of the active ingredient. did. The capsule was washed and dried

Tablets A number of tablets were prepared in conventional manner, the dosage units being 100 mg of 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 of lactose. . Appropriate coatings may be applied to increase palatability or slow absorption.

The compounds of the present invention can also be used as reagents or standards in biochemical studies of neurological function, neurological dysfunction and neurological disorders.

Although the invention has been described and illustrated with respect to certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The present invention is therefore not limited to the specific embodiments described and illustrated, but may be changed or modified without departing from the spirit of the invention, the full scope of which is set forth in the following claims. is described.

----------続き Continued on the front page (51) Int.Cl. 7 identification symbol FI theme coat 7 (Reference) A61P 3/04 A61P 3/04 3/08 3/08 9/00 9/00 15/08 15/08 25 / 00 25/00 25/06 25/06 25/08 25/08 25/22 25/22 25/24 25/24 25/28 25/28 25/30 25/30 29/00 29/00 31/18 31/18 37/04 37/04 37/06 37/06 43/00 43/00 111 111 (C07D 487/04 (C07D 487/04 251: 00 251: 00 231: 00) 231: 00) (C07D 487 / 04 (C07D 487/04 239: 00 239: 00 (31) Priority claim number 09 / 015,001 (32) Priority date January 28, 1998 (1998. 1.28) (33) Priority claim Country United States (US) (81) Designated country EP (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), EA (AM, AZ, BY, KG KZ, MD, RU, TJ, TM), AU, BR, CA, CN, CZ. EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN (72) Inventor Gilligan Paul United States 19810 Wilmington Pennington Drive, Delaware 2629 (72) Inventor Chowbat Robert United States 19382 Pennsylvania West Chester Killarney Lane 1193 (72) Inventor Urbanitis Argilios Georgi Os United States 19348 Pennsylvania Kennett Square Willow Glen Drive 101 F-term (reference) 4C050 AA01 BB05 CC07 EE04 FF02 FF05 GG04 HH04 4C086 AA01 AA02 AA03 CB05 MA01 MA04 NA14 ZA05 ZA06 ZA08 ZA12 ZA16 ZA36 ZA54 ZA66 ZAZ ZAZ ZC ZC

Patent Citations (5)

Publication number	Priority date	Publication date	Assignee	Title
Family To Family Citations				
TW574214B *	1994-06-08	2004-02-01	Pfizer	Corticotropin releasing factor antagonists
EP0770088B1 *	1995-05-12	1999-07-14	Neurogen Corporation	Novel deazapurine derivatives; a new class of crf1 specific ligands
EP0880523B1 *	1996-02-07	2006-08-16	Neurocrine Biosciences, Inc.	Pyrazolopyrimidines as crf receptor antagonists
AT375344T *	1996-07-24	2007-10-15	Bristol Myers Squibb Pharma Co	AZOLOTRIAZINE AND PYRIMIDINE
JP3621706B2 *	1996-08-28	2005-02-16	ファイザー・インク	Substituted 6,5-hetero-bicyclic derivatives

* Cited by examiner, † Cited by third party

Cited By (29)

Publication number	Priority date	Publication date	Assignee	Title
JP2006522097A *	2003-04-04	2006-09-28	ファルマシア・アンド・アップジョン・カンパニー・エルエルシー	Pyrrolo (1,2-b) pyridazine compounds and their use as CFR-1 receptor antagonists
JP2007515474A *	2003-12-22	2007-06-14	エスピー・ファルムコ・プエルト・リコ・インコーポレイテッド	CRF receptor antagonists and methods related thereto
JP2008503444A *	2004-02-13	2008-02-07	エスピー・ファルムコ・プエルト・リコ・インコーポレイテッド	CRF receptor antagonist, its preparation, its pharmaceutical composition and its use
JP2008517067A *	2004-10-19	2008-05-22	エスピー・ファルムコ・プエルト・リコ・インコーポレイテッド	Pyrazolo [1,5-alpha] pyrimidinyl derivatives useful as corticotropin releasing factor (CRF) receptor antagonists
JP2018522861A *	2015-06-24	2018-08-16	キュロヴィル・アクチボラグ	Pyrazolo [1,5-a] triazine-4-amine derivatives useful for therapy
JP2020538832A *	2017-08-14	2020-10-29	スプルースバイオサイエンシズインコーポレイテッド	Corticotropin-releasing factor receptor antagonist
Family To Family Citations				
AU4331500A	1999-04-06	2000-10-23	Du Pont Pharmaceuticals Company	Pyrazolotriazines as crf antagonists
US6432989B1	1999-05-27	2002-08-13	Pfizer Inc	Use of CRF antagonists to treat circadian rhythm disorders
AT318267T *	1999-09-30	2006-03-15	Neurogen Corp	SOME ALKYLENDIAMINE-SUBSTITUTED HETEROCYCLES
PL354675A1	1999-09-30	2004-02-09	Neurogen Corporation	Certain alkylene diamine-substituted pyrazolo[1,5-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines
US6525067B1	1999-11-23	2003-02-25	Pfizer Inc	Substituted heterocyclic derivatives
WO2001087889A1 *	2000-05-18	2001-11-22	Neurocrine Biosciences, Inc.	Crf receptor antagonists and methods relating thereto

CA2417661A1 *	2000-08-02	2002-02-07	Malope Company Limited	Diagnosis and treatment of non-ulcer dyspepsia based on hypothalamic-pituitary-adrenal axis abnormality
US20030125330A1	2001-03-13	2003-07-03	Gilligan Paul J.	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
FR2842809A1 *	2002-07-26	2004-01-30	Greenpharma Sas	NOVEL SUBSTITUTED PYRAZOLO [1,5-a] -1,3,5-TRIAZINES AND THEIR ANALOGUES, PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME, USE AS A MEDICAMENT AND METHODS FOR THEIR PREPARATION
US7056926B2	2003-04-04	2006-06-06	Pfizer Inc	Pyrrolo[1,2-B]pyridazine compounds and their uses
PE20070855A1 *	2005-12-02	2007-10-14	Bayer Pharmaceuticals Corp	DERIVATIVES OF 4-AMINO-PYRROLOTRIAZINE SUBSTITUTE AS KINASE INHIBITORS
US7851468B2 *	2006-05-15	2010-12-14	Cephalon, Inc.	Substituted pyrazolo[3,4-d]pyrimidines
US10166271B2	2006-06-21	2019-01-01	The Regents Of The University Of California	Methods for promoting hair growth
US8895745B2	2006-12-22	2014-11-25	Astex Therapeutics Limited	Bicyclic heterocyclic compounds as FGFR inhibitors
JP5442449B2	2006-12-22	2014-03-12	アステックス、セラピューティックス、リミテッド	New compounds
GB0720038D0	2007-10-12	2007-11-21	Astex Therapeutics Ltd	New compounds
GB0720041D0	2007-10-12	2007-11-21	Astex Therapeutics Ltd	New Compounds
GB0810902D0	2008-06-13	2008-07-23	Astex Therapeutics Ltd	New compounds
GB0906472D0	2009-04-15	2009-05-20	Astex Therapeutics Ltd	New compounds
GB0906470D0	2009-04-15	2009-05-20	Astex Therapeutics Ltd	New compounds
EP3610890A1	2012-11-14	2020-02-19	The Johns Hopkins University	Methods and compositions for treating schizophrenia
CN104876958B *	2015-05-18	2017-04-19	南方医科大学	2-aminopyrrolo[1,2-f][1,2,4]triazine compounds, and synthesis method and application thereof
CN112500416B *	2019-07-30	2021-12-17	厦门宝太生物科技股份有限公司	Preparation method of pyrazolotriazine compound intermediate

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

Similar Documents

Publication	Publication Date	Title
JP2002501922A	2002-01-22	Azolotriazines and azolopyrimidines
KR100548853B1	2006-02-02	Azolo Triazines and Pyrimidines
US6060478A	2000-05-09	Azolo triazines and pyrimidines
US6124289A	2000-09-26	Azolo triazines and pyrimidines
US6191131B1	2001-02-20	Azolo triazines and pyrimidines
US6960583B2	2005-11-01	Pyrazolotriazines as CRF antagonists
US6313124B1	2001-11-06	Tetrazine bicyclic compounds
JP4194539B2	2008-12-10	Azolotriazines and Azolopyrimidines
US20020022632A1	2002-02-21	Pyrrolo [3,4-d] pyrimidines as corticotropin releasing factor (CRF) antagonists
US7678793B2	2010-03-16	Azolo triazines and pyrimidines
US20030008885A1	2003-01-09	Azolo triazines and pyrimidines
CA2532925C	2009-10-20	Azolo triazines and pyrimidines
AU2002300983B2	2005-06-09	Azolo Triazines And Pyrimidines
AU2823602A	2002-05-02	Azolo triazines and pyrimidines

Priority And Related Applications

Applications Claiming Priority (7)

Application	Filing date	Title
US09/014,734	1998-01-28	
US09/015,002	1998-01-28	
US09/014,734	1998-01-28	Tetrazine bicyclic compounds
US09/015,001	1998-01-28	Azolo triazines and pyrimidines
US09/015,002	1998-01-28	Azolo triazines and pyrimidines
US09/015,001	1998-01-28	
PCT/US1999/001824	1999-01-28	Azolo triazines and pyrimidines

Legal Events

Date	Code	Title	Description
2006-01-26	A521	Request for written amendment filed	**Free format text**: JAPANESE INTERMEDIATE CODE: A523 **Effective date**: 20060127
2006-01-26	A621	Written request for application examination	**Free format text**: JAPANESE INTERMEDIATE CODE: A621 **Effective date**: 20060127
2006-01-26	RD04	Notification of resignation of power of attorney	**Free format text**: JAPANESE INTERMEDIATE CODE: A7424 **Effective date**: 20060127
2008-07-14	A131	Notification of reasons for refusal	**Free format text**: JAPANESE INTERMEDIATE CODE: A131 **Effective date**: 20080711
2008-10-10	A521	Request for written amendment filed	**Free format text**: JAPANESE INTERMEDIATE CODE: A523 **Effective date**: 20081009
2008-10-30	TRDD	Decision of grant or rejection written	
2008-11-05	A01	Written decision to grant a patent or to grant a registration (utility model)	**Free format text**: JAPANESE INTERMEDIATE CODE: A01 **Effective date**: 20081104
2008-11-06	A01	Written decision to grant a patent or to grant a registration (utility model)	**Free format text**: JAPANESE INTERMEDIATE CODE: A01
2008-11-21	A711	Notification of change in applicant	**Free format text**: JAPANESE INTERMEDIATE CODE: A712 **Effective date**: 20081120
2008-11-27	A61	First payment of annual fees (during grant procedure)	**Free format text**: JAPANESE INTERMEDIATE CODE: A61 **Effective date**: 20081120
2008-12-12	R150	Certificate of patent or registration of utility model	**Free format text**: JAPANESE INTERMEDIATE CODE: R150
2008-12-15	FPAY	Renewal fee payment (event date is renewal date of database)	**Free format text**: PAYMENT UNTIL: 20111212 **Year of fee payment**: 3
2011-12-01	FPAY	Renewal fee payment (event date is renewal date of database)	**Free format text**: PAYMENT UNTIL: 20111212 **Year of fee payment**: 3
2011-12-06	FPAY	Renewal fee payment (event date is renewal date of database)	**Free format text**: PAYMENT UNTIL: 20121212 **Year of fee payment**: 4
2012-11-29	FPAY	Renewal fee payment (event date is renewal date of database)	**Free format text**: PAYMENT UNTIL: 20121212 **Year of fee payment**: 4

2012-12-04	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20131212 Year of fee payment: 5
2013-12-03	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2014-12-09	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2015-12-08	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2016-12-12	LAPS	Cancellation because of no payment of annual fees	

Concepts

machine-extracted

Download Filter table

Name	Image	Sections	Count	Query match
N1C=ND=C2N=CC=CZ1		title,description	2	0.000
N1N=NC=C2N=CC=CZ1		title	1	0.000
chronic kidney disease		claims,abstract,description	32	0.000
disease		claims,abstract,description	23	0.000
Anxiety		claims,abstract,description	15	0.000
Anxiety disease		claims,abstract,description	15	0.000
anxiety		claims,abstract,description	15	0.000
antagnostic		claims,abstract,description	10	0.000
Cardiovascular disease		claims,abstract,description	6	0.000
heart disease		claims,abstract,description	5	0.000
compounds		claims,description	1334	0.000
methoxy group		claims,description	1052	0.000
2-ethylpiperid-1-yl		claims,description	345	0.000
cyclopropyl group		claims,description	93	0.000
ethanol		claims,description	63	0.000
2-propynyl group		claims,description	58	0.000
cyclobutyl amino group		claims,description	48	0.000
mixture		claims,description	44	0.000
n-propyl group		claims,description	42	0.000
sodium chloride		claims,description	25	0.000
salts		claims,description	24	0.000
drug		claims,description	15	0.000
argon		claims,description	13	0.000
Praseodymium		claims,description	12	0.000
drugs		claims,description	11	0.000
disordered eating		claims,description	7	0.000
eating disease		claims,description	7	0.000
Alzheimer's disease		claims,description	6	0.000
Human immunodeficiency virus		claims,description	6	0.000

Mammalia	claims,description	6	0.000
mood disease	claims,description	6	0.000
n-butyl group	claims,description	6	0.000
post-traumatic stress disease	claims,description	6	0.000
Supranuclear palsy	claims,description	5	0.000
pharmaceutical composition	claims,description	5	0.000
Amyotrophic lateral sclerosis	claims,description	4	0.000
Anorexia Nervosa	claims,description	4	0.000
drug carrier	claims,description	4	0.000
fertility	claims,description	4	0.000
inflammatory disease	claims,description	4	0.000
syndrome	claims,description	4	0.000
Affective disease	claims,description	3	0.000
Craniocerebral Trauma	claims,description	3	0.000
Drug dependence	claims,description	3	0.000
Drug withdrawal syndrome	claims,description	3	0.000
Epilepsy	claims,description	3	0.000
Gastrointestinal Tract	claims,description	3	0.000
Hypoglycaemia	claims,description	3	0.000
immunosuppression	claims,description	3	0.000
Infertility	claims,description	3	0.000
Obesity	claims,description	3	0.000
Spinal Cord Injury	claims,description	3	0.000
Stroke	claims,description	3	0.000
Ulcers	claims,description	3	0.000
diethylamino group	claims,description	3	0.000
diseases by infectious agent	claims,description	3	0.000
hypoglycaemic	claims,description	3	0.000
immunosuppresive	claims,description	3	0.000
infertility	claims,description	3	0.000
infertility	claims,description	3	0.000
obesity	claims,description	3	0.000
ulcer	claims,description	3	0.000
Headache	claims,description	2	0.000
Irritability	claims,description	2	0.000
headache	claims,description	2	0.000
hemorrhagic	claims,description	2	0.000
Psychiatric disease	abstract,description	7	0.000
antagonist	abstract,description	7	0.000
corticotropin	abstract,description	7	0.000

Nervous System Disease	abstract,description	6	0.000
Neurological disorder	abstract,description	6	0.000
releasing hormone	abstract,description	6	0.000
Colon	abstract,description	5	0.000
Hypersensitivity	abstract,description	4	0.000
Cardiac disease	abstract,description	3	0.000
immune system disease	abstract,description	3	0.000
allergic hypersensitivity disease	abstract,description	3	0.000
hypersensitivity	abstract,description	3	0.000

Show all concepts from the description section

Data provided by IFI CLAIMS Patent Services

About Send Feedback Public Datasets Terms Privacy Policy

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 487/04, A61K 31/505 // (C07D 487/04, 239:00, 231:00) (C07D 487/04, 251:00, 231:00) (C07D 487/04, 249:00, 239:00) (C07D 487/04, 251:00, 249:00)

A1

(11) International Publication Number: **WO 98/03510**

(43) International Publication Date: 29 January 1998 (29.01.98)

(21) International Application Number: PCT/US97/13072

(22) International Filing Date: 23 July 1997 (23.07.97)

(30) Priority Data:

60/023,290	24 July 1996 (24.07.96)	US
08/686,047	24 July 1996 (24.07.96)	US
Not furnished	23 July 1997 (23.07.97)	US

(71) Applicant: THE DU PONT MERCK PHARMACEUTICAL COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

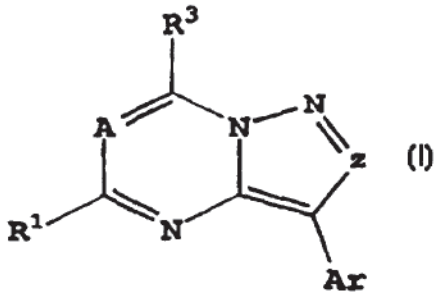
(72) Inventors: ARVANITIS, Argyrios, Georgious; 101 Willow Glen Drive, Kennett Square, PA 19348 (US). CHORVAT, Robert, John; 1193 Killarney Lane, West Chester, PA 19382 (US).

(74) Agent: FERGUSON, Blair, Q.; The du Pont Merck Pharmaceutical Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

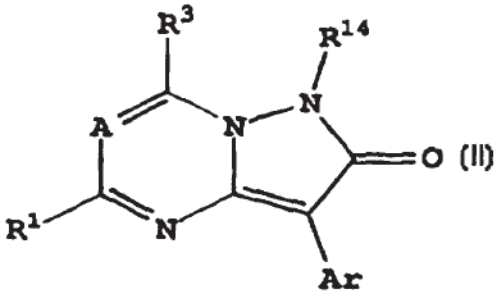
(81) Designated States: AM, AU, AZ, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KG, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AZOLO TRIAZINES AND PYRIMIDINES



(I)



(II)

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of formula (I) or (II) and their 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.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TITLE

AZOLO TRIAZINES AND PYRIMIDINES

FIELD OF THE INVENTION

This invention relates 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 psychopathological disturbance and stress, by administration of certain [1,5-*a*]-pyrazolo-1,3,5-triazines, [1,5-*a*]-1,2,3-triazolo-1,3,5-triazines, [1,5-*a*]-pyrazolo-pyrimidines and [1,5-*a*]-1,2,3-triazolo-pyrimidines.

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**)].

There has also been a role postulated for CRF 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-

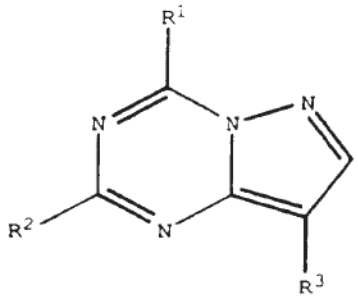
dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)].

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 (α-helical CRF_{9-41}) 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)].

Several publications describe corticotropin releasing factor antagonist compounds and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application US94/11050 , Pfizer WO 95/33750, Pfizer WO 95/34563, Pfizer WO 95/33727 and Pfizer EP 0778 277 A1.

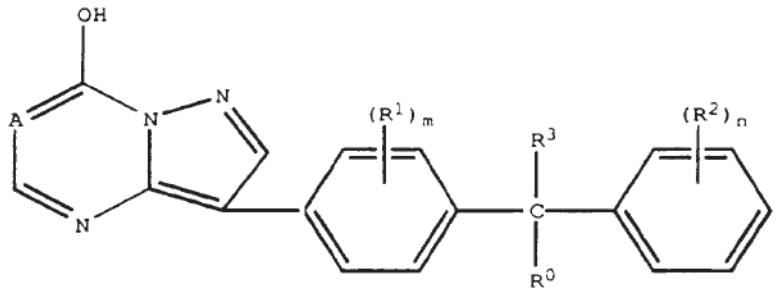
Insofar as is known, [1,5-*a*]-pyrazolo-1,3,5-triazines, [1,5-*a*]-1,2,3-triazolo-1,3,5-triazines, [1,5-*a*]-pyrazolo-pyrimidines and [1,5-*a*]-1,2,3-triazolo-pyrimidines, have not been previously reported as corticotropin releasing factor antagonist compounds useful in the treatment of psychiatric disorders and neurological diseases. However, there have been publications which teach some of these compounds for other uses.

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



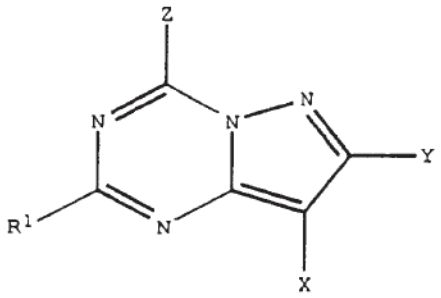
where R^1 is OH or alkanoyl, R^2 is H, OH, or SH, and R^3 is an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

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



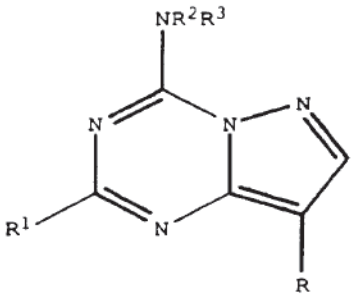
where A is CH or N, R^0 and R^3 are H or alkyl, and R^1 and R^2 are H, alkyl, alkoxyl, alkylthio, nitro, etc., and states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and prostatic carcinoma.

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



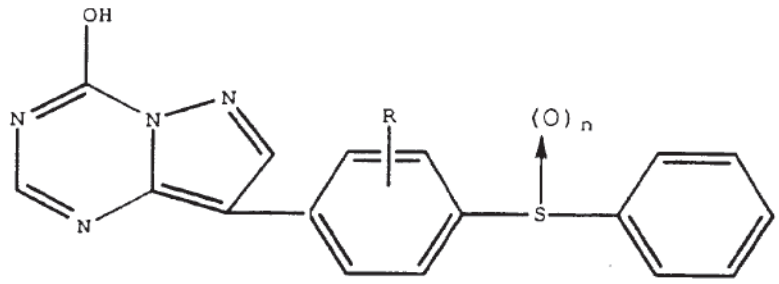
where R1 is CH_3, C_2H_5 or C_6H_5, X is H, C_6H_5, m-$CH_3C_6H_4$, CN, COOEt, Cl, I or Br, Y is H, C_6H_5, o-$CH_3C_6H_4$, or p-$CH_3C_6H_4$, and Z is OH, H, CH_3, C_2H_5, C_6H_5, n-C_3H_7, i-C_3H_7, SH, SCH_3, NHC_4H_9, or $N(C_2H_5)_2$, and states that the compounds are c-AMP phosphodiesterase inhibitors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

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



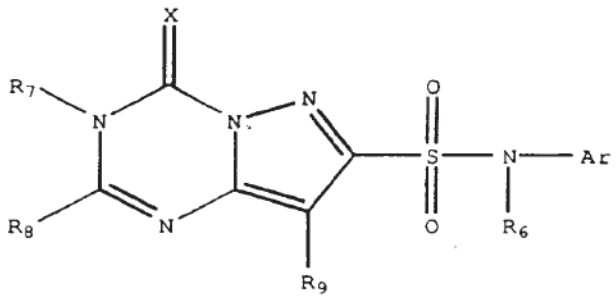
where R^1 is H or alkyl, R^2 is H or alkyl, R^3 is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

US 5,137,887 discloses pyrazolotriazines of the formula



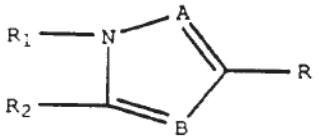
where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

US 4,892,576 discloses pyrazolotriazines of the formula

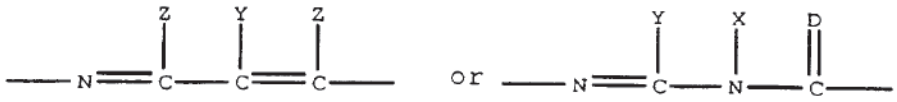


where X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, R_6-R_8 are H, alkyl, etc., and R_9 is H, alkyl, phenyl, etc. The patent states that the compounds are useful as herbicides and plant growth regulants.

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

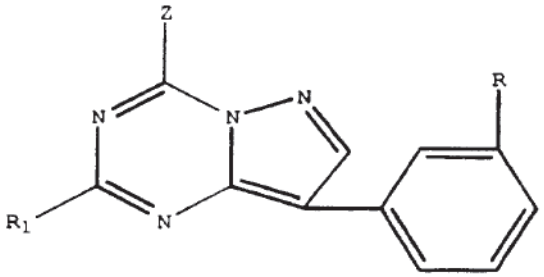


where A can be N, B can be CR_3, R_3 can be phenyl or substituted phenyl, etc., R is $-N(R_4)SO_2R_5$ or $-SO_2N(R_6)R_7$ and R_1 and R_2 can be taken together to form



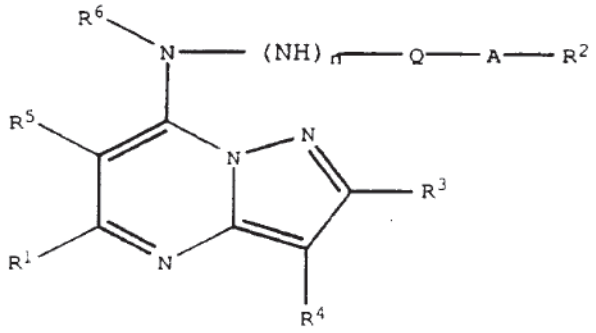
where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

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



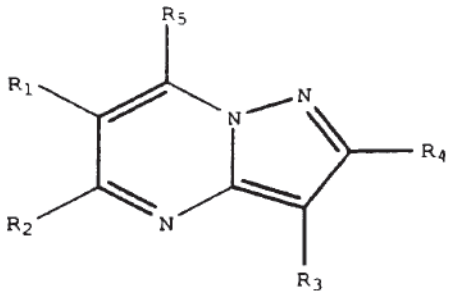
where Z is H, OH, CH_3, C_2H_5, C_6H_5, n-C_3H_7, iso-C_3H_7, SH, SCH_3, NH(n-C_4H_9), or $N(C_2H_5)_2$, R is H or CH_3, and R_1 is CH_3 or C_2H_5. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control,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

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



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

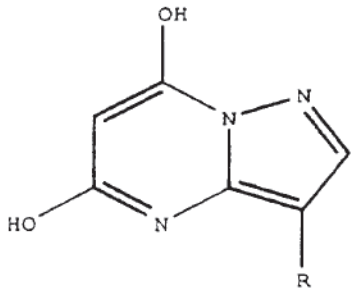
EP 0 591 528 (Otsuka,1991) discloses anti-inflammatory use of pyrazolopyrimidines represented by the formula



where R_1, R_2, R_3 and R_4 are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R_5

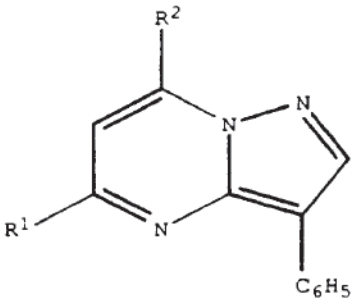
is SR_6 or NR_7R_8, R_6 is pyridyl or optionally substituted phenyl, and R_7 and R_8 are H or optionally substituted phenyl.

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



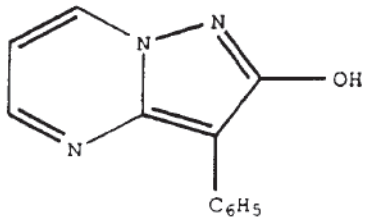
where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

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

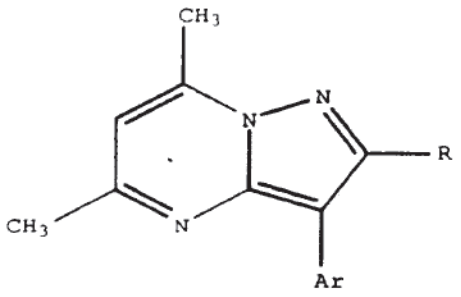


where R^1 is CF_3, C_2F_5, or C_6H_4F, and R^2 is CH_3, C_2H_5, CF_3, or C_6H_4F.

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



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



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

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

SUMMARY OF THE INVENTION

In accordance with one 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 a mammal.

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 a mammal.

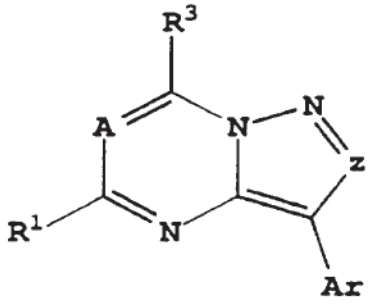
According to another aspect, the present invention provides novel compounds of Formulae (1) and (2) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds of Formulae (1) and (2), 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 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.

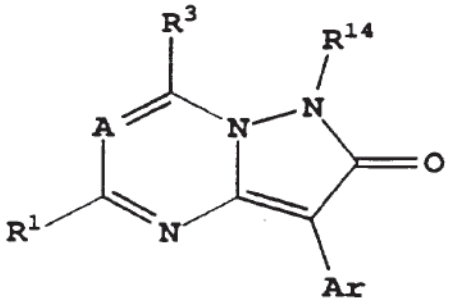
DETAILED DESCRIPTION OF INVENTION

[1] The present invention 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 Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

A is N or CR;

Z is N or CR^2;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached to an unsaturated carbon atom;

R is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl;

R^1 is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, $-NR^6S(O)_nR^7$, $S(O)_nNR^6R^7$, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is selected from:

-H, OR^7, SH, $S(O)_nR^{13}$, COR^7, CO_2R^7, $OC(O)R^{13}$, NR^8COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^8CO_2R^{13}$, NR^6R^7, $NR^{6a}R^{7a}$, $N(OR^7)R^6$, $CONR^6R^7$, aryl, heteroaryl and heterocyclyl, or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, NO_2, halo, CN, C_1-C_4 haloalkyl, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7, R^{6a} and R^{7a} are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{14} is selected from C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_3-C_8 cycloalkyl, or C_4-C_{12} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, and C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl and C_1-C_6 alkylsulfonyl;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10}

cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

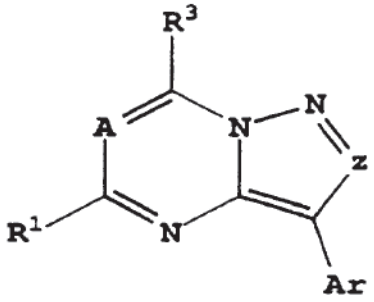
heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2,

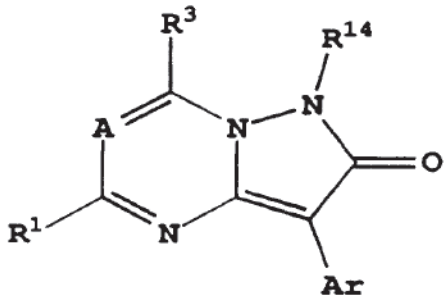
[2] Preferred methods of the present invention are methods in wherein in the compound of Formulae (1) or (2), Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

[3] Further preferred methods of the above invention are methods wherein, in the compound of Formulae (1) or (2), A is N, Z is CR^2, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3, and R^3 is $NR^{6a}R^{7a}$.

[4] The present invention comprises compounds of Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein:

A is N or CR;

Z is N or CR^2;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached to an unsaturated carbon atom;

R is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl;

R^1 is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, $-NR^6S(O)_nR^7$, $S(O)_nNR^6R^7$, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is selected from:

-H, OR^7, SH, $S(O)_nR^{13}$, COR^7, CO_2R^7, $OC(O)R^{13}$, NR^8COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^8CO_2R^{13}$, NR^6R^7, $NR^{6a}R^{7a}$, $N(OR^7)R^6$, $CONR^6R^7$, aryl, heteroaryl and heterocyclyl, or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, NO_2, halo, CN, C_1-C_4 haloalkyl, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7, R^{6a} and R^{7a} are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3

substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine; N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{14} is selected from C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_3-C_8 cycloalkyl, or C_4-C_{12} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected

at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, and C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl and C_1-C_6 alkylsulfonyl;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2,

with the provisos that:

(1) when A is N, Z is CR^2, R^2 is H, R^3 is $-OR^7$ or $-OCOR^{13}$, and R^7 is H, then R^1 is not H, OH or SH;

(2) when A is N, Z is CR^2, R^1 is CH_3 or C_2H_5, R^2 is H, and R^3 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 $N(C_2H_5)_2$, then Ar is not phenyl or m-CH_3-phenyl;

(3) when A is N, Z is CR^2, R^2 is H, and Ar is pyridyl, pyrimidinyl or pyrazinyl, and R^3 is $NR^{6a}R^{7a}$, then R^{6a} and R^{7a} are not H or alkyl;

(4) when A is N, Z is CR^2, and R^2 is $SO_2NR^6R^7$, then R^3 is not OH or SH;

(5) when A is CR and Z is CR^2, then R^2 is not-$NR^6SO_2R^7$ or $-SO_2NR^6R^7$;

(6) when A is N, Z is CR^2 and R^2 is $-NR^6SO_2R^7$ or $-SO_2NR^6R^7$, then R^3 is not OH or SH;

(7) when A is N, Z is CR^2, R^1 is methyl or ethyl, R^2 is H, and R^3 is H, OH, CH_3, C_2H_5, C_6H_5, n-C_3H_7,

iso-C_3H_7, SH, SCH_3, $NH(n\text{-}C_4H_9)$, or $N(C_2H_5)_2$, then Ar is not unsubstituted phenyl or m-methylphenyl;

(8) when A is CR, Z is CR^2, R^2 is H, phenyl or alkyl, R^3 is NR^8COR^7 and Ar is phenyl or phenyl substituted with phenylthio, then R^7 is not aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocycly(C_1-C_4 alkyl);

(9) when A is CR, Z is CR^2, R^2 is H or alkyl, Ar is phenyl, and R^3 is SR^{13} or $NR^{6a}R^{7a}$, then R^{13} is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or

(10) when A is CH, Z is CR^2, R^1 is OR^{11}, R^2 is H, R^3 is OR^7, and R^7 and R^{11} are both H, then Ar is not phenyl, p-Br-phenyl, p-Cl-phenyl, p-$NHCOCH_3$-phenyl, p-CH_3-phenyl, pyridyl or naphthyl;

(11) when A is CH, Z is CR^2, R^2 is H, Ar is unsubstituted phenyl, and R^3 is CH_3, C_2H_5, CF_3 or C_6H_4F, then R_1 is not CF_3 or C_2F_5;

(12) when A is CR, R is H, Z is CR^2, R^2 is OH, and R^1 and R^3 are H, then Ar is not phenyl;

(13) when A is CR, R is H, Z is CR^2, R^2 is OH or NH_2, R^1 and R^3 are CH_3, then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl.

[5] Preferred compounds of the above invention are compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof with the additional provisos that: (1) when A is N, R^1 is H, C_1-C_4 alkyl, halo, CN, C_1-C_{12} hydroxyalkyl, C_1-C_4

alkoxyalkyl or $SO_2(C_1-C_4$ alkyl), R^3 is $NR^{6a}R^{7a}$ and R^{6a} is unsubstituted C_1-C_4 alkyl, then R^{7a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C_3-C_6 cycloalkyl; and (2) A is N, R^1 is H, C_1-C_4 alkyl, halo, CN, C_1-C_{12} hydroxyalkyl, C_1-C_4 alkoxyalkyl or $SO_2(C_1-C_4$ alkyl), R^3 is $NR^{6a}R^{7a}$ and R^{7a} is unsubstituted C_1-C_4 alkyl, then R^{6a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C_3-C_6 cycloalkyl.

[6] Preferred compounds of the above invention also include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

[7]. Preferred compounds of the above invention also include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N, Z is CR^2, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3, and R^3 is $NR^{6a}R^{7a}$.

[11] More preferred compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N.

[12] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[13] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[14] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

[15] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

[16] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2.

[17] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[18] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

[19] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-; and

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

[20] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from

C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and -aryl or heteroaryl.

[21] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is selected from:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15},

CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[22] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

[23] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$,

$R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[24] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

[25] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

[26] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, -COR^{15},

CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

[27] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

-C_1-C_4 alkyl, each such C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[28] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl,

cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[29] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

[30] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[31] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

- -Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents,
- $-R^3$ is $NR^{6a}R^{7a}$ or OR^7 and
- $-R^1$ and R^2 are independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl.

[32] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

- -H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

[33] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

[34] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

-C_1-C_4 alkyl, each such C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[35] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[36] More preferred compounds of the above invention also include compounds and isomers thereof,

stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

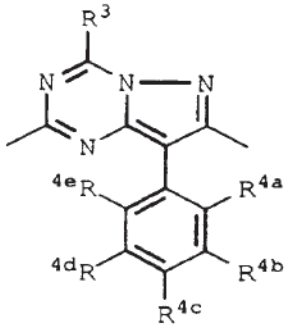
-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

[37] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[38] Specifically preferred compounds of the above invention are compounds of Formula (50)



FORMULA (50)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, selected from the group consisting of:

a compound of Formula (50) wherein R^3 is $-NHCH(n\text{-}Pr)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)(n\text{-}Bu)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-(n\text{-}Pr)(CH_2cPr)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(n\text{-}Bu)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Me)(Ph)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(n\text{-}Pr)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(n\text{-}Pr)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-OEt$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CN)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-OCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(n\text{-}Pr)(CH_2cPr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2N(Me)_2)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(cPr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(n\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(n\text{-}Bu)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2CH_2OMe)(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is morpholino, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NH(c\text{-}Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is CN, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NH(CH_2OMe)(CH_2-iPr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(n-Pr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OEt)(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-$NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-$NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NH(Et)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)(CH_2CH_2OH)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2c\text{-}Pr)(n\text{-}Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is CN, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OH)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and

a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.

[39] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[40] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[41] More preferred are compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is CR.

[42] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[43] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[44] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

[45] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

[46] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2.

[47] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is

phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[48] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

[49] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

[50] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[51] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

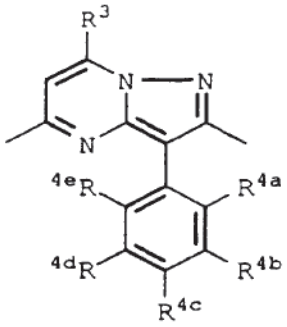
-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents,

-R^3 is $NR^{6a}R^{7a}$ or OR^7 and

-R^1 and R^2 are independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl.

[52] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[53] Specifically preferred compounds of the above invention are compounds of Formula (51)



FORMULA (51)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:

a compound of Formula (51) wherein R^3 is $-NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(n\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(n\text{-}Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(n\text{-}Pr)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NEt_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.

[54] More specifically preferred is 7-(3-pentylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[55] More specifically preferred is 7-(Diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[56] More specifically preferred is 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and

pharmaceutically acceptable salt or pro-drug forms thereof.

The present invention also provides pharmaceutical compositions comprising compounds of Formulae (1) and (2) and a pharmaceutically acceptable carrier.

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" includes both branched and straight-chain alkyl having the specified number of carbon atoms. Commonly used abbreviations have the following meanings: Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl. The prefix "n" means a straight chain alkyl. The prefix "c" means a cycloalkyl. The prefix "(*S*)" means the S enantiomer and the prefix "(*R*)" means the R enantiomer. 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 "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis,

Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of Formulae (1) and (2). 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.

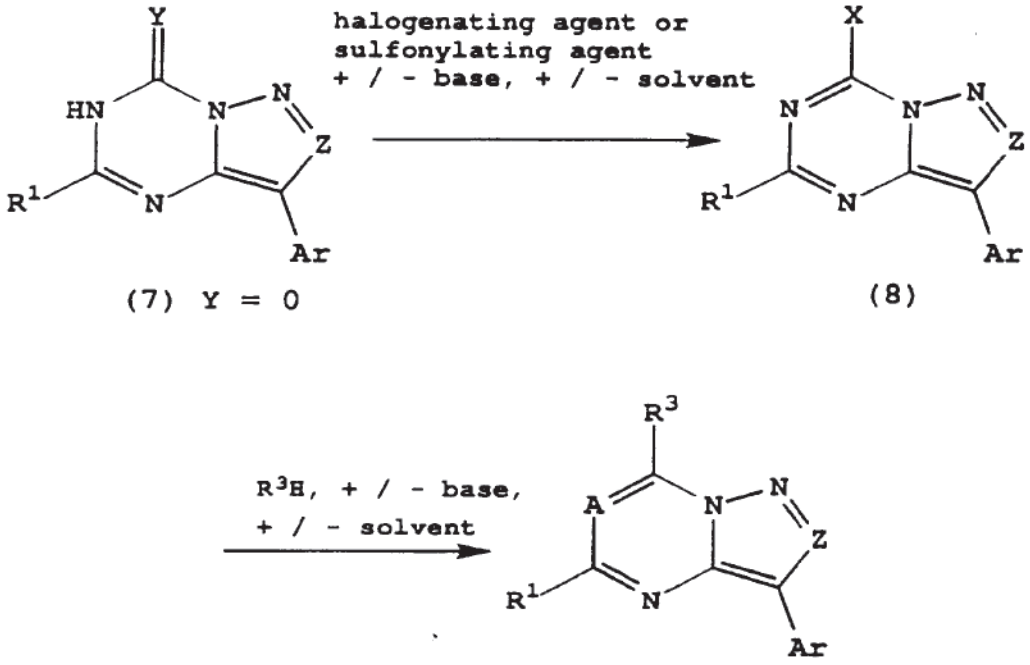
"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds 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 (II); 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 or depression in a host.

Syntheses

Some compounds of Formula (1) may be prepared from intermediate compounds of Formula (7), using the procedures outlined in Scheme 1:

SCHEME 1



(7) Y = O (8) (1) A = N

Compounds of Formula (7) (where Y is O) may be treated 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 -80°C to 250°C to give products of Formula (8) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkane-sulfonyloxy). 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 (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl 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, alkali metal

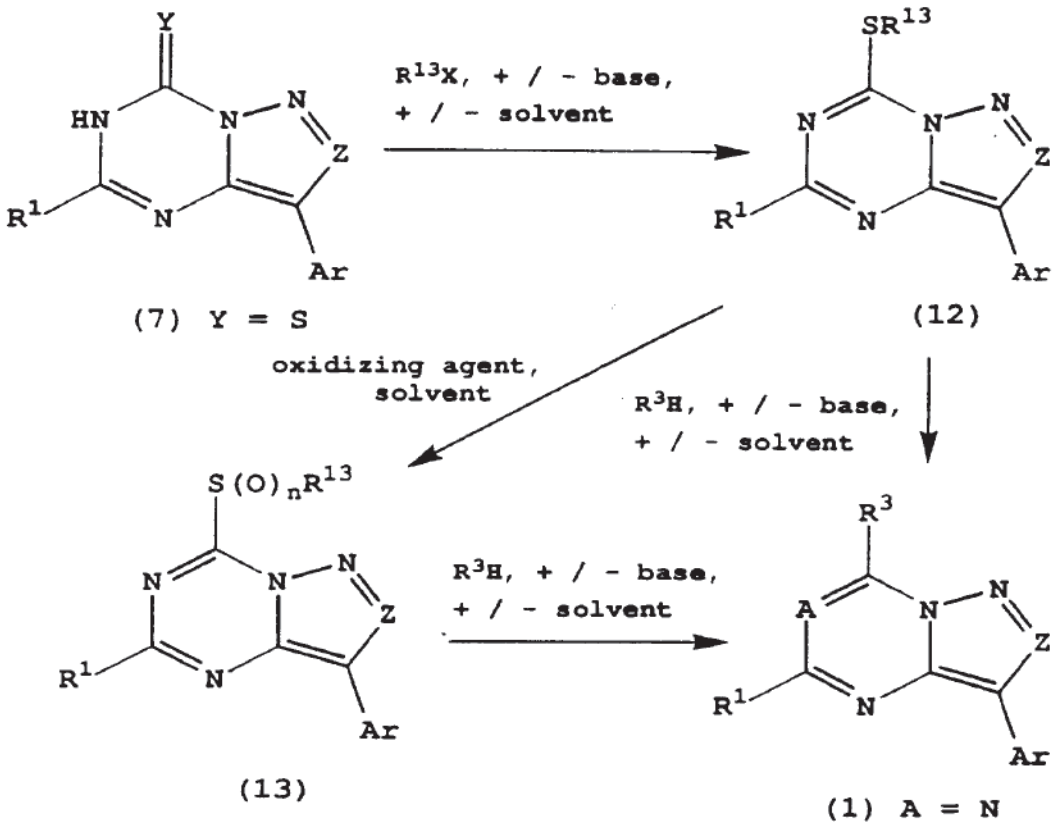
hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), 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, 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 dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

Compounds of Formula (8) may be reacted with compounds of Formula R^3H (where R^3 is defined as above except R^3 is not SH, COR^7, CO_2R^7, aryl or heteroaryl) 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 (1). 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 dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

Scheme 2 delineates the procedures for converting intermediate compounds of Formula (7) (where Y is S) to some compounds of Formula (1).

SCHEME 2



Compounds of Formula (7) (where Y is S) may be treated with an alkylating agent $R^{13}X$ (where R^{13} is defined as above, except R^{13} is not aryl or heteroaryl) 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. 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 hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium

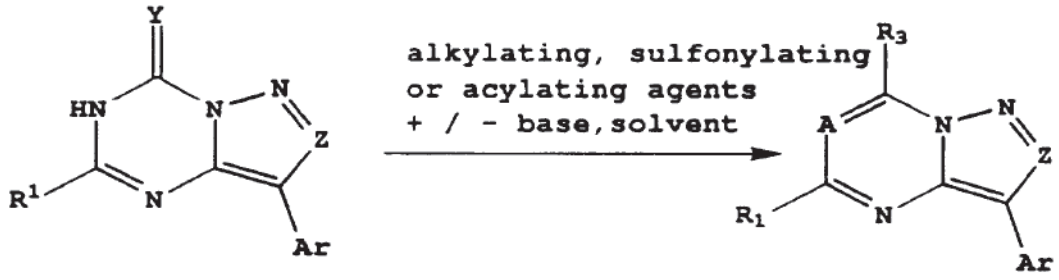
bis(trimethylsilyl)amide), trialkyl amines (prefereably N,N-di-isopropyl-N-ethyl amine or triethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, 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 dichloromethane). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme 1 above. Alternatively, compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may be oxidized to compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) by treatment with an oxidizing agent in the presence of an inert solvent at temperatures ranging from -80°C to 250°C. Oxidizing agents include, but are not limited to, hydrogen peroxide, alkane or aryl peracids (preferably peracetic acid or m-chloro-perbenzoic acid), dioxirane, oxone, or sodium periodate. Inert solvents may include, but are not limited to, alkanones (3 to 10 carbons, preferably acetone), water, alkyl alcohols (1 to 6 carbons), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens

(preferably dichloromethane) or combinations thereof. The choices of oxidant and solvent are known to those skilled in the art (cf. Uemura, S., Oxidation of Sulfur, Selenium and Tellurium, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 7, 762-769). Preferred reaction temperatures range from -20°C to 100°C. Compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme (1) above.

Compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$, may be prepared from compounds of Formula (7), where Y is NH, by the procedures depicted in Scheme 3.

SCHEME 3



(7) Y = NH

(1)

A = N;
R_3 = NR^6R^7, NR^8COR^7, $N(COR^7)_2$, $NR_8CONR^6R^7$, $NR_8CO_2R_{13}$

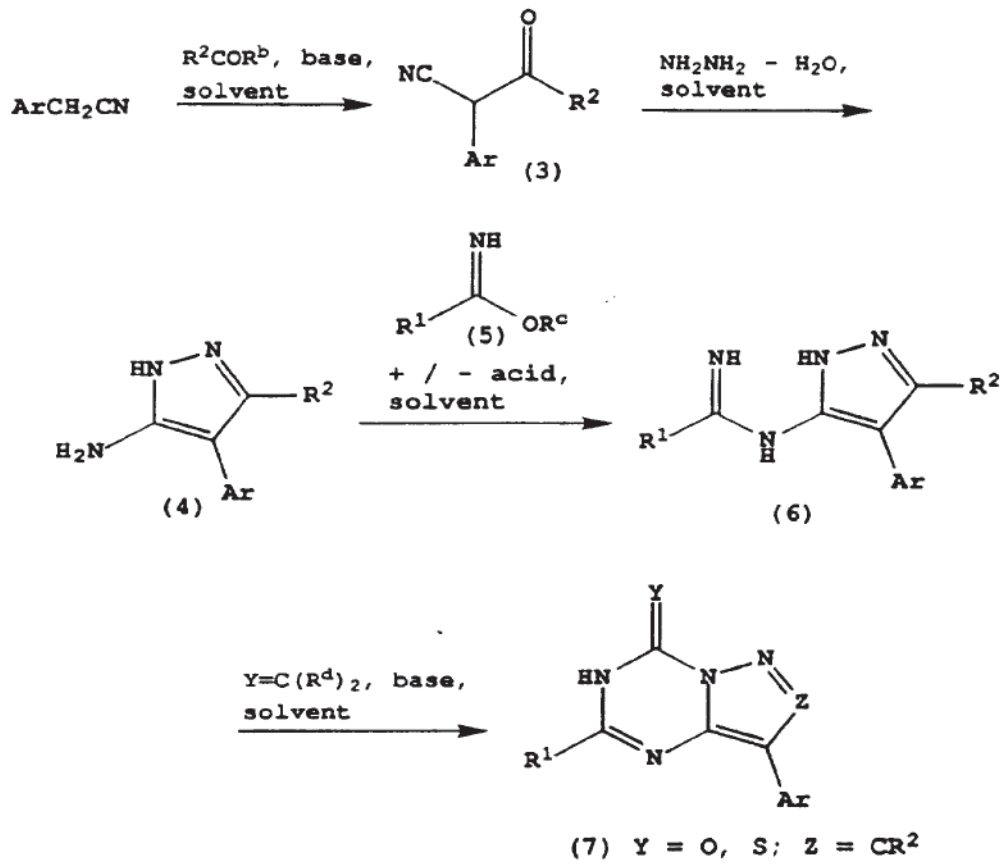
Reaction of compounds of Formula (7), where Y is NH, with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with

combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$. Alkylating agents may include, but are not limited to, C_1-C_{10} alkyl -halides, -tosylates, -mesylates or -triflates; C_1-C_{10} haloalkyl(1 - 10 halogens)-halides, -tosylates, -mesylates or -triflates; C_2-C_8 alkoxyalkyl-halides, -tosylates, -mesylates or -triflates; C_3-C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4-C_{12} cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; or heterocyclyl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C_1-C_{10} alkanoyl halides or anhydrides, C_1-C_{10} haloalkanoyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkanoyl halides or anhydrides, C_3-C_6 cycloalkanoyl halides or anhydrides, C_4-C_{12} cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C_1-C_4) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides, heteroaryl(C_1-C_4) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C_1-C_4) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C_1-C_{10} alkylsulfonyl halides or anhydrides, C_1-C_{10} haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkylsulfonyl halides or anhydrides, C_3-C_6 cycloalkylsulfonyl halides or anhydrides, C_4-C_{12} cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C_1-C_4 alkyl)-, heteroarylsulfonyl halides or anhydrides, heteroaryl(C_1-C_4 alkyl)sulfonyl halides or anhydrides,

heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C_1-C_4 alkyl)sulfonyl halides or anhydrides. 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 bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl 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) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Scheme 4 delineates procedures, which may be employed to prepare intermediate compounds of Formula (7), where Y is O, S and Z is CR^2.

SCHEME 4



Compounds of the formula $ArCH_2CN$ are reacted with compounds of the formula R^2COR^b, where R^2 is defined above and R^b is halogen, cyano, lower alkoxy (1 to 6 carbons) or lower alkanoyloxy (1 to 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 (3). 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 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, 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.

Compounds of Formula (3) may be treated with hydrazine-hydrate in the presence of an inert solvent at temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to produce compounds of Formula (4). 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). Compounds of Formula (4) may be reacted with compounds of Formula (5) (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 compounds of Formula (6). Acids may include, but are

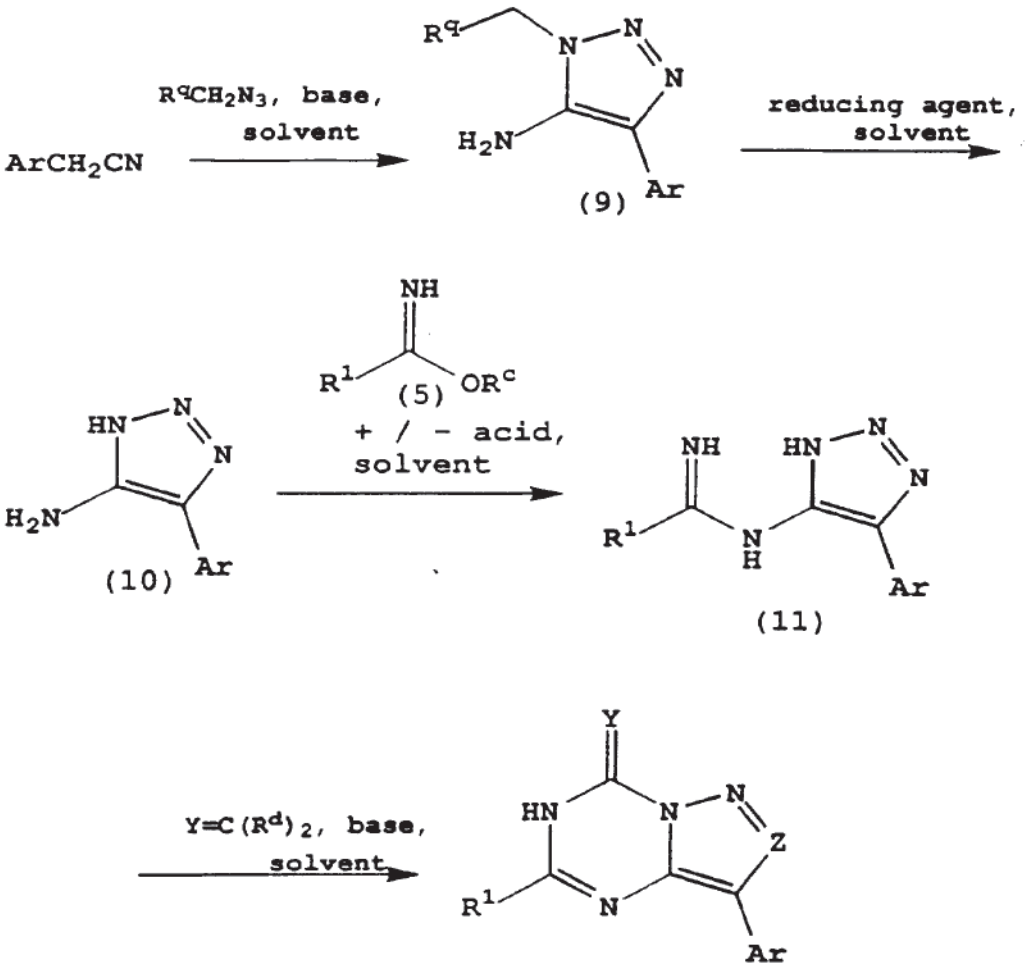
not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic 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 dichloromethane 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 ambient temprature to 100°C.

Compounds of Formula (6) may be converted to intermediate compounds of Formula (7) by treatment with compounds $C=Y(R^d)_2$ (where Y is O or S and 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). Preferred temperatures are 0°C to 150°C.

Intermediate compounds of Formula (7), where Z is N, may be synthesized according the methods outlined in Scheme 5.

SCHEME 5



Compounds of $ArCH_2CN$ are reacted with compounds of Formula $R^qCH_2N_3$ (where R^q is a phenyl group optionally substituted by H, alkyl (1 to 6 carbons) or alkoxy (1 to 6 carbons) in the presence or absence of a base in an inert solvent at temperatures ranging from 0°C to 200°C to generate compounds of Formula (9). Bases may include, but are not limited to, alkali metal hydrides

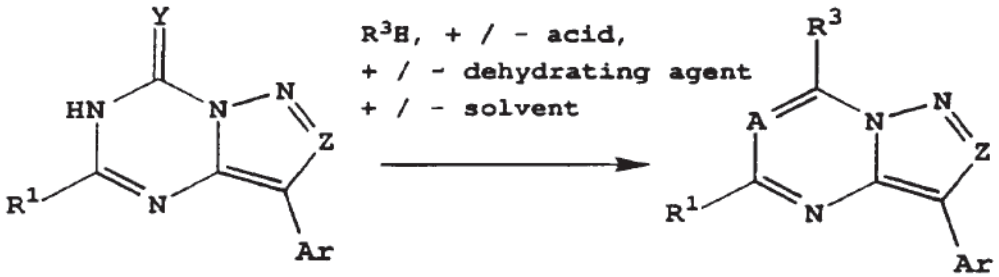
(preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide, sodium ethoxide or potassium t-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), 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), 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 ambient temperature to 100°C.

Compounds of Formula (9) may be treated with a reducing agent in an inert solvent at -100°C to 100°C to afford products of Formula (10). Reducing agents include, but are not limited to, (a) hydrogen gas in combination with noble metal catalysts such as Pd-on-carbon, PtO_2, Pt-on-carbon, Rh-on-alumina or Raney nickel, (b) alkali metals (preferably sodium) in combination with liquid ammonia or (c) ceric ammonium nitrate. 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). The preferred reaction temperatures are -50°C to 60°C. Compounds of Formula (9) are then converted to compounds of Formula (7) (where Z is N) via intermediates of Formula (11) using the reagents and reaction conditions outlined in Scheme 4 for the conversion of compounds of Formula (4) to compounds of Formula (7) (where Z is CR^2).

Compounds of Formula (1) may also be prepared from compounds of Formula (7) (where Y is O, S and Z is defined above) as outlined in Scheme 6:

SCHEME 6



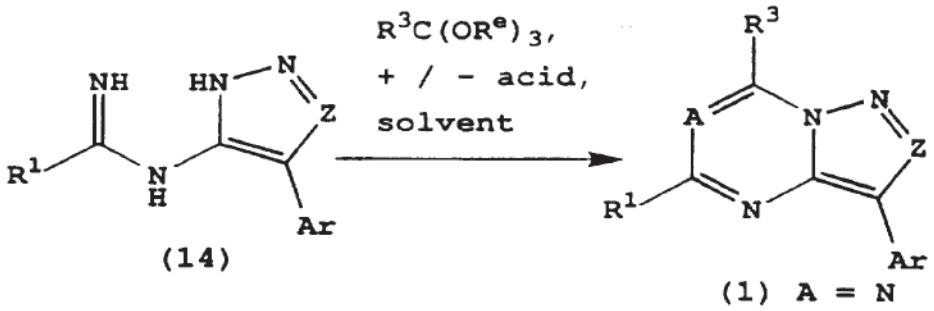
(7) Y = O, S; Z = N, CR^2 **(1) A = N**

Compounds of Formula (7) may be reacted with compounds of Formula R^3H in the presence of a dehydrating agent in an inert solvent at reaction temperatures ranging from 0°C to 250°C. Dehydrating agents include, but are not limited to, P_2O_5, molecular sieves or inorganic or organic acids. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic 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,

alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably glyme or diglyme), 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 halocarbons of 1 to 10 carbons and 1 to 10 halogens (preferably chloroform). Preferred reaction temperatures range from ambient temperature to 150°C.

Some compounds of Formula (1) (where A is N) may also be prepared by the methods shown in Scheme 7:

SCHEME 7

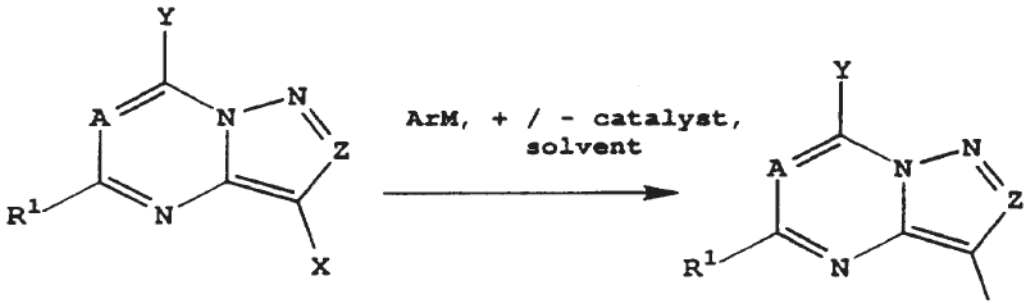


Intermediate compounds of Formula (14), where Z is defined above, may be reacted with compounds of Formula $R^3C(OR^e)3$, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic 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, 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 dichloromethane). Preferred reaction temperatures range from 50°C to 150°C.

Intermediate compounds of Formula (7) may also be synthesized by the reactions displayed in Scheme 8.

SCHEME 8



(15) Y = OH, SH NR^6R^7;
Z = N, CR^2,
X = Br, Cl, I, B(OR"")2

(7) A = N

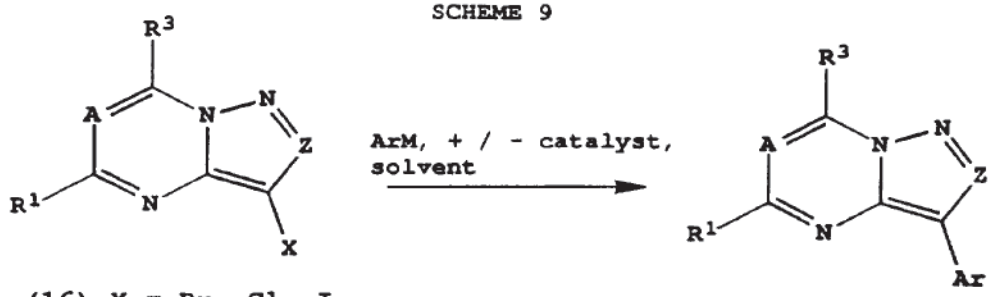
Compounds of Formula (15), (where Y is OH, SH, NR^6R^7; Z is defined above, X is Br, Cl, I, O_3SCF_3 or $B(OR"")_2$ and R"" is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides) in the presence or absence of an

organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM 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 carbonates or trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). 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 dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C.

The choices of M and X are known to those skilled in the art (cf. Imamoto, T., Organocerium Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 231-250; Knochel, P., Organozinc, Organocadmium and Organomercury Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 211-230; Knight, D.W., Coupling Reactions between sp^2 Carbon Centers, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 3, 481-520).

Compounds of Formula (1) may also be prepared using the methods shown in Scheme 9.

SCHEME 9



(16) X = Br, Cl, I, $B(OR"")_2$, O_3SCF_3

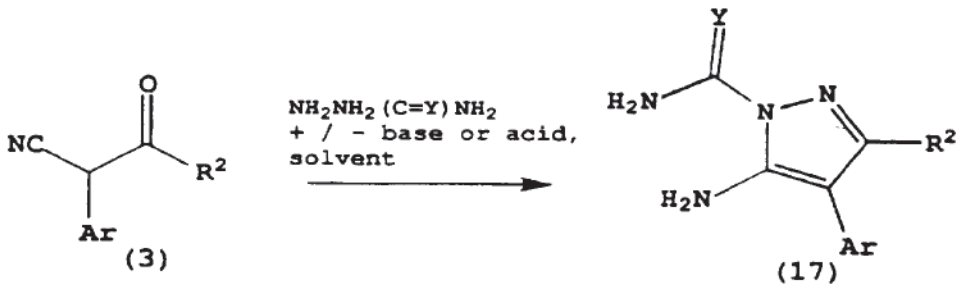
(1)

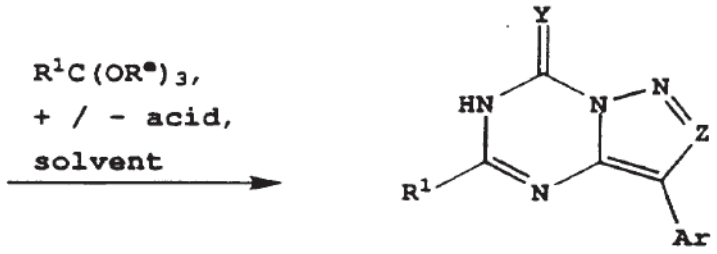
Compounds of Formula (16), where A, Z, R^1 and R^3 are defined above and X is Br, Cl, I, O_3SCF_3 or $B(OR"")_2$ and R"" is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ (see the above references in Comprehensive Organic Synthesis). 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 carbonates or trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). 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 dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably

benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C.

Intermediate compounds of Formula (7) (where Y is O, S, NH, Z is CR^2 and R^1, R^2 and Ar are defined as above) may be prepared as illustrated in Scheme 10.

SCHEME 10





(7) Y = O, S, NH; Z = CR^2,

Compounds of Formula (3) may be reacted with compounds of Formula $H_2NNH(C=Y)NH_2$, where Y is O, S or NH, in the presence or absence of a base or acid in an inert solvent at temperatures from 0°C to 250°C to produce compounds of Formula (17). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic 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

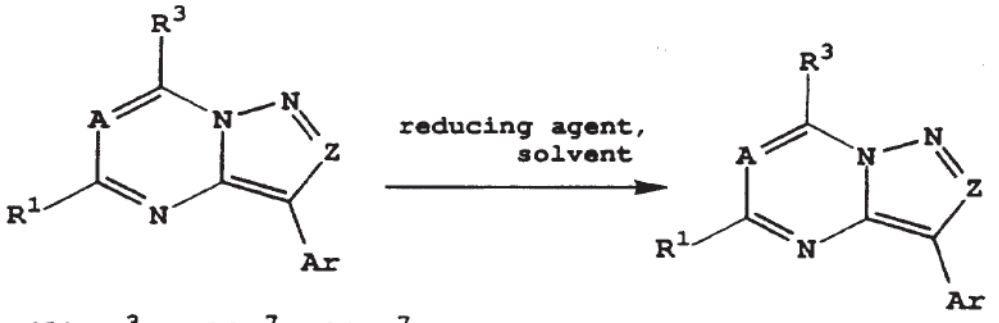
of such acids may be used. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), 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 6 carbons), 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 dichloromethane).

Preferred reaction temperatures range from 0°C to 150°C. Compounds of Formula (17) may then be reacted with compounds of Formula $R^3C(OR^e)3$, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic 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, 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 dichloromethane). Preferred reaction temperatures range from 50°C to 150°C.

In Scheme 11, the procedures which may be used to convert compounds of Formula (1), where R^3 is COR^7, CO_2R^7, NR^8COR^7 and $CONR^6R^7$, to other compounds of Formula (1), where R^3 is $CH(OH)R^7$, CH_2OH, $NR^8CH_2R^7$ and $CH_2NR^6R^7$ by treatment with a reducing agent in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 11



(1) R^3 = COR^7, CO_2R^7, $CONR^6R^7$

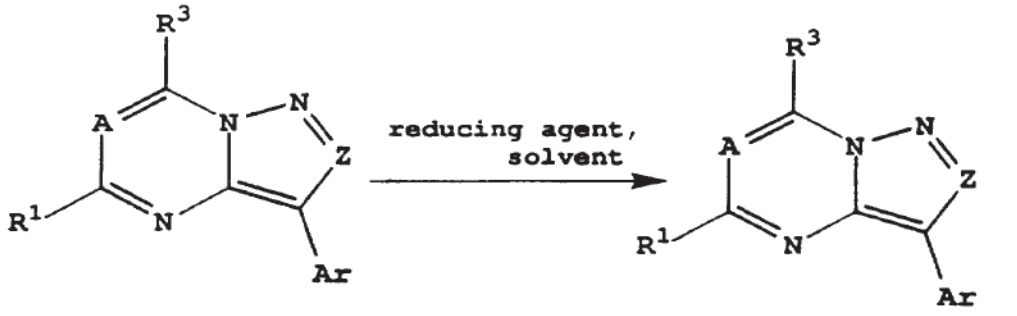
(1) R^3 = $C(OH)R^7$, CH_2OH, $CH_2NR^6R^7$

Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane, dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides, or dialkyl aluminum

hydrides (such as di-isobutylaluminum hydride). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

In Scheme 12, the procedures are shown which may be used to convert compounds of Formula (1), where R^3 is COR^7 or CO_2R^7, to other compounds of Formula (1), where R^3 is $C(OH)(R^7)_2$ by treatment with a reagent of Formula R^7M in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 12

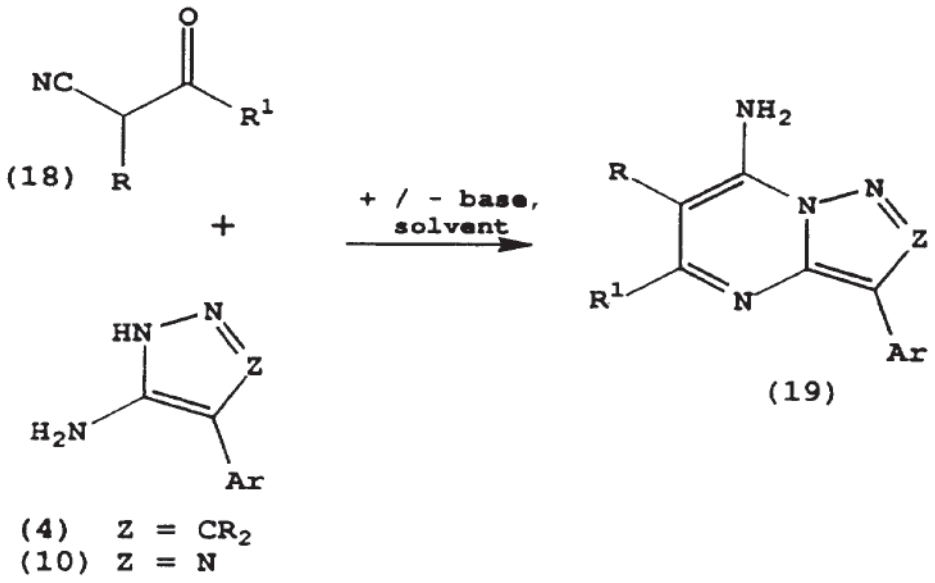


(1) $R^3 = COR^7$, CO_2R^7, (1) $R^3 = C(OH)(R^7)_2$

M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$, may be synthesized as depicted in Scheme 13.

SCHEME 13



Reaction of compounds of Formula (18), where R and R^1 are defined above, with compounds of Formula (4) or (10) in the presence or absence of base in an inert solvent may produce compounds of Formula (19) at temperatures

ranging from -50°C to 250°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), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl 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) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

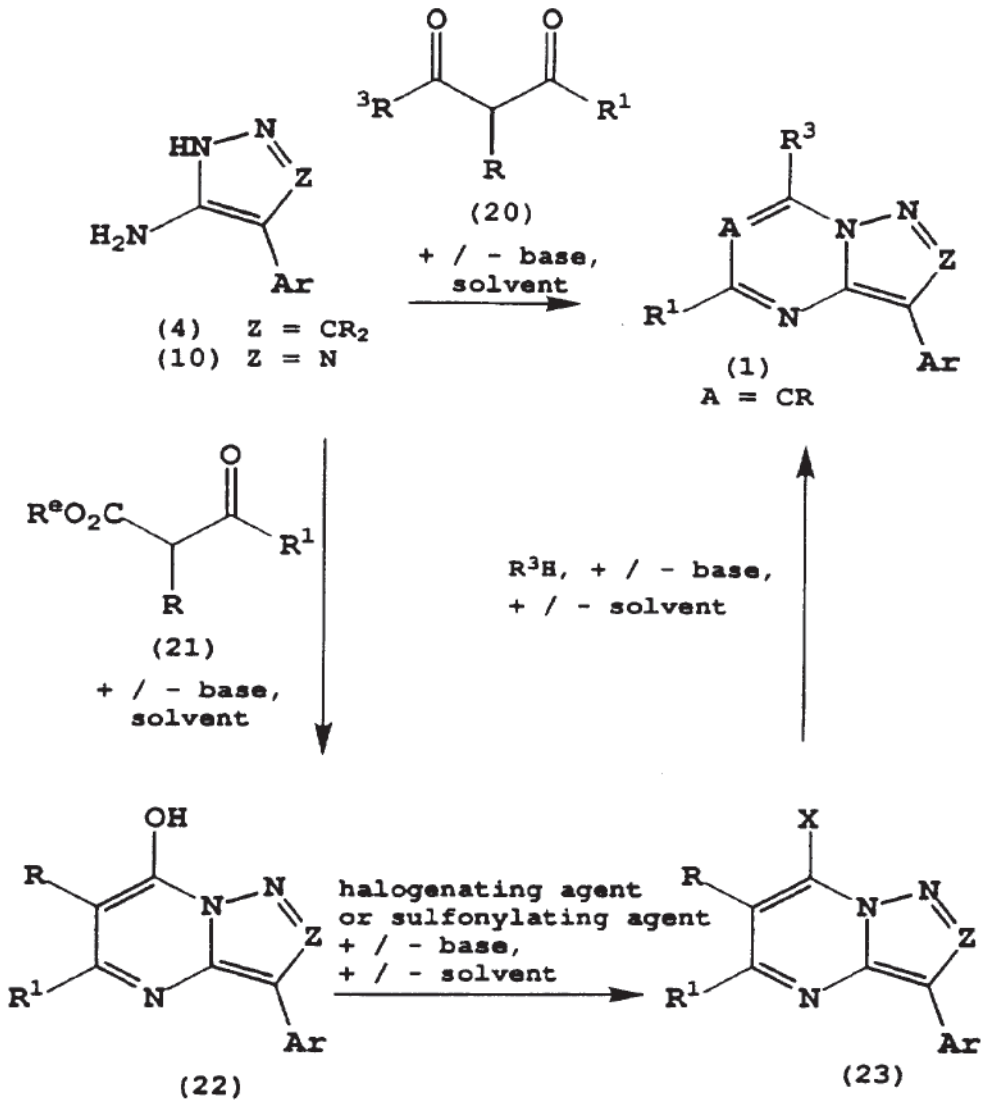
Compounds of Formula (19) may then be reacted with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$. Alkylating agents may include, but are not limited to, C_1-C_{10} alkyl -halides, -tosylates, -mesylates or -triflates; C_1-C_{10} haloalkyl(1 - 10 halogens)-halides, -tosylates, -mesylates or -triflates; C_2-C_8 alkoxyalkyl-halides, -tosylates, -mesylates or -triflates; C_3-C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4-

C_{12} cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; or heterocyclyl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C_1-C_{10} alkanoyl halides or anhydrides, C_1-C_{10} haloalkanoyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkanoyl halides or anhydrides, C_3-C_6 cycloalkanoyl halides or anhydrides, C_4-C_{12} cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C_1-C_4) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides, heteroaryl(C_1-C_4) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C_1-C_4) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C_1-C_{10} alkylsulfonyl halides or anhydrides, C_1-C_{10} haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkylsulfonyl halides or anhydrides, C_3-C_6 cycloalkylsulfonyl halides or anhydrides, C_4-C_{12} cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C_1-C_4 alkyl)-, heteroarylsulfonyl halides or anhydrides, heteroaryl(C_1-C_4 alkyl)sulfonyl halides or anhydrides, heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C_1-C_4 alkyl)sulfonyl halides or anhydrides. 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 bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl 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) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (1), where A is CR and R is defined above, may be synthesized by the methods depicted in Scheme 14.

SCHEME 14



Compounds of Formula (4) or (10) may be treated with compounds of Formula (20), where R^1 and R^3 are defined above in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula (1), where A is CR and R is defined above. 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 bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl 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) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C. Alternatively, compounds of Formula (1) where A is CR and R is defined above, may be synthesized through intermediates (22) and (23).

Compounds of Formula (4) or (10) may be treated with compounds of Formula (21), where R^1 is defined above and R^e is alkyl (1 - 6 carbons), in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula (1), where A is CR and R is defined above. 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 bis(trialkylsilyl)amides (preferably sodium

bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl 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) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C. Compounds of Formula (22) may be treated 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 -80°C to 250°C to give products of Formula (23) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkanesulfonyloxy). 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 (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl 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, 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 bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

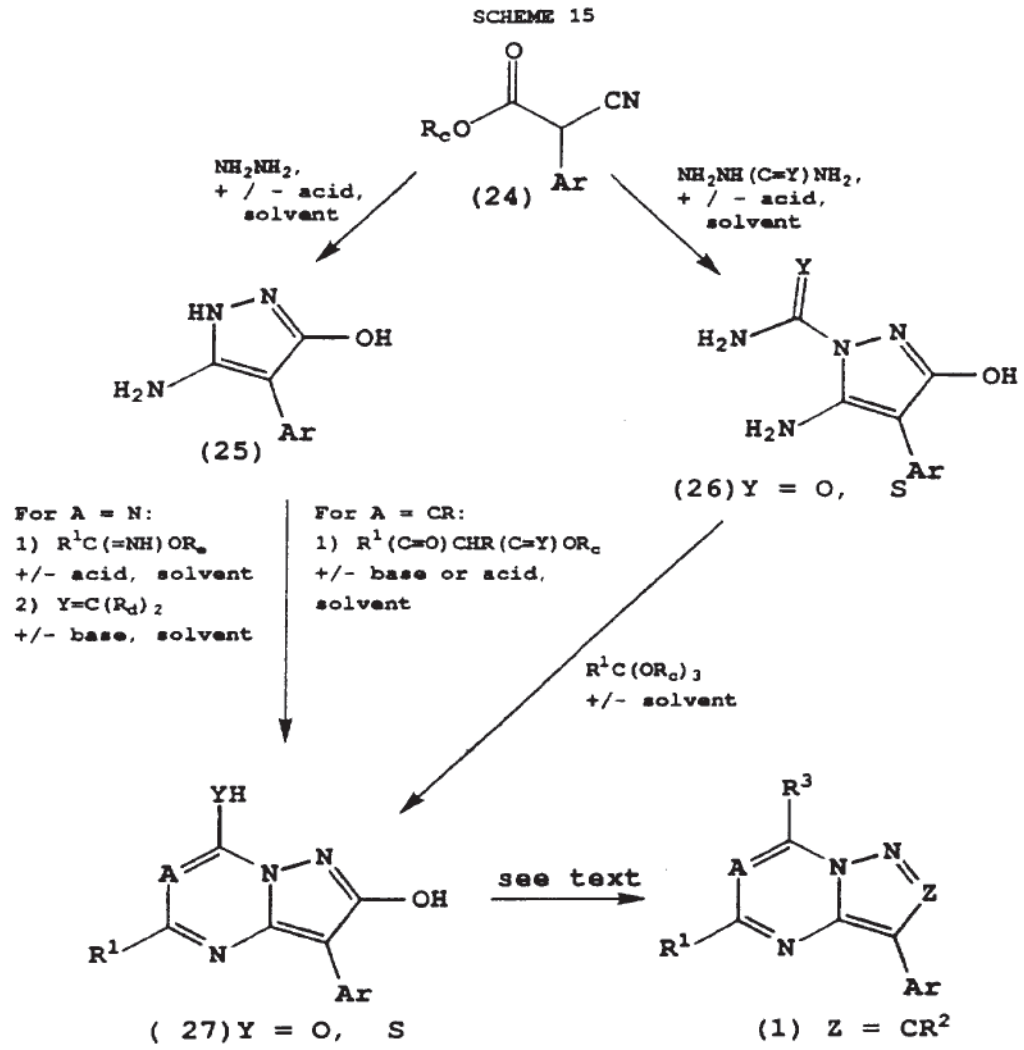
N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), 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 dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

Compounds of Formula (23) may be reacted with compounds of Formula R^3H (where R3 is defined as above except R^3 is not SH, COR^7, CO_2R^7, aryl or heteroaryl) 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 generate compounds of Formula (1). 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 dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

Some compounds of Formula (1) may also be prepared using the methods shown in Scheme 15.

SCHEME 15



A compound of Formula (24) (R_c is a lower alkyl group and Ar is defined as above) may be reacted with hydrazine in the presence or absence of an inert solvent to afford an intermediate of Formula (25), where Ar is defined as above. The conditions employed are similar to those used for the preparation of intermediate of Formula (4) from compound of Formula (3) in Scheme 4. Compounds of Formula (25), where A is N, may be reacted with reagents of the formula $R^1C(=NH)OR_e$, where R^1 is

defined above and R_e is a lower alkyl group) in the presence or absence of an acid in an inert solvent, followed by reaction with a compound of formula YisC(R_d)2 (where Y is O or S and 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 to give compounds of Formula (27) (where A is N and Y is O, S). The conditions for these transformations are the same as those employed for the conversions of compound of Formula (4) to compound of Formula (7) in Scheme 4.

Alternatively, compounds of Formula (25), where A is CR, may be reacted with compounds of the formula R^1(C=O)CHR(C=Y)OR_c (where R^1 and R are defined as above and R_c is a lower alkyl group) to give a compound of Formula (27) (where A is CR) using conditions similar to those employed for the conversion of compounds of Formula (21) to compounds of Formula (22) in Scheme 14. Intermediates of Formula (27) (where Y is O) may be treated with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H or R^2H in the presence or absence of a base in an inert solvent to give compounds of Formula (1) (where Z is CR^2).

It will be recognized by those skilled in the art that various combinations of halogenating agents, sulfonylating agents, R^3H or R^2H may be used in different orders of reaction sequences in Scheme 15 to afford compounds of Formula (1). For example, in some cases, it may be desirable to react compounds with stoichiometric amounts of halogenating agents or sulfonylating agents, react with R^2H (or R^3H), then repeat the reaction with halogenating agents or sulfonylating agents and react with R^3H (or R^2H) to give compounds of Formula (1). The reaction conditions and reagents used for these conversions are similar to the

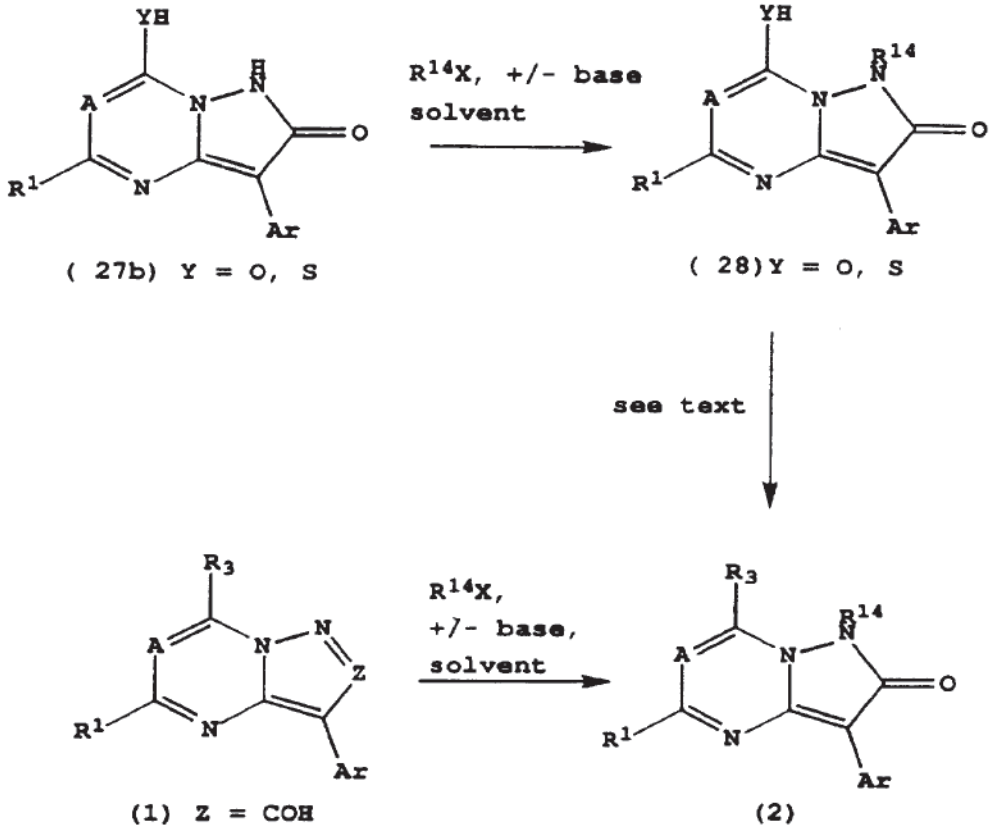
ones employed for the conversion of intermediate compounds of Formulae (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1 (where A is N).

Alternatively, compounds of Formula (27) (where Y is S) may be converted to compounds of Formula (1) in Scheme 15. Intermediate compounds of Formula (27) may be alkylated with a compound R^fX (where R^f is lower alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or absence of a base in an inert solvent to give a compound of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1) may be prepared from compounds of Formula (24), using an alternate route as depicted in Scheme 15. Compounds of Formula (24) may be converted to compounds of Formula (27) via reaction with compounds of formula $NH_2NH(C=NH)NH_2$ in the presence or absence of an acid in an inert solvent, followed by reaction with compounds $R^1C(OR_c)_3$ (where R_c is lower alkyl and R^1 is defined as above), using the conditions employed for the conversion of compounds of Formulae (3) to (17) to (7) in Scheme 10.

Some compounds of Formula (2) may be prepared by the methods illustrated in Scheme 16.

SCHEME 16



Compounds of Formula (27b) may be treated with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures of Formula (28). Compounds of Formula (28) (Y is O) may then be converted to compounds of Formula (2) by treatment with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H in the presence or absence of a base in an inert solvent to give compounds of Formula (2). The reaction conditions used for these conversions are similar to the

ones employed for the conversion of intermediate compounds (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1 (where A is N).

Alternatively, compounds of Formula (28) (Y is S) may be alkylated with a compound R^fX (where R^f is lower alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or absence of a base in an inert solvent to give a compound of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1), where Z is COH, may be converted to compounds of Formula (2) as illustrated in Scheme 16. Treatment with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures (2). It will be recognized by one skilled in the art that the methods used in Scheme 16 may also be used to prepare compounds of Formula (1) where Z is COR^7.

For Scheme 16, the terms "base" and " inert solvent" may have the meanings given below. 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 bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), 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, 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 dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on an IBM-Bruker FT-NMR (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 (using chemi-ionization (CI) with NH_3 as the carrier gas or gas chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point 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.

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-(2,4-dimethylphenyl)[1,5-a]
-pyrazolo-[1,3,5]-triazin-4(3H)-one
(Formula 7, where Y is O, R_1 is CH_3, Z is C-CH_3, Ar is 2,4-dimethylphenyl)

A. 1-Cyano-1-(2,4-dimethylphenyl)propan-2-one

Sodium pellets (9.8g, 0.43 mol) were added portionwise to a solution of 2,4-dimethylphenylacetonitrile (48 g, 0.33 mol) in ethyl acetate (150 mL) at ambient temperature. The reaction mixture was heated to reflux temperature and stirred for 16 hours. The resulting suspension was cooled to room temperature and filtered. The collected precipitate was washed with copious amounts of ether and then air-dried. The solid was dissolved in water and a 1N HCl solution was added until the pH = 5-6. The mixture was extracted with ethyl acetate (3 X 200 mL); the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to afford a white solid (45.7g, 74% yield): NMR ($CDCl_3$, 300 MHz):; CI-MS: 188 (M + H).

B. 5-Amino-4-(2,4-dimethylphenyl)-3-methylpyrazole

A mixture of 1-cyano-1-(2,4-dimethylphenyl)propan-2-one (43.8g, 0.23 mol), hydrazine-hydrate (22 mL, 0.46 mol), glacial acetic acid (45 mL, 0.78 mol) and toluene (500 mL) were stirred at reflux temperature for 18 hours in an apparatus fitted with a Dean-Stark trap. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo. The residue was dissolved in 6N HCl and the resulting solution was extracted with ether three times. A concentrated ammonium hydroxide solution was added to the aqueous layer until pH = 11. 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 pale brown viscous oil (34.6g, 75% yield): NMR ($CDCl_3$,300 MHz): 7.10 (s, 1H), 7.05 (d, 2H, J=1), 2.37 (s, 3H), 2.10 (s, 3H); CI-MS: 202 (M + H).

C. 5-Acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt

Ethyl acetamidate hydrochloride (60g, 0.48 mol) was added quickly to a rapidly stirred mixture of potassium carbonate (69.5g, 0.50 mol), dichloromethane (120 mL) and water (350 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 X 120 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, (35.0 g) was used without further purification.

Glacial aetic acid (9.7 mL, 0.17 mol) was added to a stirred mixture of 5-amino-4-(2,4-dimethylphenyl)-3-methylpyrazole (34g, 0.17 mol), ethyl acetamidate (22g, 0.25 mol) and acetonitrile (500 mL). The resulting reaction mixture was stirred at room temperature for 3 days; at the end of which time, it was concentrated in vacuo to about one-third of its original volume. The resulting suspension was filtered and the collected

solid was washed with copious amounts of ether. The white solid was dried *in vacuo* (31.4g, 61% yield): NMR (DMSO-d_6,300 MHz): 7.00 (s, 1H), 6.90 (dd, 2H, J=7, 1), 2.28 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.81 (s, 3H); CI-MS: 243 (M + H).

D. 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-[1,3,5]-triazin-4(3H)-one

Sodium pellets (23g, 1 mol) were added portionwise to ethanol (500 mL) with vigorous stirring. After all the sodium reacted, 5-acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt (31.2g, 0.1 mol) and diethyl carbonate (97 mL, 0.8 mol) 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 = 5-6. The aqueous layer was extracted with ethyl acetate three times; the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a pale tan solid (26g, 98% yield): NMR ($CDCl_3$,300 MHz): 7.15(s, 1H), 7.09 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H); CI-MS: 269 (M + H).

EXAMPLE 2

Preparation of
5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(6H)-one
(Formula 7, where Y is O, R_1 is CH_3, Z is N, Ar is 2,4,6-trimethylphenyl)

A. 1-Phenylmethyl-4-(2,4,6-trimethylphenyl)-5-aminotriazole

A mixture of 2,4,6-trimethylbenzyl cyanide (1.0g, 6.3 mmol), benzyl azide (0.92g, 6.9 mmol) and potassium

t-butoxide (0.78g, 6.9 mmol) in tetrahydrofuran (10mL) was stirred at ambient temperature for 2.5 days. The resulting suspension was diluted with water and 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 brown oil. Trituration with ether and filtration afforded a yellow solid (1.12g, 61% yield): NMR ($CDCl_3$,300 MHz):7.60-7.30 (m, 5H), 7.30-7.20 (m, 2H), 5.50 (s, 2H), 3.18 (br s, 2H), 2.30 (s, 3H), 2.10 (s, 6H); CI-MS: 293 (M + H).

B. 4-(2,4,6-Trimethylphenyl)-5-aminotriazole

Sodium (500 mg, 22 mmol) was added with stirring to a mixture of liquid ammonia (30 mL) and 1-phenylmethyl-4-(2,4,6-trimethylphenyl)-5-aminotriazole (1.1g, 3.8 mmol). The reaction mixture was stirred until a dark green color persisted. An ammonium chloride solution (mL) was added and the mixture was stirred while warming to ambient temperature over 16 hours. The residue was treated with a 1M HCl solution and filtered. The aqueous layer was basified with a concentrated ammonium hydroxide solution (pH = 9) and then extracted with ethyl acetate three times. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give a yellow solid (520 mg), which was homogeneous by thin layer chromatography (ethyl acetate):
NMR ($CDCl_3$,300 MHz): 6.97 (s, 2H), 3.68-3.50 (br.s, 2H), 2.32 (s, 3H), 2.10 (s, 6H); CI-MS: 203 (M + H).

C. 4-(2,4,6-Trimethylphenyl)-5-acetamidinotriazole, acetic acid salt

A mixture of 4-(2,4,6-trimethylphenyl)-5-aminotriazole (400 mg, 1.98 mmol), ethyl acetamidate (261 mg, 3 mmol) and glacial acetic acid (0.1 mL, 1.98 mmol) in acetonitrile (6 mL) was stirred at ambient

temperature for 4 hours. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. Drying *in vacuo* afforded a white solid (490 mg, 82% yield): NMR (DMSO-d_6,300 MHz):7.90-7.70 (br s, 0.5H), 7.50-7.20 (br. s, 0.5H), 6.90 (s, 2H), 6.90 (s, 2H), 3.50-3.10 (br s, 3H), 2.30-2.20 (br s, 3H), 2.05 (d, 1H, J = 7), 1.96 (s, 6H), 1.87 (s, 6H); CI-MS: 244 (M + H).

D. 5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(4H)-one

Sodium (368 mg, 16.2 mmol) was added with stirring to ethanol (10 mL) at room temperature. After the sodium had reacted, 4-(2,4,6-trimethylphenyl)-5-acetamidino-triazole, acetic acid salt (490 mg, 1.6 mmol) and diethyl carbonate (1.6 mL, 13 mmol) were added. The reaction mixture was stirred at reflux temperature for 5 hours, then cooled to room temperature. The reaction mixture was diluted with water; a 1N HCl solution was added until pH = 5-6 and three extractions with ethyl acetate were performed. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a yellow residue. Trituration with ether and filtration afforded a yellow solid (300 mg, 69% yield): NMR ($CDCl_3$,300 MHz): 6.98 (s, 2H), 2.55 (s, 3H), 2.35 (s, 3H), 2.10 (s, 6H); CI-MS: 270 (M + H).

EXAMPLE 3

Preparation of 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine

(Formula 1, where R^3 is $CH(CHCO_2CH_3)_2$, R_1 is CH_3, Z is C-CH_3, Ar is 2,4-dimethylphenyl)

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]- pyrazolotriazine

A mixture of 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a] -pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed *in vacuo*. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction (Rf = 0.5) Solvent was removed in vacuo to afford a yellow oil (1.0g, 68% yield): NMR ($CDCl_3$,300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7,1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

B. 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine

Sodium hydride (60% in oil, 80 mg, 2 mmol) was washed with hexanes twice, decanted after each washing and taken up in anhydrous tetrahydrofuran (THF, 1 mL). A solution of diethyl malonate (0.32g, 2 mmol) in THF (2 mL) was added dropwise over 5 min, during which time vigorous gas evolution ensued. A solution of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]- pyrazolotriazine (0.5g, 1.75 mmol) in THF (2 mL) was added and the reaction mixture was then stirred under a nitrogen atmosphere for 48 hours. The resulting suspension was poured onto water and extracted three times with ethyl acetate. The combined organic layers were washed once with brine, dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown

oil. Column chromatography (ethyl acetate:hexanes::1:9) afforded, after removal of solvent *in vacuo*, a pale yellow solid (Rf = 0.2, 250 mg, 35% yield): mp 50-52°C; NMR ($CDCl_3$, 300 MHz): 12.35 (br.s, 1H, 7.15-7.00 (m, 3H), 4.40 (q, 2H, J = 7), 4.30 (q, 2H, J = 7), 2.4, 2.35, 2.3, 2.2, 2.1 (5 s, 12H), 1.4 (t, 3H, J = 7), 1.35-1.25 (m, 3H); CI-HRMS: Calcd: 411.2032, Found: 411.2023.

EXAMPLE 6

Preparation of 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

(Formula 1, where R^3 is $NHCH(CH_2OCH_3)_2$, R_1 is CH_3, Z is $C-CH_3$, Ar is 2,4-dichlorophenyl)

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]- pyrazolotriazine

A mixture of 2,7-dimethyl-8-(2,4 dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed in vacuo. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction (Rf = 0.5) Solvent was removed *in vacuo* to afford a yellow oil (1.0g, 68% yield): NMR ($CDCl_3$,300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7,1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

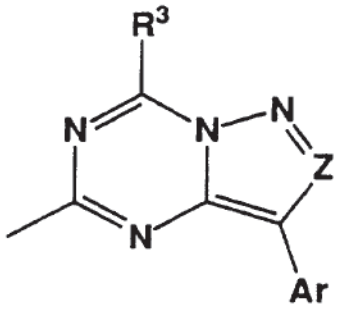
B. 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4- dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

A mixture of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Part A, 570 mg, 1.74 mmol), 1,3-dimethoxypropyl-2-aminopropane (25mg, 2.08 mmol) and ethanol (10 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was poured onto water (25 mL) and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo*. Column chromatography (CH_2Cl_2:CH_3OH::50:1) afforded one fraction. Removal of solvent *in vacuo* gave a solid (250 mg, 35% yield): mp 118-120°C; NMR ($CDCl_3$,300 MHz): 7.50 (s, 1H), 7.28 (dd, 2H, J = 8,1), 6.75 (d, 1H, J = 8), 4.70-4.58 (m, 1H), 3.70-3.55 (m, 4H), 3.43 (s, 6H), 2.50 (s, 3H), 2.35 (s, 3H); CI-HRMS: Calcd: 409.1072, Found: 409.1085; Analysis Calcd. for $C_{18}H_{21}Cl_2N_5O_2$: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.

Using the above procedures and modifications known to one skilled in the art of organic synthesis, the following additional examples of Tables 1-4 may be prepared.

The examples delineated in TABLE 1 may be prepared by the methods outlined in Examples 1, 2, 3 or 6. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

TABLE 1



Ex.	Z	R_3	Ar	mp(°C)
6[a]	C-Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph	118-120
7[b]	C-Me	$NHCHPr_2$	2,4-Cl_2-Ph	114-116
8[c]	C-Me	NEtBu	2,4-Cl_2-Ph	oil
9[d]	C-Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Cl_2-Ph	oil
10[e]	C-Me	$N(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph	oil
11[f]	C-Me	NH-3-heptyl	2,4-Cl_2-Ph	90-92
12[g]	C-Me	$NHCH(Et)CH_2OMe$	2,4-Cl_2-Ph	179-181
13[h]	C-Me	NEt_2	2,4-Cl_2-Ph	133-134
14[i]	C-Me	$NHCH(CH_2OEt)_2$	2,4-Cl_2-Ph	oil
15[j]	C-Me	NH-3-pentyl	2,4-Cl_2-Ph	139-140
16[k]	C-Me	NMePh	2,4-Cl_2-Ph	60-62
17[l]	C-Me	NPr_2	2,4-Cl_2-Ph	oil
18[m]	C-Me	NH-3-hexyl	2,4-Cl_2-Ph	130-132
19	C-Me	morpholino	2,4-Cl_2-Ph	
20	C-Me	$N(CH_2Ph)CH_2CH_2OMe$	2,4-Cl_2-Ph	
21	C-Me	$NHCH(CH_2Ph)CH_2OMe$	2,4-Cl_2-Ph	
22	C-Me	NH-4-tetrahydropyranyl	2,4-Cl_2-Ph	
23	C-Me	NH-cyclopentyl	2,4-Cl_2-Ph	
24	C-Me	1,2,3,4-tetrahydro-isoquinolinyl	2,4-Cl_2-Ph	
25	C-Me	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	2,4-Cl_2-Ph	
26[n]	C-Me	OEt	2,4-Cl_2-Ph	141-143
27	C-Me	$OCH(Et)CH_2OMe$	2,4-Cl_2-Ph	

	28	C-Me	OCH_2Ph	2,4-Cl_2-Ph	
	29	C-Me	O-3-pentyl	2,4-Cl_2-Ph	
	30	C-Me	SEt	2,4-Cl_2-Ph	
	31	C-Me	S(O)Et	2,4-Cl_2-Ph	
5	32	C-Me	SO_2Et	2,4-Cl_2-Ph	
	33	C-Me	$CH(CO_2Et)_2$	2,4-Cl_2-Ph	
	34	C-Me	$C(Et)(CO_2Et)_2$	2,4-Cl_2-Ph	
	35	C-Me	$CH(Et)CH_2OH$	2,4-Cl_2-Ph	
	36	C-Me	$CH(Et)CH_2OMe$	2,4-Cl_2-Ph	
10	37	C-Me	$CONMe_2$	2,4-Cl_2-Ph	
	38	C-Me	$COCH_3$	2,4-Cl_2-Ph	
	39	C-Me	$CH(OH)CH_3$	2,4-Cl_2-Ph	
	40	C-Me	C(OH)Ph-3-pyridyl	2,4-Cl_2-Ph	
	41	C-Me	Ph	2,4-Cl_2-Ph	
15	42	C-Me	2-CF_3-Ph	2,4-Cl_2-Ph	
	43	C-Me	2-Ph-Ph	2,4-Cl_2-Ph	
	44	C-Me	3-pentyl	2,4-Cl_2-Ph	
	45	C-Me	cyclobutyl	2,4-Cl_2-Ph	
	46	C-Me	3-pyridyl	2,4-Cl_2-Ph	
20	47	C-Me	$CH(Et)CH_2CONMe_2$	2,4-Cl_2-Ph	
	48	C-Me	$CH(Et)CH_2CH_2NMe_2$	2,4-Cl_2-Ph	
	49[o]	C-Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-Ph	125-127
	50	C-Me	$NHCHPr_2$	2,4,6-Me_3-Ph	
	51	C-Me	NEtBu	2,4,6-Me_3-Ph	
25	52	C-Me	$NPr(CH_2$-c-$C_3H_5)$	2,4,6-Me_3-Ph	
	53[ae]	C-Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-Ph	123-124
	54	C-Me	NH-3-heptyl	2,4,6-Me_3-Ph	
	55[ac]	C-Me	$NHCH(Et)CH_2OMe$	2,4,6-Me_3-Ph	145-146
	56[ah]	C-Me	NEt_2	2,4,6-Me_3-Ph	88-90
30	57[ai]	C-Me	$NHCH(CH_2OEt)_2$	2,4,6-Me_3-Ph	132-134
	58[ad]	C-Me	NH-3-pentyl	2,4,6-Me_3-Ph	134-135
	59	C-Me	NMePh	2,4,6-Me_3-Ph	
	60	C-Me	NPr_2	2,4,6-Me_3-Ph	
	61	C-Me	NH-3-hexyl	2,4,6-Me_3-Ph	
35	62	C-Me	morpholino	2,4,6-Me_3-Ph	
	63	C-Me	$N(CH_2Ph)CH_2CH_2OMe$	2,4,6-Me_3-Ph	

	64	C-Me	NHCH(CH_2Ph)CH_2OMe	2,4,6-Me_3-Ph	
	65	C-Me	NH-4-tetrahydropyranyl	2,4,6-Me_3-Ph	
	66	C-Me	NH-cyclopentyl	2,4,6-Me_3-Ph	
	67	C-Me	1,2,3,4-tetrahydro-isoquinolinyl	2,4,6-Me_3-Ph	
	68	C-Me	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	2,4,6-Me_3-Ph	
	69	C-Me	OEt	2,4,6-Me_3-Ph	
	70	C-Me	OCH(Et)CH_2OMe	2,4,6-Me_3-Ph	
	71	C-Me	OCH_2Ph	2,4,6-Me_3-Ph	
	72	C-Me	O-3-pentyl	2,4,6-Me_3-Ph	
	73	C-Me	SEt	2,4,6-Me_3-Ph	
	74	C-Me	S(O)Et	2,4,6-Me_3-Ph	
	75	C-Me	SO_2Et	2,4,6-Me_3-Ph	
	76	C-Me	CH(CO_2Et)$_2$	2,4,6-Me_3-Ph	
	77	C-Me	C(Et)(CO_2Et)$_2$	2,4,6-Me_3-Ph	
	78	C-Me	CH(Et)CH_2OH	2,4,6-Me_3-Ph	
	79	C-Me	CH(Et)CH_2OMe	2,4,6-Me_3-Ph	
	80	C-Me	$CONMe_2$	2,4,6-Me_3-Ph	
	81	C-Me	$COCH_3$	2,4,6-Me_3-Ph	
	82	C-Me	CH(OH)CH_3	2,4,6-Me_3-Ph	
	83	C-Me	C(OH)Ph-3-pyridyl	2,4,6-Me_3-Ph	
	84	C-Me	Ph	2,4,6-Me_3-Ph	
	85	C-Me	2-CF_3-Ph	2,4,6-Me_3-Ph	
	86	C-Me	2-Ph-Ph	2,4,6-Me_3-Ph	
	87	C-Me	3-pentyl	2,4,6-Me_3-Ph	
	88	C-Me	cyclobutyl	2,4,6-Me_3-Ph	
	89	C-Me	3-pyridyl	2,4,6-Me_3-Ph	
	90	C-Me	CH(Et)CH_2CONMe_2	2,4,6-Me_3-Ph	
	91	C-Me	CH(Et)$CH_2CH_2NMe_2$	2,4,6-Me_3-Ph	
	92[p]	C-Me	NHCH(CH_2OMe)$_2$	2,4-Me_2-Ph	44-45
	93[q]	C-Me	N(CH_2CH_2OMe)$_2$	2,4-Me_2-Ph	oil
	94[r]	C-Me	NHCH(Et)CH_2OMe	2,4-Me_2-Ph	102-104
	95[s]	C-Me	NH-3-pentyl	2,4-Me_2-Ph	102-104
	96[t]	C-Me	NEt_2	2,4-Me_2-Ph	oil
	97[u]	C-Me	N(CH_2CN)$_2$	2,4-Me_2-Ph	148-150

	98[v]	C-Me	NHCH(Me)CH_2OMe	2,4-Me_2-Ph	102-104
	99[w]	C-Me	OCH(Et)CH_2OMe	2,4-Me_2-Ph	oil
	100[x]	C-Me	NPr-c-C_3H_5	2,4-Me_2-Ph	oil
	101[y]	C-Me	NHCH(Me)CH_2NMe_2	2,4-Me_2-Ph	47-48
5	102[z]	C-Me	N(c-C_3H_5)CH_2CH_2CN	2,4-Me_2-Ph	117-118
	103[aa]	C-Me	N(Pr)CH_2CH_2CN	2,4-Me_2-Ph	oil
	104[ab]	C-Me	N(Bu)CH_2CH_2CN	2,4-Me_2-Ph	oil
	105	C-Me	$NHCHPr_2$	2,4-Me_2-Ph	
	106	C-Me	NEtBu	2,4-Me_2-Ph	
10	107	C-Me	NPr(CH_2-c-C_3H_5)	2,4-Me_2-Ph	
	108	C-Me	NH-3-heptyl	2,4-Me_2-Ph	
	109	C-Me	NEt_2	2,4-Me_2-Ph	
	110	C-Me	NHCH(CH_2OEt)$_2$	2,4-Me_2-Ph	
	111	C-Me	NH-3-pentyl	2,4-Me_2-Ph	
15	112	C-Me	NMePh	2,4-Me_2-Ph	
	113	C-Me	NPr_2	2,4-Me_2-Ph	
	114	C-Me	NH-3-hexyl	2,4-Me_2-Ph	
	115	C-Me	morpholino	2,4-Me_2-Ph	
	116	C-Me	N(CH_2Ph)CH_2CH_2OMe	2,4-Me_2-Ph	
20	117	C-Me	NHCH(CH_2Ph)CH_2OMe	2,4-Me_2-Ph	
	118	C-Me	NH-4-tetrahydropyranyl	2,4-Me_2-Ph	
	119	C-Me	NH-cyclopentyl	2,4-Me_2-Ph	
	120	C-Me	1,2,3,4-tetrahydro-isoquinolinyl	2,4-Me_2-Ph	
25	121	C-Me	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	2,4-Me_2-Ph	
	122	C-Me	OEt	2,4-Me_2-Ph	
	123	C-Me	OCH(Et)CH_2OMe	2,4-Me_2-Ph	
	124	C-Me	OCH_2Ph	2,4-Me_2-Ph	
30	125	C-Me	O-3-pentyl	2,4-Me_2-Ph	
	126	C-Me	SEt	2,4-Me_2-Ph	
	127	C-Me	S(O)Et	2,4-Me_2-Ph	
	128	C-Me	SO_2Et	2,4-Me_2-Ph	
	3	C-Me	CH(CO_2Et)$_2$	2,4-Me_2-Ph	50-52
35	129	C-Me	C(Et)(CO_2Et)$_2$	2,4-Me_2-Ph	

	130	C-Me	$CH(Et)CH_2OH$	$2,4\text{-}Me_2\text{-}Ph$	
	131	C-Me	$CH(Et)CH_2OMe$	$2,4\text{-}Me_2\text{-}Ph$	
	132	C-Me	$CH(Et)CH_2OEt$	$2,4\text{-}Me_2\text{-}Ph$	
	133	C-Me	$CONMe_2$	$2,4\text{-}Me_2\text{-}Ph$	
5	134	C-Me	$COCH_3$	$2,4\text{-}Me_2\text{-}Ph$	
	135	C-Me	$CH(OH)CH_3$	$2,4\text{-}Me_2\text{-}Ph$	
	136	C-Me	C(OH)Ph-3-pyridyl	$2,4\text{-}Me_2\text{-}Ph$	
	137	C-Me	Ph	$2,4\text{-}Me_2\text{-}Ph$	
	138	C-Me	$2\text{-}CF_3\text{-}Ph$	$2,4\text{-}Me_2\text{-}Ph$	
10	139	C-Me	2-Ph-Ph	$2,4\text{-}Me_2\text{-}Ph$	
	140	C-Me	3-pentyl	$2,4\text{-}Me_2\text{-}Ph$	
	141	C-Me	cyclobutyl	$2,4\text{-}Me_2\text{-}Ph$	
	142	C-Me	3-pyridyl	$2,4\text{-}Me_2\text{-}Ph$	
	143	C-Me	$CH(Et)CH_2CONMe_2$	$2,4\text{-}Me_2\text{-}Ph$	
15	144	C-Me	$CH(Et)CH_2CH_2NMe_2$	$2,4\text{-}Me_2\text{-}Ph$	
	145[bc]	C-Me	$NHCH(CH_2OMe)_2$	2-Me-4-MeO-Ph	45-46
	146[bd]	C-Me	$N(CH_2CH_2OMe)_2$	2-Me-4-MeO-Ph	oil
	147[be]	C-Me	$NHCH(Et)CH_2OMe$	2-Me-4-MeO-Ph	86-88
	148[bf]	C-Me	$N(Pr)CH_2CH_2CN$	2-Me-4-MeO-Ph	oil
20	149	C-Me	$OCH(Et)CH_2OMe$	2-Me-4-MeO-Ph	
	150[af]	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-MeO-Ph	88-90
	151[al]	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-MeO-Ph	oil
	152[ag]	C-Me	$NHCH(Et)CH_2OMe$	2-Br-4-MeO-Ph	95-97
	153	C-Me	$N(Pr)CH_2CH_2CN$	2-Br-4-MeO-Ph	
25	154	C-Me	$OCH(Et)CH_2OMe$	2-Br-4-MeO-Ph	
	155	C-Me	$NHCH(CH_2OMe)_2$	$2\text{-Me-4-}NMe_2\text{-Ph}$	
	156	C-Me	$N(CH_2CH_2OMe)_2$	$2\text{-Me-4-}NMe_2\text{-Ph}$	oil
	157	C-Me	$NHCH(Et)CH_2OMe$	$2\text{-Me-4-}NMe_2\text{-Ph}$	
	158	C-Me	$N(Pr)CH_2CH_2CN$	$2\text{-Me-4-}NMe_2\text{-Ph}$	
30	159	C-Me	$OCH(Et)CH_2OMe$	$2\text{-Me-4-}NMe_2\text{-Ph}$	
	160	C-Me	$NHCH(CH_2OMe)_2$	$2\text{-Br-4-}NMe_2\text{-Ph}$	
	161	C-Me	$N(CH_2CH_2OMe)_2$	$2\text{-Br-4-}NMe_2\text{-Ph}$	
	162	C-Me	$NHCH(Et)CH_2OMe$	$2\text{-Br-4-}NMe_2\text{-Ph}$	
	163	C-Me	$N(Pr)CH_2CH_2CN$	$2\text{-Br-4-}NMe_2\text{-Ph}$	
35	164	C-Me	$OCH(Et)CH_2OMe$	$2\text{-Br-4-}NMe_2\text{-Ph}$	
	165	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-i-Pr-Ph	

	166	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-i-Pr-Ph	
	167	C-Me	$NHCH(Et)CH_2OMe$	2-Br-4-i-Pr-Ph	
	168	C-Me	$N(Pr)CH_2CH_2CN$	2-Br-4-i-Pr-Ph	
	169	C-Me	$OCH(Et)CH_2OMe$	2-Br-4-i-Pr-Ph	
5	170	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-Me-Ph	
	171	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-Me-Ph	
	172	C-Me	$NHCH(Et)CH_2OMe$	2-Br-4-Me-Ph	
	173	C-Me	$N(Pr)CH_2CH_2CN$	2-Br-4-Me-Ph	
	174	C-Me	$OCH(Et)CH_2OMe$	2-Br-4-Me-Ph	
10	175[ar]	C-Me	$NHCH(CH_2OMe)_2$	2-Me-4-Br-Ph	108-109
	176	C-Me	$N(CH_2CH_2OMe)_2$	2-Me-4-Br-Ph	
	177	C-Me	$NHCH(Et)CH_2OMe$	2-Me-4-Br-Ph	
	178	C-Me	$N(Pr)CH_2CH_2CN$	2-Me-4-Br-Ph	
	179	C-Me	$OCH(Et)CH_2OMe$	2-Me-4-Br-Ph	
15	180	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph	
	181	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph	
	182	C-Me	$NHCH(CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph	
	183	C-Me	$N(CH_2CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph	
	184	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph	
20	185	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph	
	186	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-CF_3-Ph	
	187	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-CF_3-Ph	
	188	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph	
	189	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph	
25	190	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph	
	191	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph	
	192	C-Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph	
	193	C-Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph	
	194	C-Me	$NHCH(CH_2OMe)_2$	4-(COMe)-2-Br-Ph	
30	195	C-Me	$N(CH_2CH_2OMe)_2$	4-(COMe)-2-Br-Ph	
	196	C-Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl	
	197	C-Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl	
	198	C-Me	$NHCH(CH_2OMe)_2$	2,4-$(Br)_2$-Ph	
	199	C-Me	$N(CH_2CH_2OMe)_2$	2,4-$(Br)_2$-Ph	
35	200	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph	
	201	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph	

202	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
203	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
204	C-Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
205	C-Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
206	C-Me	$NHCH(CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
207	C-Me	$N(CH_2CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
208	C-Me	$NHCH(CH_2OMe)_2$	2-I-4-i-Pr-Ph
209	C-Me	$N(CH_2CH_2OMe)_2$	2-I-4-i-Pr-Ph
210	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph
211	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph
212	C-Me	$NHCH(CH_2OMe)_2$	2,4-[SMe]2-Ph
213	C-Me	$N(CH_2CH_2OMe)_2$	2,4-[SMe]2-Ph
214	C-Me	$NHCH(CH_2OMe)_2$	2,4-[SO_2Me]2-Ph
215	C-Me	$N(CH_2CH_2OMe)_2$	2,4-[SO_2Me]2-Ph
216	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
217	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
218	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
219	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
220	C-Me	$NHCH(CH_2OMe)_2$	2-$N(Me)_2$-4-Me-Ph
221	C-Me	$N(CH_2CH_2OMe)_2$	2-$N(Me)_2$-4-Me-Ph
222	C-Me	$NHCH(CH_2OMe)_2$	2-MeS-4,6-$(Me)_2$-Ph
223	C-Me	$N(CH_2CH_2OMe)_2$	2-MeS-4,6-$(Me)_2$-Ph
224	C-Me	$NHCH(CH_2OMe)_2$	2-(CH_3CO)-4,6-$(Me)_2$-Ph
225	C-Me	$N(CH_2CH_2OMe)_2$	2-(CH_3CO)-4,6-$(Me)_2$-Ph
226	H	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph
227	H	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph
228	CF3	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph
229	CF3	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph
230	N	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-Ph
231	N	$NHCHPr_2$	2,4,6-Me_3-Ph
232	N	NEtBu	2,4,6-Me_3-Ph
233	N	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4,6-Me_3-Ph
234	N	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-Ph
235	N	NH-3-heptyl	2,4,6-Me_3-Ph
236	N	$NHCH(Et)CH_2OMe$	2,4,6-Me_3-Ph
237	N	NEt_2	2,4,6-Me_3-Ph

	238	N	$NHCH(CH_2OEt)_2$	2,4,6-Me_3-Ph
	239	N	NH-3-pentyl	2,4,6-Me_3-Ph
	240	N	NMePh	2,4,6-Me_3-Ph
	241	N	NPr_2	2,4,6-Me_3-Ph
5	242	N	NH-3-hexyl	2,4,6-Me_3-Ph
	243	N	morpholino	2,4,6-Me_3-Ph
	244	N	$N(CH_2Ph)CH_2CH_2OMe$	2,4,6-Me_3-Ph
	245	N	$NHCH(CH_2Ph)CH_2OMe$	2,4,6-Me_3-Ph
	246	N	NH-4-tetrahydropyranyl	2,4,6-Me_3-Ph
10	247	N	NH-cyclopentyl	2,4,6-Me_3-Ph
	248	N	1,2,3,4-tetrahydro-isoquinolinyl	2,4,6-Me_3-Ph
	249	N	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	2,4,6-Me_3-Ph
15	250	N	OEt	2,4,6-Me_3-Ph
	251	N	$OCH(Et)CH_2OMe$	2,4,6-Me_3-Ph
	252	N	OCH_2Ph	2,4,6-Me_3-Ph
	253	N	O-3-pentyl	2,4,6-Me_3-Ph
	254	N	SEt	2,4,6-Me_3-Ph
20	255	N	S(O)Et	2,4,6-Me_3-Ph
	256	N	SO_2Et	2,4,6-Me_3-Ph
	257	N	$CH(CO_2Et)_2$	2,4,6-Me_3-Ph
	258	N	$C(Et)(CO_2Et)_2$	2,4,6-Me_3-Ph
	259	N	$CH(Et)CH_2OH$	2,4,6-Me_3-Ph
25	260	N	$CH(Et)CH_2OMe$	2,4,6-Me_3-Ph
	261	N	$CONMe_2$	2,4,6-Me_3-Ph
	262	N	$COCH_3$	2,4,6-Me_3-Ph
	263	N	$CH(OH)CH_3$	2,4,6-Me_3-Ph
	264	N	C(OH)Ph-3-pyridyl	2,4,6-Me_3-Ph
30	265	N	Ph	2,4,6-Me_3-Ph
	266	N	2-CF_3-Ph	2,4,6-Me_3-Ph
	267	N	2-Ph-Ph	2,4,6-Me_3-Ph
	268	N	3-pentyl	2,4,6-Me_3-Ph
	269	N	cyclobutyl	2,4,6-Me_3-Ph
35	270	N	3-pyridyl	2,4,6-Me_3-Ph
	271	N	$CH(Et)CH_2CONMe_2$	2,4,6-Me_3-Ph

	272	N	$CH(Et)CH_2CH_2NMe_2$	2,4,6-Me_3-Ph
	273	N	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph
	274	N	$NHCHPr_2$	2,4-Me_2-Ph
	275	N	NEtBu	2,4-Me_2-Ph
	276	N	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Me_2-Ph
	277	N	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph
	278	N	NH-3-heptyl	2,4-Me_2-Ph
	279	N	$NHCH(Et)CH_2OMe$	2,4-Me_2-Ph
	280	N	NEt_2	2,4-Me_2-Ph
	281	N	$NHCH(CH_2OEt)_2$	2,4-Me_2-Ph
	282	N	NH-3-pentyl	2,4-Me_2-Ph
	283	N	NMePh	2,4-Me_2-Ph
	284	N	NPr_2	2,4-Me_2-Ph
	285	N	NH-3-hexyl	2,4-Me_2-Ph
	286	N	morpholino	2,4-Me_2-Ph
	287	N	$N(CH_2Ph)CH_2CH_2OMe$	2,4-Me_2-Ph
	288	N	$NHCH(CH_2Ph)CH_2OMe$	2,4-Me_2-Ph
	289	N	NH-4-tetrahydropyranyl	2,4-Me_2-Ph
	290	N	NH-cyclopentyl	2,4-Me_2-Ph
	291	N	1,2,3,4-tetrahydro-isoquinolinyl	2,4-Me_2-Ph
	292	N	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	2,4-Me_2-Ph
	293	N	OEt	2,4-Me_2-Ph
	294	N	$OCH(Et)CH_2OMe$	2,4-Me_2-Ph
	295	N	OCH_2Ph	2,4-Me_2-Ph
	296	N	O-3-pentyl	2,4-Me_2-Ph
	297	N	SEt	2,4-Me_2-Ph
	298	N	S(O)Et	2,4-Me_2-Ph
	299	N	SO_2Et	2,4-Me_2-Ph
	300	N	$CH(CO_2Et)_2$	2,4-Me_2-Ph
	301	N	$C(Et)(CO_2Et)_2$	2,4-Me_2-Ph
	302	N	$CH(Et)CH_2OH$	2,4-Me_2-Ph
	303	N	$CH(Et)CH_2OMe$	2,4-Me_2-Ph
	304	N	$CONMe_2$	2,4-Me_2-Ph
	305	N	$COCH_3$	2,4-Me_2-Ph

306	N	CH(OH)CH_3	2,4-Me_2-Ph	
307	N	C(OH)Ph-3-pyridyl	2,4-Me_2-Ph	
308	N	Ph	2,4-Me_2-Ph	
309	N	2-CF_3-Ph	2,4-Me_2-Ph	
310	N	2-Ph-Ph	2,4-Me_2-Ph	
311	N	3-pentyl	2,4-Me_2-Ph	
312	N	cyclobutyl	2,4-Me_2-Ph	
313	N	3-pyridyl	2,4-Me_2-Ph	
314	N	CH(Et)CH_2CONMe_2	2,4-Me_2-Ph	
315	N	CH(Et)$CH_2CH_2NMe_2$	2,4-Me_2-Ph	
316[an]	C-Me	NEt_2	2-Br-4-MeO-Ph	oil
317[am]	C-Me	NH-3-pentyl	2-Br-4-MeO-Ph	oil
318[aj]	C-Me	NHCH(CH_2CH_2OMe)CH_2OMe	2,4,6-Me_3-Ph	101-103
319[ao]	C-Me	NH(c-C_3H_5)	2,4-Me_2-Ph	oil
320[ak]	C-Me	morpholino	2,4,6-Me_3-Ph	139-141
321[ap]	C-Me	NHCH(CH_2OMe)$_2$	2-CN-4-Me-Ph	152-153
322[aq]	C-Me	N(c-C_3H_5)CH_2CH_2CN	2,4,6-Me_3-Ph	149-151
324[as]	C-Me	NHCH(CH_2CH_2OMe)CH_2OMe	2-Me-4-Br-Ph	115-117
325[at]	C-Me	NHCH(CH_2OMe)$_2$	2,5-Me_2-4-MeO-Ph	55-57
326[au]	C-Me	N(CH_2CH_2OMe)$_2$	2,5-Me_2-4-MeO-Ph	72
327[av]	C-Me	NH-3-pentyl	2,5-Me_2-4-MeO-Ph	45-47
328[aw]	C-Me	NEt_2	2,5-Me_2-4-MeO-Ph	oil
329[ax]	C-Me	NHCH(CH_2OMe)$_2$	2-Cl-4-MePh	80-81
330[ay]	C-Me	NCH(Et)CH_2OMe	2-Cl-4-MePh	77-79
331[az]	C-Me	N(CH_2CH_2OMe)$_2$	2-Cl-4-MePh	oil
332[ba]	C-Me	(S)-NHCH(CH_2CH_2OMe)CH_2OMe	2-Cl-4-MePh	139-140
333[bb]	C-Me	N(c-C_3H_5)CH_2CH_2CN	2,5-Me_2-4-MeOPh	120-122
334[bg]	C-Me	NEt_2	2-Me-4-MeOPh	oil
335[bh]	C-Me	OEt	2-Me-4-MeOPh	oil
336[bi]	C-Me	(S)-NHCH(CH_2CH_2OMe)CH_2OMe	2-Me-4-MeOPh	oil
337[bj]	C-Me	N(c-C_3H_5)CH_2CH_2CN	2-Me-4-MeOPh	129
338[bk]	C-Me	NHCH(CH_2CH_2OEt)$_2$	2-Me-4-MeOPh	amorph.
339	C-Me	N(c-C_3H_5)CH_2CH_2CN	2,4-Cl_2-Ph	109-110
340	C-Me	(S)-NHCH(CH_2CH_2OMe)CH_2OMe	2,4-Cl_2-Ph	93-94
341	C-Me	NH-3-pentyl	2-Me-4-BrPh	118-119
342	C-Me	N(CH_2CH_2OMe)$_2$	2-Me-4-BrPh	oil

	343	C-Me	NHCH(CH_2-iPr)CH_2OMe	2,4-Me_2-Ph	oil
	344	C-Me	NHCH(Pr)CH_2OMe	2,4-Me_2-Ph	94-95
	345	C-Me	NHCH(Et)CH_2OEt	2,4-Me_2-Ph	76-77
	346	C-Me	NHCH(CH_2OMe)CH_2CH_2OMe	2-Me-4-Me_2NPh	oil
5	347	C-Me	NEt_2	2-Me-4-ClPh	oil
	348	C-Me	NH-3-pentyl	2-Me-4-ClPh	122-124
	349	C-Me	N(CH_2CH_2OMe)$_2$	2-Me-4-ClPh	oil
	350	C-Me	NHCH(CH_2OMe)$_2$	2-Me-4-ClPh	122-123
	351	C-Me	NEt_2	2-Me-4-ClPh	oil
10	352	C-Me	NEt_2	2-Cl-4-MePh	oil
	353	C-Me	NH-3-pentyl	2-Cl-4-MePh	120-121
	354	C-Me	NHCH(CH_2OMe)$_2$	2-Cl-4-MeOPh	
	355[bl]	C-Me	N(CH_2CH_2OMe)$_2$	2-Cl-4-MeOPh	oil
	356[bm]	C-Me	NHCH(Et)CH_2OMe	2-Cl-4-MeOPh	108-110
15	357[bn]	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-4-MeOPh	127-129
	358[bo]	C-Me	NEt_2	2-Cl-4-MeOPh	oil
	359[bp]	C-Me	NH-3-pentyl	2-Cl-4-MeOPh	77-79
	360	C-Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4-MeOPh	
	361	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4-MeOPh	
20	362	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4-MeOPh	
	363	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4-MeOPh	
	364	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh	
	365	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh	
	366	C-Me	NHCH(CH_2OMe)$_2$	2-Cl-4,5-$(MeO)_2$Ph	
25	367	C-Me	N(CH_2CH_2OMe)$_2$	2-Cl-4,5-$(MeO)_2$Ph	
	368	C-Me	NHCH(Et)CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph	
	369	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,5-$(MeO)_2$Ph	
	370	C-Me	NEt_2	2-Cl-4,5-$(MeO)_2$Ph	
	371	C-Me	NH-3-pentyl	2-Cl-4,5-$(MeO)_2$Ph	
30	372	C-Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph	
	373	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph	
	374[bq]	C-Me	NHCH(CH_2OMe)$_2$	2-Br-4,5-$(MeO)_2$Ph	137-138
	375	C-Me	N(CH_2CH_2OMe)$_2$	2-Br-4,5-$(MeO)_2$Ph	
	376[br]	C-Me	NHCH(Et)CH_2OMe	2-Br-4,5-$(MeO)_2$Ph	147-148
35	377	C-Me	N(c-Pr)CH_2CH_2CN	2-Br-4,5-$(MeO)_2$Ph	
	378[bs]	C-Me	NEt_2	2-Br-4,5-$(MeO)_2$Ph	52-58

379	C-Me	NH-3-pentyl	2-Br-4,5-$(MeO)_2$Ph
380	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
381	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
382	C-Me	NHCH$(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
383	C-Me	N$(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
384	C-Me	NHCH(Et)CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
385	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,6-$(MeO)_2$Ph
386	C-Me	NEt_2	2-Cl-4,6-$(MeO)_2$Ph
387	C-Me	NH-3-pentyl	2-Cl-4,6-$(MeO)_2$Ph
388	C-Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
389	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
390	C-Me	NHCH$(CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
391	C-Me	N$(CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
392	C-Me	NHCH(Et)CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
393	C-Me	N(c-Pr)CH_2CH_2CN	2-Me-4,6-$(MeO)_2$Ph
395	C-Me	NEt_2	2-Me-4,6-$(MeO)_2$Ph
396	C-Me	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph
397	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
398	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
399	C-Me	N(c-Pr)CH_2CH_2CN	2-Br-4,6-$(MeO)_2$Ph
400	C-Me	NEt_2	2-Br-4,6-$(MeO)_2$Ph
401	C-Me	NH-3-pentyl	2-Br-4,6-$(MeO)_2$Ph
402	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
403	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
404	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
405	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
406	C-Me	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
407	C-Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh
408	C-Me	NHCH(Et)CH_2OMe	2-MeO-4-MePh
409	C-Me	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
410	C-Me	NEt_2	2-MeO-4-MePh
411	C-Me	NH-3-pentyl	2-MeO-4-MePh
412	C-Me	NHCH(Et)CH_2CH_2OMe	2-MeO-4-MePh
413	C-Me	NHCH(Me)CH_2CH_2OMe	2-MeO-4-MePh
414	C-Me	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
415	C-Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh

416	C-Me	NHCH(Et)CH_2OMe	2-Me0-4-MePh	
417	C-Me	N(c-Pr)CH_2CH_2CN	2-Me0-4-MePh	
418	C-Me	NEt_2	2-Me0-4-MePh	
419	C-Me	NH-3-pentyl	2-Me0-4-MePh	
420	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me0-4-MePh	
421	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me0-4-MePh	
423[bt]	C-Me	NHCH($CH_2OMe)_2$	2-Me0-4-ClPh	oil
424	C-Me	N($CH_2CH_2OMe)_2$	2-Me0-4-ClPh	
425	C-Me	NHCH(Et)CH_2OMe	2-Me0-4-ClPh	
426	C-Me	N(c-Pr)CH_2CH_2CN	2-Me0-4-ClPh	
427	C-Me	NEt_2	2-Me0-4-ClPh	
428	C-Me	NH-3-pentyl	2-Me0-4-ClPh	
429	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me0-4-ClPh	
430	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me0-4-ClPh	

NOTES FOR TABLE 1:

a) Analysis Calcd: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.

b) CI-HRMS: Calcd: 406.1565, Found: 405.1573 (M + H); Analysis Calcd: C: 59.11; H: 6.20; N: 17.23; Cl: 17.45; Found: C: 59.93; H: 6.34; N: 16.50; Cl: 16.95;
NMR ($CDCl_3$, 300 MHz): 0.95 (t, J = 8, 4H), 1.30-1.40 (m, 4H), 1.50-1.75 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.30-4.45 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H)

c) CI-HRMS: Calcd: 392.1409, Found: 392.1388 (M + H);
NMR ($CDCl_3$, 300 MHz): 1.00 (t, J =8, 3H), 1.35 (t, J = 8, 3H), 1.41 (q, J = 8, 2H), 1.65-1.85 (m, 2H), 2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.20 (m, 4H), 7.30 (s, 2H), 7.50 (s, 1H).

d) CI-HRMS: Calcd: 404.1409, Found: 404.1408 (M + H);
NMR($CDCl_3$, 300 MHz): 0.35-0.45 (m, 2H), 0.52-0.62 (m, 2H), 0.98 (t, J = 8, 3H), 1.70-1.90 (m, 2H),

2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.02 (m, 2H), 4.02-4.20 (m, 2H), 7.30 (s, 2H), 7.50 (s, 1H).

e) CI-HRMS: Calcd: 424.1307, Found: 424.1307 (M + H): NMR ($CDCl_3$, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.75 (t, J = 8, 4H), 4.20-4.45 (m, 4H), 7.30 (s, 2H), 7.50 (s, 1H).

f) CI-HRMS: Calcd: 406.1565, Found: 406.1578 (M + H); NMR ($CDCl_3$, 300 MHz): 0.90 (t, J = 8, 3H), 1.00 (t, J = 8, 3H), 1.28-1.45 (m, 4H), 1.50-1.80 (m, 4H), 2.35 (s, 3H), 2.50 (s, 3H), 4.20-4.35 (m, 1H), 6.10-6.23 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).

g) CI-HRMS: Calcd: 394.1201, Found: 394.1209 (M + H); NMR ($CDCl_3$, 300 MHz): 1.02 (t, J = 8, 3H), 1.65-1.90 (m, 2H), 2.35 (s, 3H), 2.48 (s, 3H), 3.40 (s, 3H), 3.50-3.60 (m, 2H), 4.35-4.45 (brs, 1H), 6.50-6.60 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).

h) CI-HRMS: Calcd: 364.1096, Found: 364.1093 (M + H); Analysis: Calcd: C: 56.05; H: 5.27; N: 19.23; Cl: 19.46; Found: C: 55.96; H: 5.24; N: 18.93; Cl: 19.25;
NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 8, 6H), 2.30 (3, 3H), 2.40 (s, 3H), 3.95-4.15 (m, 4H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).

i) CI-HRMS: Calcd: 438.1464, Found: 438.1454 (M + H); NMR ($CDCl_3$, 300 MHz): 1.22 (t, J = 8, 6H), 2.35 (s, 3H), 2.47 (s, 3H), 3.39 (q, J = 8, 4H), 3.65 (dd, J = 8, 1, 2H), 3.73 (dd, J = 8, 1, 2H), 4.55-4.65 (m, 1H), 6.75 (d, J = 8, 1H), 7.30 (d, J = 1, 2H), 7.50 (s, 1H).

j) CI-HRMS: Calcd: 378.1252, Found: 378.1249 (M + H); Analysis: Calcd: C: 57.15; H: 5.61; N: 18.51; Cl: 18.74; Found: C: 57.56; H: 5.65; N: 18.35; Cl: 18.45;
NMR ($CDCl_3$, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.35 (s, 3H), 2.50

(s, 3H), 4.15-4.25 (m, 1H), 6.18 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H).

k) CI-HRMS: Calcd: 398.0939, Found: 398.0922 (M + H); Analysis: Calcd: C: 60.31; H: 4.30; N: 17.58; Cl: 17.80; Found: C: 60.29; H: 4.59; N: 17.09; Cl: 17.57;
NMR ($CDCl_3$, 300 MHz): 2.05 (s, 3H), 2.50 (s, 3H), 3.78 (s, 3H), 7.20-7.45 (m, 7H), 7.50 (d, J = 1, 1H).

l) CI-HRMS: Calcd: 392.1409, Found: 392.1391 (M + H); NMR ($CDCl_3$, 300 MHz): 0.98 (t, J = 8, 6H), 1.70-1.85 (m, 4H), 2.30 (s, 3H), 2.40 (s, 3H), 3.80-4.10 (m, 4H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).

m) CI-HRMS: Calcd: 392.1409, Found: 392.1415 (M + H); Analysis: Calcd: C: 58.17; H: 5.92; N: 17.85; Cl: 18.07; Found: C: 58.41; H: 5.85: N: 18.10; Cl: 17.75;
NMR ($CDCl_3$, 300 MHz): 0.90-1.05 (m, 6H), 1.35-1.55 (m, 2H), 1.55-1.85 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.20-4.35 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).

n) CI-HRMS: Calcd: 337.0623, Found: 337.0689 (M + H); Analysis: Calcd: C: 53.43; H: 4.18; N: 16.62; Cl: 21.03, Found: C: 53.56; H: 4.33; N: 16.56; Cl: 20.75;
NMR ($CDCl_3$, 300 MHz): 1.60 (t, J = 8, 3H), 2.40 (s, 3H), 2.55 (s, 3H), 4.80 (q, J = 8, 2H), 7.30 (d, J = 8, 1H), 7.35 (dd, J = 8, 1, 1H), 7.55 (d, J = 1, 1H).

o) CI-HRMS: Calcd: 383.2321, Found: 383.2309 (M + H); NMR ($CDCl_3$, 300 MHz): 2.00 (s, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.45 (s, 3H), 3.45 (s, 6H), 3.61 (dd, J = 8, 8, 2H), 3.70 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 6.94 (s, 2H).

p) CI-HRMS: Calcd: 370.2243, Found: 370.2246 (M + H);

Analysis: Calcd: C: 65.02; H: 7.38; N: 18.96;
Found: C: 65.22; H: 7.39; N: 18.71;
NMR ($CDCl_3$, 300 MHz): 2.18 (s, 3H), 2.30 (s, 3H), 2.45 (s, 3H), 3.45 (s, 6H), 3.60 (dd, J = 8, 8, 2H), 3.69 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 7.05 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.10 (s, 1H).

q) CI-HRMS: Calcd: 384.2400, Found: 384.2393 (M + H);
NMR ($CDCl_3$, 300 MHz): 2.16 (s, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 3.40 (s, 6H), 3.77 (t, J = 8, 4H), 4.20-4.45 (m, 4H), 7.02 (d, J = 8, 1H) 7.05 (s, 1H), 7.10 (d, J = 7, 1H).

r) CI-HRMS: Calcd: 354.2294, Found: 354.2271 (M + H);
Analysis: Calcd: C: 67.96; H: 7.71; N: 19.81;
Found: C: 67.56; H: 7.37; N: 19.60;
NMR ($CDCl_3$, 300 MHz): 1.03 (t, J = 8, 3H), 1.65-1.88 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 3.40 (s, 3H), 3.50-3.62 (m, 2H), 4.30-4.45 (m, 1H), 6.51 (d, J = 8, 1H), 7.04 (d, J = 8, 1H), 7.10 (d, J =8, 1H), 7.12 (s, 1H).

s) CI-HRMS: Calcd: 338.2345, Found: 338.2332 (M + H);
Analysis: Calcd: C: 71.18; H: 8.06; N: 20.75;
Found: C: 71.43; H: 7.80; N: 20.70;
NMR ($CDCl_3$, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.19 (s, 3H), 2.30 (s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 4.15-4.26 (m, 1H), 6.17 (d, J = 8, 1H), 7.06 (d, J = 8, 1H), 7.10 (d, J = 1, 1H), 7.13 (s, 1H).

t) CI-HRMS: Calcd: 324.2188, Found: 324.2188 (M + H);
NMR ($CDCl_3$, 300 MHz): 1.25 (t, J = 8, 6H), 2.16 (s, 3H), 2.28 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 3.95-4.20 (m, 4H), 7.05 (dd, J = 8, 1, 1H), 7.07 (s, 1H), 7.10 (d, J = 1, 1H)

u) CI-HRMS: Calcd: 346.1780, Found: 346.1785 (M + H);
Analysis: Calcd: C: 66.07; H: 5.54; N: 28.39;
Found: C: 66.07; H: 5.60; N: 27.81;

NMR ($CDCl_3$, 300 MHz): 2.15 (s, 3H), 2.32 (s, 3H) 2.17 (s, 3H), 2.52 (s, 3H), 5.25-5.35 (m, 4H), 7.08 (s, 2H), 7.15 (s, 1H).

v) CI-HRMS: Calcd: 340.2137, Found: 340.2137 (M + H); Analysis: Calcd: C: 67.23; H: 7.42; N: 20.63; Found:C: 67.11; H: 7.39; N: 20.26; NMR ($CDCl_3$, 300 MHz): 1.40 (d, J = 8, 3H), 2.16 (s, 3H), 2.32 (s, 3H), 2.35 (s, 3H), 2.47 (s, 3H), 3.42 (s, 3H), 3.50-3.60 (m, 2H), 4.50-4.15 (m, 1H), 6.56 (d, J = 8, 1H), 7.00-7.15 (m, 3H).

w) CI-HRMS: Calcd: 355.2134, Found: 355.2134 (M + H); NMR ($CDCl_3$, 300 MHz): 1.05 (t, J = 8, 3H), 1.85-2.00 (m, 2H), 2.17 (s, 3H), 2.36 (s, 6H), 2.50 (s, 3H), 3.41 (s, 3H), 3.45 (dd, J = 8, 3, 1H), 3.82 (dd, J = 8, 1, 1H), 5.70-5.80 (m, 1H), 7.00-7.20 (m, 3H).

x) CI-HRMS: Calcd: 364.2501, Found: 364.2501 (M + H); NMR ($CDCl_3$, 300 MHz): 0.35-0.43 (m, 2H), 0.50-0.60 (m, 2H), 0.98 (t, J = 8, 3H), 1.20-1.30 (m, 1H), 1.72-1.90 (m, 2H), 2.18 (s, 3H) 2.28 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 3.88-4.03 (m, 2H), 4.03-4.20 (m, 2H), 7.00-7.15 (m, 3H).

y) CI-HRMS: Calcd: 353.2454, Found: 353.2454 (M + H); Analysis: Calcd: C: 68.15; H: 8.02; N: 23.84; Found: C: 67.43; H: 7.81; N: 23.45; NMR ($CDCl_3$, 300 MHz): 1.38 (d, J = 8, 3H), 2.18 (s, 3H), 2.30-2.40 (m, 12H), 2.47 93, 3H), 2.60-2.75 (m, 2H), 4.30-4.50 (m, 1H), 6.60-6.70 (m, 1H), 7.00-7.15 (m, 3H).

z) CI-HRMS: Calcd: 361.2140, Found: 361.2128 (M + H); NMR ($CDCl_3$, 300 MHz): 0.75-0.83 (m, 2H), 1.00-1.10 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 2.85 (t, J = 8, 2H), 3.30-3.40 (m, 1H), 4.40-4.55 (m, 2H), 7.00-7.18 (m, 3H).

aa) CI-HRMS: Calcd: 363.2297, Found: 363.2311 (M + H);

NMR ($CDCl_3$, 300 MHz): 1.01 (t, 3H, J=8), 1.75-1.90 (m,2H), 2.15 (s,3H), 2.19 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 2.98 (t, 2H, J = 8), 3.97-4.15 (m, 2H), 4.15-4.30 (m, 2H), 7.03(d, 1H, 1H), 7.08 (d, 1H, J = 8), 7.10 (s, 1H).

ab) CI-HRMS: Calcd: 363.2297, Found: 363.2295 (M + H); NMR ($CDCl_3$, 300 MHz): 1.01 (t, 3H, J = 8), 1.35-1.55 (m, 2H), 1.75-1.90 (m, 2H), 2.15 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 2.46 (s, 3H), 4.10-4.30 (m, 2H), 4.95-5.10 (br s, 2H), 7.05 (d, 1H, J = 8), 7.10 (d, 1H, J = 8), 7.15 (s, 1H).

ac) CI-HRMS: Calcd: 368.2450, Found: 368.2436; Analysis: Calcd: C, 68.62, H, 7.95, N, 19.06; Found: C, 68.73, H, 7.97, N, 19.09; NMR ($CDCl_3$, 300 MHz): 1.05 (t, J = 8, 3H), 1.70-1.90 (m, 2H), 2.01 (d, J = 3, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46, 2.465 (s, s, 3H), 3.42, 3.48 (s, s, 3H), 3.53-3.63 (m, 2H), 4.35-4.45 (m, 1H), 6.73 (d, J = 8, 1H), 6.97 (s, 2H).

(ad) CI- HRMS: Calcd: 352.2501, Found: 352.2500 (M + H): Analysis: Calcd: C: 71.76; H: 8.33; N: 19.92, Found: C: 71.55; H: 8.15; N: 19.28; NMR ($CDCl_3$, 300 MHz): 1.01(t, J = 8, 6H), 1.58 -1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.02 (s, 6H), 2.19 (s, 3H), 2.45 (s, 3H), 4.12-4.28 (m, 1H), 6.18 (d, J = 8, 1H), 6.95 (s, 2H).

(ae) CI- HRMS: Calcd: 398.2556, Found: 398.2551 (M + H); Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62, Found: C: 66.74; H: 7.79; N: 17.70; NMR ($CDCl_3$, 300 MHz): 2.00 (s, 6H), 2.12 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.40 (s, 6H), 3.78 (t, J = 8, 4H), 4.25-4.40 (m, 4H), 6.93 (s, 2H).

(af) CI-HRMS: Calcd: 450.1141, Found: 450.1133 (M + H); Analysis: Calcd: C: 50.67; H: 5.37; N: 15.55; Br: 17.74; Found: C: 52.36; H: 5.84; N: 14.90; Br: 17.44;

NMR ($CDCl_3$, 300 MHz): 2.32 (s, 3H), 2.57 (s, 3H), 3.42 (s, 6H), 3.60 (q, J = 8, 2H), 3.69 (q, J = 8, 2H), 3.82 (s, 3H), 4.60-4.70 (m, 1H), 6.73 (d, J = 8, 1H), 6.93 (dd, J = 8, 1, 1H), 7.22 (d, J = 8, 1H).

ag) CI-HRMS: Calcd: 434.1192, Found: 434.1169 (M + H); Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br: 18.40; Found: C: 52.57; H: 5.60; N: 15.98; Br: 18.22;
NMR ($CDCl_3$, 300 MHz): 1.00-1.07 (m, 3H), 1.65-1.85 (m, 2H), 2.35 (s, 3H), 2.46, 2.47 (s, s, 3H), 3.40, 3.45 (s, s, 3H), 3.83 (s, 3H), 4.35-4.45 (m, 1H), 6.55 (d, J = 8, 1H), 6.92 (dd, J = 8, 1, 1H), 7.20-7.30 (m, 2H).

ah) CI-HRMS: Calcd: 337.2266, Found: 337.2251 (M + H); Analysis: Calcd: C: 70.18; H: 8.06; N: 20.75; Found: C: 70.69; H: 7.66; N: 20.34;
NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 8, 6H), 2.01 (s, 6H), 2.15 (s, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 4.07 (q, J = 8, 4H), 6.93 (s, 2H).

ai) CI-HRMS: Calcd: 412.2713, Found: 412.2687 (M + H); Analysis: Calcd: C: 67.13; H: 8.08; N: 17.02; Found : C: 67.22; H: 7.85; N: 17.13;
NMR ($CDCl_3$, 300 MHz):1.24 (t, J = 8, 6H), 2.00 (s, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.43 (s, 3H), 3.60 (q, J = 8, 4H), 3.66 (dd, J = 8, 3, 2H), 3.75 (dd, J = 8, 3, 2H), 4.55-4.65 (m, 1H), 6.75 (d, J = 8, 1H), 6.95 (s, 2H).

aj) CI-HRMS: Calcd: 398.2556, Found: 398.2545 (M + H); Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62; Found: C: 66.87; H: 7.62; N: 17.75;
NMR ($CDCl_3$, 300 MHz): 1.95-2.10 (m, 8H), 2.20 (s, 3H), 2.32 (s, 3H), 2.44 (s, 3H), 3.38 (s, 3H), 3.42 (s, 3H), 3.50-3.70 (m, 4H), 4.58-4.70 (m, 1H), 6.87 (d, J = 8, 1H), 6.95 (s, 2H).

ak) CI-HRMS: Calcd: 338.1981, Found: 338.1971 (M + H);

Analysis: Calcd: C: 67.63; H: 6.87; N: 20.06;
Found: C: 67.67; H: 6.82; N: 20.31;
NMR ($CDCl_3$, 300 MHz): 2.15 (s, 3H), 2.29 (s, 3H), 2.35 (s, 3H), 2.43 (s, 3H), 3.90 (t, J = 8, 4H), 4.35-4.45 (m, 4H), 7.00-7.15 (m, 3H).

al) CI-HRMS: Calcd: 464.1297, Found: 464.1297 (M + H);
NMR ($CDCl_3$, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.75 (t, J = 8, 4H), 3.83 (s, 3H), 4.20-4.50 (m, 4H), 6.93 (dd, J = 8, 1, 1H), 7.20 (s, 1H), 7.24 (d, J = 1, 1H).

am) CI-HRMS: Calcd: 418.1242, Found: 418.1223 (M + H);
NMR ($CDCl_3$, 300 MHz): 1.00 (t, d, J = 8, 1, 6H), 1.55-1.75 (m, 4H), 2.34 (s, 3H), 2.49 (s, 3H), 2.84 (s, 3H), 4.15-4.27 (m, 1H), 6.19 (d, J = 8, 1H), 6.93 (dd, J = 8, 1, 1H), 7.21-7.30 (m, 2H).

an) CI-HRMS: Calcd: 404.1086, Found: 404.1079(M + H);
NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 8, 6H), 2.28 (s, 3H), 2.40 (s, 3H), 3.83 (s, 3H), 3.90-4.08 (m, 2H), 4.08-4.20 (m, 2H), 6.92 (dd, J = 8, 1, 1H), 7.20-7.25 (m, 2H).

ao) CI-HRMS: Calcd: 308.1875, Found: 308.1872 (M + H);
NMR ($CDCl_3$, 300 MHz): 0.75-0.80 (m, 2H), 0.93-1.00 (m, 2H), 2.16 (s, 3H), 2.28 (s, 3H), 2.35 (s, 3H), 2.53 (s, 3H), 3.00-3.10 (m, 1H), 6.50-6.55 (m, 1H), 7.00-7.15 (m, 3H).

ap) CI-HRMS: Calcd: 397.1988, Found: 397.1984 (M + H);
NMR ($CDCl_3$, 300 MHz): 2.43 (s, 3H), 2.50 (s, 3H), 3.43 (s, 3H), 3.61 (dd, J = 8, 8, 2H), 3.69 (dd,J = 8, 8, 2H), 3.88 (s, 3H), 4.58-4.70 (m, 1H), 6.75 (d, J = 8, 1H), 7.20 (dd, J = 8, 1, 1H), 7.25 (d, J = 1, 1H), 7.40 (s, 1H).

aq) CI-HRMS: Calcd: 375.2297, Found: 375.2286 (M + H);
Analysis: Calcd: C: 70.56; H: 7.01; N: 22.44;
Found: C: 70.49; H: 6.99; N: 22.45;
NMR ($CDCl_3$, 300 MHz): 0.79-0.85 (m, 2H), 1.00-1.05 (m, 1H), 2.00 (s, 6H), 2.19 (s, 3H), 2.32 (s, 3H),

2.44 (s, 3H), 2.84 (t, J = 8, 2H), 3.30-3.40 (m, 1H), 4.50 (t, J = 8, 2H), 6.95 (s, 2H).

ar) CI-HRMS: Calcd: 434.1192, Found: 434.1189 (M + H); Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br: 18.40; Found: C: 52.75; H: 5.59; N: 16.09; Br: 18.67;
NMR ($CDCl_3$, 300 MHz): 2.19 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.43 (s, 6H), 3.60 (dd, J = 8, 8, 2H), 3.70 (dd, J = 8,8, 2H), 4.58-4.70 (m, 1H), 6.71 (d, J = 8, 1H), 7.08 (d, J = 8, 1H), 7.37 (dd, J = 8, 1, 1H), 7.45 (d, J = 1, 1H).

as) CI-HRMS: Calcd: 448.1348, Found: 448.1332 (M + H); Analysis: Calcd: C: 53.58; H: 5.85; N: 16.62; Br: 17.82; Found: C: 53.68; H: 5.74; N: 15.52; Br: 13.03;
NMR ($CDCl_3$, 300 MHz): 1.95-2.10 (m, 2H), 2.20 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.67 (m, 4H), 4.55-4.70 (m, 1H), 6.89 (d, J = 8, 1H), 7.05 (d, J = 8, 1H), 7.35 (dd, J = 8, 1, 1H), 7.47 (d, J = 1, 1H).

at) CI-HRMS: Calcd: 400.2349, Found: 400.2348 (M + H); Analysis: Calcd: C: C: 63.14; H: 7.32; N: 17.53; Found: C:63.40; H: 7.08; N: 17.14;
NMR ($CDCl_3$, 300 MHz): 2.16 (s, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46 (s, 3H), 3.42 (s, 6H), 3.60 (q, J = 8, 2H), 3.70 (q, J = 8, 2H), 3.85 (s, 3H), 4.59-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 6.76 (s, 1H), 6.96 (s, 1H).

au) CI-HRMS: Calcd: 414.2505, Found: 414.2493 (M + H); NMR ($CDCl_3$, 300 MHz): 2.15 (s, 3H), 2.19 (s, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, J = 8, 4H), 3.84 (s, 3H), 4.20-4.45 (m, 4H), 6.77 (s, 1H), 6.93 (s, 1H).

av) CI-HRMS: Calcd: 368.2450, Found: 368.2447 (M + H); NMR ($CDCl_3$, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-1.85 (m, 4H), 2.19 (s, 3H), 2.20 (s, 3H), 2.30 (s,

3H), 2.47 (s, 3H), 3.88 (s, 3H), 4.10-4.30 (m, 1H), 6.15 (d, J = 8, 1H), 6.78 (s, 1H), 6.98 (s, 1H).

aw) CI-HRMS: Calcd: 353.2216, Found: 353.2197 (M + H); NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 8, 6H), 2.17 (s, 3H), 2.19 (s, 3H), 2.28 (s, 3H), 2.40 (s, 3H), 3.85 (s, 3H), 3.90-4.20 (m, 4H), 6.78 (s, 1H), 6.95 (s, 1H).

ax) CI-HRMS: Calcd: 390.1697, Found: 390.1688 (M + H); Analysis: Calcd: C: 58.53; H: 6.20; N: 17.96; Cl: 9.09; Found: C: 58.95; H: 6.28; N: 17.73; Cl: 9.15; NMR ($CDCl_3$, 300 MHz): 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (s, 3H), 3.42 (s, 6H), 3.60 (dd, J = 8, 8, 2H) 3.68 (dd, J = 8, 8, 2H), 4.59-4.72 (m, 1H), 6.72 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.23 (d, J = 8, 1H), 7.32 (s, 1H).

ay) CI-HRMS: Calcd: 374.1748, Found: 374.1735 (M + H); Analysis: Calcd: C: 61.04; H: 6.47; N: 18.73; Cl: 9.48; Found: C: 61.47; H: 6.54; N: 18.23; Cl: 9.61; NMR ($CDCl_3$,300 MHz): 1.01 (t, J = 8, 3H), 1.62-1.88 (m, 4H), 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (d, J = 1, 3H), 3.40, 3.45 (s, s, 3H), 3.50-3.64 (m, 2H), 4.38-4.47 (m, 1H), 6.53 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.12 (s, 1H).

az) CI-HRMS: Calcd: 404.1853, Found: 404.1839 (M + H); NMR ($CDCl_3$, 300 MHz): 2.29 (s, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, J = 8, 4H), 4.20-4.45 (m, 4H), 7.11 (d, J = 8, 1H), 7.22 (d, J = 8, 1H), 7.31 (s, 1H).

ba) CI-HRMS: Calcd: 404.1853, Found: 404.1859 (M + H); Analysis: C: 59.47; H: 6.50; N: 17.34; Cl: 8.79; Found: C: 59.73; H: 6.46; N: 17.10; Cl: 8.73; NMR ($CDCl_3$, 300 MHz): 1.95-2.08 (m, 2H), 2.35 (s, 3H), 2.38 (s, 3H), 2.46 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.65 (m, 4H), 4.56-4.70 (m, 1H), 6.85 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.45 (d, J = 8, 1H), 7.32 (s, 1H).

bb) CI-HRMS: Calcd: 391.2246, Found: 391.2258 (M + H); Analysis: C: 67.67; H: 6.71; N: 21.52; Found: C: 67.93; H: 6.70; N: 21.48;
NMR ($CDCl_3$, 300 MHz): 0.76-0.84 (m, 2H), 0.84-0.91 (m, 2H), 1.00-1.08 (m, 2H), 2.15 (s, 3H), 2.20 (s, 3H), 2.29 (s, 3H), 2.45 (s, 3H), 2.85 (t, J = 8, 2H), 3.28-3.30 (m, 1H), 3.85 (s, 3H), 6.78 (s, 1H), 6.95 (s, 1H).

bc) CI-HRMS: Calcd: 386.2192, Found: 386.2181 (M + H); Analysis: C: 62.32; H: 7.06; N: 18.17; Found: C: 62.48; H: 6.83; N: 18.15;
NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.7 (br.d, 1H, J = 8), 4.7-4.6 (m, 1H), 3.85 (s, 3H), 3.70-3.55 (m, 4H), 3.45 (s, 6H), 2.5 (s, 3H), 2.3 (s, 3H), 2.15 (s, 3H).

bd) CI-HRMS: Calcd: 400.2349, Found: 400.2336 (M + H);
NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 7), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 7,1), 4.45-4.25 (br.s, 4H), 3.75 (t, 4H, J = 7), 3.4 (s, 6H), 2.4 (s, 3H), 2.25 (s, 3H), 2.15 (s, 3H).

be) CI-HRMS: Calcd: 370.2243, Found: 370.2247 (M + H); Analysis: C: 65.02; H: 7.38; N: 18.96; Found: C: 65.28; H: 7.27; N: 18.71;
NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.5 (br. d, 1H, J = 1), 4.5-4.3 (m, 1H), 3.85 (s, 3H), 3.65-3.5 (m, 2H), 3.4 (s, 2H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.9-1.7 (m, 2H), 1.05 (t, 3H, J = 7).

bf) CI-HRMS: Calcd: 379.2246, Found: 379.2248 (M + H);
NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8,1), 4.3-4.0 (m, 4H), 3.85 (s, 3H), 3.0 (t, 2H, J = 7), 2.45 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.9-1.8 (m, 2H), 1.0 (t, 3H, J = 7).

bg) CI-HRMS: Calcd: 340.2137, Found: 340.2122 (M + H);

NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8,1), 4.2-4.0 (br.m, 4H), 3.85 (s, 3H, 2.4 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.35 (t, 6H, J = 7).

bh) CI-HRMS: Calcd: 313.1665, Found: 313.6664 (M + H).

bi) CI-HRMS: Calcd: 400.2349, Found: 400.2346 (M + H); NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 7), 6.9-6.75 (m, 3H), 4.7-4.55 (m, 1H), 3.8 (s, 3H), 3,7-3.5 (m, 4H), 3.45 (s, 3H), 3.35 (s, 3H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 2.1-1.95 (m, 2H).

bj) CI-HRMS: Calcd: 377.2090, Found: 377.2092 (M + H); Analysis: C: 67.00; H: 6.44; N: 22.32; Found: C: 67.35; H: 6.44; N: 22.23; NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8,1), 4.55-4.4 (m, 2H), 3.85 (s, 3H), 3.4-3.3 (m, 1H), 2.85 (t, 2H, J = 7), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.1-1.0 (m, 2H), 0.85-0.75 (m, 2H).

bk) CI-HRMS: Calcd: 413.2427, Found: 413.2416 (M + H); NMR ($CDCl_3$, 300Hz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8,1), 4.6 (m, 1H), 3.85 (s, 3H), 3.75-3.6(m, 4H), 3.6 (q, 4H, J = 7), 2.5 (s, 3H), 2.3 s, 3H), 2.2 (s, 3H), 1.25 (t, 6H, J = 7).

bl) CI-HRMS: Calcd: 420.1802, Found: 420.1825(M + H);

bm) CI-HRMS: Calcd: 390.1697, Found: 390.1707(M + H);

bn) CI-HRMS: Calcd: 397.1465, Found: 397.1462(M + H);

bo) CI-HRMS: Calcd: 360.1513, Found: 360.1514(M + H);

bp) CI-HRMS: Calcd: 374.1748, Found: 374.1737(M + H);

bq) CI-HRMS: Calcd: 479.1155, Found: 479.1154(M + H);

br) CI-HRMS: Calcd: 463.1219, Found: 463.1211(M + H); Analysis Calcd: C: 51.96, H: 5.23, N, 15.15, Br: 17.28; Found: C: 52.29, H: 5.62, N: 14.79, Br: 17.47

bs) CI-HRMS: Calcd: 433.1113, Found: 433.1114(M, ^{79}Br);

bt) NH_3-CI MS: Calcd: 406, Found: 406 (M + H)+;

NMR ($CDCl_3$, 300 MHz) : δ 7.28 (d, J=10Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.7 (d, J=9, 1H), 4.63 (m, 1H), 3.79 (s, 3H), 3.6 (m, 4H), 3.42 (s, 6H), 2.47 (s, 3H), 2.32 (s, 3H).

EXAMPLE 431

Preparation of 2,4,7-dimethyl-8-(4-methoxy-2-methylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Formula 1, where R^3 is CH_3, R_1 is CH_3, Z is C-CH_3, Ar is 2,4-dimethylphenyl)

5-Acetamidino-4-(4-methoxy-2-methylphenyl)-3-methylpyrazole, acetic acid salt (602 mg, 2 mmol) was mixed with a saturated $NaHCO_3$ solution (10 mL). The aqueous mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was taken up in toluene (10 mL) and trimethyl orthoacetate (0.36 g, 3 mmol) was added to the suspension. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere and stirred for 16 hours. After being cooled to ambient temperature, the reaction mixture was concentrated in vacuo to give an oily solid. Column chromatography ($CHCl_3$:MeOH::9:1) afforded, after removal of solvent in vacuo, a yellow viscous oil (Rf = 0.6, 210 mg, 37% yield): NMR ($CDCl_3$, 300 MHz): 7.15 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.85 (dd, 1H, J = 8,1), 3.85 (s, 3H), 2.95 (s, 3H), 2.65 (s, 3H), 2.4 (s, 3H), 2.15 (s, 3H); CI-HRMS: Calcd: 283.1559, Found: 283.1554 (M + H).

EXAMPLE 432

7-hydroxy-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (Formula 1 where A is CH, R1 is Me, R3 is OH, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

5-Amino-4-(2-chloro-4-methylphenyl)-3-methylpyrazole (1.86 g, 8.4 mmol) was dissolved in glacial acetic acid (30 mL) with stirring. Ethyl acetoacetate (1.18 mL, 9.2 mmol) was then added dropwise to the resulting solution. The reaction mixture was then heated to reflux temperature and stirred for 16 hours, then cooled to room temperature. Ether (100 mL) was added and the resulting precipitate was collected by filtration. Drying in vacuo afforded a white solid (1.0 g, 42% yield): NMR ($CDCl_3$, 300Hz): 8.70 (br.s 1H), 7.29 (s, 1H), 7.21-7.09 (m, 2H), 5.62 (s, 1H), 2.35 (s, 6H), 2.29 (s, 3H); CI-MS: 288 (M+H).

EXAMPLE 433

7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (Formula 1 where A is CH, R1 is Me, R3 is Cl, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

A mixture of 7-hydroxy-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (1.0 g, 3.5 mmol), phosphorus oxychloride (2.7 g, 1.64 mL, 17.4 mmol), N,N-diethylaniline (0.63 g, 0.7 mL, 4.2 mmol) and toluene (20 mL) was stirred at reflux temperature for 3 hours, then it was cooled to ambient temperature. The volatiles were removed in vacuo. Flash chromatography (EtOAc:hexane::1:2) on the residue gave 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (900 mg, 84% yield) as a yellow oil: NMR

($CDCl_3$, 300Hz): 7.35 (s, 1H), 7.28-7.26 (m, 1H), 71.6 (d, 1H, J = 7), 6.80 (s, 1H), 2.55 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H); CI- MS: 306 (M+H).

EXAMPLE 434

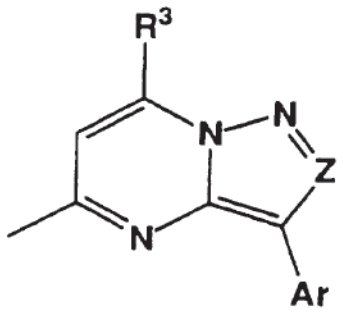
7-(pentyl-3-amino)-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine

(Formula 1 where A is CH, R1 is Me, R3 is pentyl-3-amino, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

A solution of 3-pentylamine (394mg, 6.5 mmol) and 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (200 mg, 0.65 mmol) in dimethylsulfoxide (DMSO, 10 mL) was stirred at 150°C for 2 hours; then it was cooled to ambient temperature. The reaction mixture was then poured onto water (100 mL) and mixed. Three extractions with dichloromethane, washing the combined organic layers with brine, drying over $MgSO_4$, filtration and removal of solvent in vacuo produced a yellow solid. Flash chromatography (EtOAc:hexanes::1:4) afforded a white solid (140 mg, 60% yield): mp 139-141°C; NMR ($CDCl_3$, 300Hz):7.32 (s, 1H), 7.27 (d, 1H, J = 8), 7.12 (d, 1H, J = 7), 6.02 (d, 1H, J = 9), 5.78 (s, 1H), 3.50-3.39 (m, 1H), 2.45 (s, 3H), 2.36 (s, 6H), 1.82-1.60 (m, 4H), 1.01 (t, 6H, J = 8); Analysis Calcd for $C_{20}H_{25}ClN_4$: C, 67.31, H, 7.06, N, 15.70, Cl: 9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.

The examples delineated in TABLE 2 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, EtOAc is ethyl acetate.

TABLE 2



Ex.	Z	R_3	Ar	mp(°C)
435[b]	C-Me	$N(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph	71-73
436[c]	C-Me	N(Bu)Et	2,4-Cl_2-Ph	86-87
437[d]	C-Me	$NHCH(Et)CH_2OMe$	2,4-Cl_2-Ph	110-111
438[e]	C-Me	$N(Pr)CH_2CH_2CN$	2,4-Cl_2-Ph	83-85
439[f]	C-Me	NH-3-pentyl	2,4-Cl_2-Ph	175-176
440[g]	C-Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph	107
441[h]	C-Me	$NHCH(Et)_2$	2,4-Me_2-Ph	oil
442[i]	C-Me	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph	103-105
443[j]	C-Me	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph	87-89
444[k]	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2,4-Me_2-Ph	133(dec)
445[l]	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl,4-MePh	77-78
446[m]	C-Me	$NHCH(CH_2OMe)_2$	2-Cl,4-MePh	131-133
447[n]	C-Me	$NHCH(Et)_2$	2-Cl,4-MePh	139-141
448[o]	C-Me	NEt_2	2,4-Me_2-Ph	92-94
449[p]	C-Me	$N(Pr)CH_2CH_2CN$	2,4-Me_2-Ph	143-144
450[q]	C-Me	$N(Bu)CH_2CH_2CN$	2,4-Me_2-Ph	115-117
451[r]	C-Me	$NHCH(Et)CH_2OMe$	2,4-Me_2-Ph	oil
452[s]	C-Me	$NHCH(Et)_2$	2-Me,4-MeOPh	104-106
453[t]	C-Me	$NHCH(CH_2OMe)_2$	2-Me,4-MeOPh	115-116
454[u]	C-Me	$N(CH_2CH_2OMe)_2$	2-Me,4-MeOPh	oil
455[v]	C-Me	(S)-$NHCH(CH_2CH_2OMe)$-(CH_2OMe)	2-Me,4-MeOPh	oil
456[w]	C-Me	(S)-$NHCH(CH_2CH_2OMe)$-(CH_2OMe)	2,4-Me_2-Ph	oil

	457[x]	C-Me	$N(CH_2CH_2OMe)_2$	2-Me,4-ClPh	oil
	458[y]	C-Me	NHEt	$2,4-Me_2$-Ph	oil
	459[z]	C-Me	$NHCH(Et)_2$	2-Me,4-ClPh	94-96
	460[aa]	C-Me	$NHCH(CH_2OMe)_2$	2-Me,4-ClPh	113-114
	461[ab]	C-Me	N(Ac)Et	$2,4-Me_2$-Ph	oil
	462[ac]	C-Me	(S)-$NHCH(CH_2CH_2OMe)$-(CH_2OMe)	2-Me,4-ClPh	oil
	463[ad]	C-Me	$N(Pr)CH_2CH_2CN$	2-Me,4-MeOPh	118-119
	464[ae]	C-Me	NEt_2	2-Me,4-MeOPh	97-99
	465[af]	C-Me	(S)-$NHCH(CH_2CH_2OMe)$-(CH_2OMe)	2-Cl,4-MePh	101-103
	466[ag]	C-Me	NEt_2	2-Cl,4-MePh	129-130
	467[ah]	C-Me	$N(c-Pr)CH_2CH_2CN$	2-Me,4-MeOPh	177-178
	468[ai]	C-Me	$N(c-Pr)CH_2CH_2CN$	2-Cl,4-MePh	162-163
	469[aj]	C-Me	$NHCH(Et)CH_2OMe$	2-Me,4-MeOPh	oil
	470[ak]	C-Me	$NHCH(Et)CH_2OMe$	2-Cl,4-MePh	111-113
	471	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MeOPh	
	472	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MeOPh	
	473	C-Me	$NHCH(Et)CH_2OMe$	2-Cl-4-MeOPh	
	474	C-Me	$N(c-Pr)CH_2CH_2CN$	2-Cl-4-MeOPh	
	475	C-Me	NEt_2	2-Cl-4-MeOPh	
	476	C-Me	NH-3-pentyl	2-Cl-4-MeOPh	
	477	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4-MeOPh	
	478	C-Me	$NHCH(Me)CH_2CH_2OMe$	2-Cl-4-MeOPh	
	479	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-Br-4-MeOPh	
	480	C-Me	$NHCH(Me)CH_2CH_2OMe$	2-Br-4-MeOPh	
	481	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-Me-4-MeOPh	
	482	C-Me	$NHCH(Me)CH_2CH_2OMe$	2-Me-4-MeOPh	
	483	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph	
	484	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph	
	485	C-Me	$NHCH(Et)CH_2OMe$	2-Cl-4,5-$(MeO)_2$Ph	
	486	C-Me	$N(c-Pr)CH_2CH_2CN$	2-Cl-4,5-$(MeO)_2$Ph	
	487	C-Me	NEt_2	2-Cl-4,5-$(MeO)_2$Ph	99-101
	488	C-Me	NH-3-pentyl	2-Cl-4,5-$(MeO)_2$Ph	169-170
	489	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4,5-$(MeO)_2$Ph	

490	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph	
491	C-Me	NHCH$(CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph	90-93
492	C-Me	N$(CH_2CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph	110
493	C-Me	NHCH(Et)CH_2OMe	2-Br-4,5-$(MeO)_2$Ph	
494	C-Me	N(c-Pr)CH_2CH_2CN	2-Br-4,5-$(MeO)_2$Ph	
495	C-Me	NEt_2	2-Br-4,5-$(MeO)_2$Ph	
496	C-Me	NH-3-pentyl	2-Br-4,5-$(MeO)_2$Ph	
497	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph	
498	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph	
499	C-Me	NHCH$(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph	
500	C-Me	N$(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph	
501	C-Me	NHCH(Et)CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph	
502	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,6-$(MeO)_2$Ph	
503	C-Me	NEt_2	2-Cl-4,6-$(MeO)_2$Ph	
504	C-Me	NH-3-pentyl	2-Cl-4,6-$(MeO)_2$Ph	
505	C-Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph	
506	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph	
507	C-Me	NHCH$(CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph	
508	C-Me	N$(CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph	
509	C-Me	NHCH(Et)CH_2OMe	2-Me-4,6-$(MeO)_2$Ph	
510	C-Me	N(c-Pr)CH_2CH_2CN	2-Me-4,6-$(MeO)_2$Ph	
511	C-Me	NEt_2	2-Me-4,6-$(MeO)_2$Ph	
512	C-Me	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph	
513	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph	
514	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph	
515	C-Me	N(c-Pr)CH_2CH_2CN	2-Br-4,6-$(MeO)_2$Ph	
516	C-Me	NEt_2	2-Br-4,6-$(MeO)_2$Ph	
517	C-Me	NH-3-pentyl	2-Br-4,6-$(MeO)_2$Ph	
518	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph	
519	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph	
520	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh	
521	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh	
522	C-Me	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh	
523	C-Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh	
524	C-Me	NHCH(Et)CH_2OMe	2-MeO-4-MePh	
525	C-Me	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh	

526	C-Me	NEt_2	2-MeO-4-MePh
527	C-Me	NH-3-pentyl	2-MeO-4-MePh
528	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-MeO-4-MePh
529	C-Me	$NHCH(Me)CH_2CH_2OMe$	2-MeO-4-MePh
530	C-Me	$NHCH(CH_2OMe)_2$	2-MeO-4-MePh
531	C-Me	$N(CH_2CH_2OMe)_2$	2-MeO-4-MePh
532	C-Me	$NHCH(Et)CH_2OMe$	2-MeO-4-MePh
533	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-MeO-4-MePh
534	C-Me	NEt_2	2-MeO-4-MePh
535	C-Me	NH-3-pentyl	2-MeO-4-MePh
536	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-MeO-4-MePh
537	C-Me	$NHCH(Me)CH_2CH_2OMe$	2-MeO-4-MePh
538	C-Me	$NHCH(CH_2OMe)_2$	2-MeO-4-ClPh
539	C-Me	$N(CH_2CH_2OMe)_2$	2-MeO-4-ClPh
540	C-Me	$NHCH(Et)CH_2OMe$	2-MeO-4-ClPh
541	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-MeO-4-ClPh
542	C-Me	NEt_2	2-MeO-4-ClPh
543	C-Me	NH-3-pentyl	2-MeO-4-ClPh
544	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-MeO-4-ClPh
545	C-Me	$NHCH(Me)CH_2CH_2OMe$	2-MeO-4-ClPh

NOTES FOR TABLE 2:

b) CI-HRMS: Calcd: 423.1355; Found: 423.1337 (M + H).

c) Analysis: Calcd: C, 61.38, H, 6.18, N, 14.32: Found: C, 61.54, H, 6.12, N, 14.37.

d) Analysis: Calcd: C: 58.02, H, 5.65, N, 14.24; Found: C, 58.11, H, 5.52, N, 14.26.

e) Analysis: Calcd: C, 59.71, H, 5.26, N, 14.85; Found: C, 59.94, H, 5.09, N, 17.23.

f) Analysis: Calcd: C, 60.48, H, 5.89, N, 14.85, Found: C, 60.62, H, 5.88, N, 14.82.

h) CI-HRMS: Calcd: 337.2388; Found: 337.2392 (M + H).

i) Analysis: Calcd: C, 68.45, H, 7.669, N, 15.21, Found: C, 68.35, H, 7.49 N, 14.91.

j) Analysis: Calcd: C, 69.08, H, 7.915, N, 14.65, Found: C, 68.85, H, 7.83, N, 14.54.

k) Analysis: Calcd: C, 73.51, H, 7.01, N, 19.48, Found: C, 71.57, H, 7.15, N, 19.12.

l) CI-HRMS: Calcd: 403.1899; Found: 403.1901 (M + H).

m) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl. 9.13; Found: C, 61.90, H, 6.66, N, 13.62, Cl, 9.25.

n) Analysis: Calcd: C, 67.31, H, 7.06, N, 15.70, Cl. 9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.

o) Analysis: Calcd: C, 74.50, H, 8.14, N, 17.38, Found: C, 74.43, H, 7.59, N, 17.16.

p) Analysis: Calcd: C, 73.10, H, 7.54, N, 19.37, Found: C, 73.18, H, 7.59, N, 18.81.

q) Analysis: Calcd: C, 73.57, H, 7.78, N, 18.65, Found: C, 73.55, H, 7.79, N, 18.64.

r) CI-HRMS: Calcd: 353.2333; Found: 353.2341 (M + H).

s) Analysis: Calcd: C, 71.56, H, 8.02, N, 15.90, Found: C, 71.45, H, 7.99, N, 15.88.

t) Analysis: Calcd: C, 65.60, H, 7.34, N, 14.57, Found: C, 65.42, H, 7.24, N, 14.37.

u) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).

v) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).

w) CI-HRMS: Calcd: 383.2450; Found: 383.2447 (M + H).

x) CI-HRMS: Calcd: 403.1887; Found: 403.1901 (M + H).

y) CI-HRMS: Calcd: 295.1919; Found: 295.1923 (M + H).

z) Analysis: Calcd: C, 67.31, H, 7.06, N, 15.70, Found: C, 67.12, H, 6.86, N, 15.53.

aa) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl, 9.13; Found: C, 62.06, H, 6.37, N, 14.25, Cl, 9.12.

ab) CI-HRMS: Calcd: 337.2017; Found: 337.2028 (M + H).

ac) CI-HRMS: Calcd: 403.1893; Found: 403.1901 (M + H).

ad) Analysis: Calcd: C, 70.00, H, 7.22, N, 18.55, Found: C, 70.05, H, 7.22, N, 18.36.

ae) Analysis: Calcd: C, 70.98, H, 7.74, N, 16.55, Found: C, 71.15, H, 7.46, N, 16.56.

ag) Analysis: Calcd: C, 66.59, H, 6.76, N, 16.34,
Found: C, 66.69, H,6.82, N, 16.20.

ah) Analysis: Calcd: C, 70.38, H, 6.71, N, 18.65,
Found: C, 70.35, H,6.82, N, 18.83.

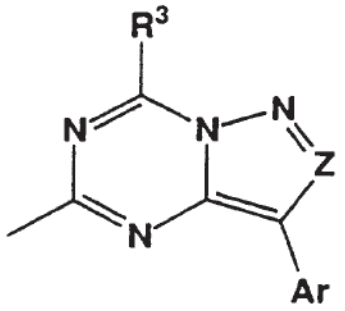
ai) Analysis: Calcd: C, 66.39, H, 5.85, N, 18.44, Cl, 9.33;
Found: C, 66.29, H, 5.51, N, 18.36, Cl, 9.31.

aj) CI-HRMS: Calcd: 369.2278; Found: 369.2291 (M + H).

ak) Analysis: Calcd: C, 64.42, H, 6.77, N, 15.02,
Found: C, 64.59, H,6.51, N, 14.81.

The examples delineated in TABLE 3 may be prepared by the methods outlined in Examples 1, 2, 3 or 6. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

TABLE 3



Ex.	Z	R_3	Ar	mp(°C)
546[a]	C-Me	$NHCH(Et)_2$	2-Me-4-Me_2N-Ph	164-166
547[b]	C-Me	S-$NHCH(CH_2CH_2OMe)$-CH_2OMe	2,4-Me2-Ph	oil
548[c]	C-Me	S-$NHCH(CH_2CH_2OMe)$-CH_2OMe	2-Me-4-Cl-Ph	oil
549[d]	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-Me-4-Cl-Ph	115-116

550[e]	C-Me	NHCH(Et)CH_2CN	2-Me-4-Cl-Ph	131-132
551[f]	C-Me	$N(Et)_2$	2,3-Me_2-4-OMe-Ph	oil
552[g]	C-Me	$N(CH_2CH_2OMe)CH_2CH_2OH$	2,4-Cl_2-Ph	oil
553[h]	C-Me	$N(CH_2CH_2OMe)_2$	2,3-Me_2-4-OMe-Ph	oil
554[i]	C-Me	$NHCH(Et)_2$	2,3-Me_2-4-OMePh	123-124
555[j]	C-Me	$N(CH_2$-c-Pr)Pr	2-Me-4-Cl-Ph	oil
556[k]	C-Me	N(c-Pr)CH_2CH_2CN	2,3-Me_2-4-OMePh	158-160
557	C-Me	N(c-Pr)Et	2-Cl-4-OMePh	
558	C-Me	N(c-Pr)Me	2-Cl-4-OMePh	
559	C-Me	N(c-Pr)Pr	2-Cl-4-OMePh	
560	C-Me	N(c-Pr)Bu	2-Cl-4-OMePh	
561[l]	C-Me	$N(Et)_2$	2-Cl-4-CN-Ph	115-117
562	C-Me	$N(c\text{-}Pr)_2$	2-Cl-4-OMe	127-129
563[m]	C-Me	$NHCH(CH_2OH)_2$	2,4-Cl_2-Ph	128-129
564	C-Me	N(c-Pr)Et	2-Br-4,5-(MeO)2Ph	
565	C-Me	N(c-Pr)Me	2-Br-4,5-(MeO)2Ph	
566	C-Me	NH-c-Pr	2-Me-4-MeOPh	126-128
567	C-Me	NHCH(Et)CH2OH	2-Me-4-MeOPh	60-62
568	C-Me	NMe_2	2-Br-4,5-(MeO)2Ph	
569	C-Me	$NHCH(Et)_2$	2-Me-4-MeOPh	103-105
570	C-Me	N(c-Pr)Et	2-Me-4-MeOPh	173-174
571	C-Me	NH-2-pentyl	2,4-Cl_2-Ph	118-120
572	C-Me	NHCH(Et)CH2CN	2,4-Cl_2-Ph	141-142
573	C-Me	NHCH(Pr)CH2OMe	2,4-Cl_2-Ph	87-88
574	C-Me	NHCH(CH2-iPr)CH2OMe	2,4-Cl_2-Ph	amorphous
575	C-Me	NH-2-butyl	2,4-Me_2-Ph	oil
576	C-Me	NH-2-pentyl	2,4-Me_2-Ph	oil
577	C-Me	NH-2-hexyl	2,4-Me_2-Ph	oil
578	C-Me	NHCH(i-Pr)Me	2,4-Me_2-Ph	oil
579	C-Me	NHCH(Me)CH2-iPr	2,4-Me_2-Ph	oil
580	C-Me	NHCH(Me)-c-C6H11	2,4-Me_2-Ph	oil
581	C-Me	NH-2-indanyl	2,4-Me_2-Ph	oil
582	C-Me	NH-1-indanyl	2,4-Me_2-Ph	oil
583	C-Me	NHCH(Me)Ph	2,4-Me_2-Ph	oil
584	C-Me	NHCH(Me)CH_2-(4-ClPh)	2,4-Me_2-Ph	oil

	585	C-Me	NHCH(Me)CH_2COCH_3	2,4-Me_2-Ph	oil
	586	C-Me	NHCH(Ph)CH_2Ph	2,4-Me_2-Ph	oil
	587	C-Me	NHCH(Me)$(CH_2)_3NEt_2$	2,4-Me_2-Ph	oil
	588	C-Me	NH-(2-Ph-c-C_3H_4)	2,4-Me_2-Ph	oil
5	589	C-Me	NHCH(Et)CH_2CN	2,4-Me_2-Ph	119-120
	590	C-Me	NH-3-hexyl	2,4-Me_2-Ph	oil
	591[n]	C-Me	NEt_2	2-MeO-4-ClPh	oil
	592[o]	C-Me	$NHCH(Et)_2$	2-MeO-4-ClPh	oil
	593[p]	C-Me	NHCH(Et)CH_2OMe	2-MeO-4-ClPh	oil
10	594	C-Me	NMe_2	2-MeO-4-ClPh	oil
	595[q]	C-Me	$NHCH(Et)_2$	2-OMe-4-MePh	oil
	596[r]	C-Me	NEt_2	2-OMe-4-MePh	oil
	597[s]	C-c-Pr	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph	oil
	598	C-Me	N(c-Pr)Et	2,4-Me_2-Ph	
15	599	C-Me	N(c-Pr)Et	2,4-Cl_2-Ph	
	600	C-Me	N(c-Pr)Et	2,4,6-Me_3-Ph	
	601	C-Me	N(c-Pr)Et	2-Me-4-Cl-Ph	
	602	C-Me	N(c-Rr)Et	2-Cl-4-Me-Ph	
	603	C-Me	$NHCH(c\text{-}Pr)_2$	2,4-Cl_2-Ph	
20	604	C-Me	$NHCH(c\text{-}Pr)_2$	2,4-Me_2-Ph	
	605	C-Me	$NHCH(c\text{-}Pr)_2$	2-Me-4-Cl-Ph	
	606	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-Me-Ph	
	607	C-Me	$NHCH(c\text{-}Pr)_2$	2-Me-4-OMe-Ph	
	608	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-OMe-Ph	
25	609	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-5-F-OMePh	
	610	C-Me	NEt_2	2-Cl-5-F-OMePh	
	611	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-5-F-OMePh	
	612	C-Me	$NHCH(Et)_2$	2-Cl-5-F-OMePh	
	613	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-5-F-OMePh	
30	614	C-Me	NEt_2	2,6-Me_2-pyrid-3-yl	
	615	C-Me	N(c-Pr)CH_2CH_2CN	2,6-Me_2-pyrid-3-yl	
	616	C-Me	$NHCH(Et)_2$	2,6-Me_2-pyrid-3-yl	
	617	C-Me	$N(CH_2CH_2OMe)_2$	2,6-Me_2-pyrid-3-yl	
	618	C-OH	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph	
35	619	C-OH	NEt_2	2,4-Me_2-Ph	
	620	C-OH	N(c-Pr)CH_2CH_2CN	2,4-Me_2-Ph	

621	C-OH	$NHCH(Et)_2$	$2,4\text{-}Me_2\text{-}Ph$
623	C-OH	$N(CH_2CH_2OMe)_2$	$2,4\text{-}Me_2\text{-}Ph$
624	$C\text{-}NEt_2$	$NHCH(CH_2OMe)_2$	$2,4\text{-}Me_2\text{-}Ph$
625	$C\text{-}NEt_2$	NEt_2	$2,4\text{-}Me_2\text{-}Ph$
626	$C\text{-}NEt_2$	$N(c\text{-}Pr)CH_2CH_2CN$	$2,4\text{-}Me_2\text{-}Ph$
627	$C\text{-}NEt_2$	$NHCH(Et)_2$	$2,4\text{-}Me_2\text{-}Ph$
628	$C\text{-}NEt_2$	$N(CH_2CH_2OMe)_2$	$2,4\text{-}Me_2\text{-}Ph$
629	C-Me	$NHCH(Et)_2$	2-Me-4-CN-Ph
630	C-Me	$N(CH_2CH_2OMe)_2$	2-Me-4-CN-Ph

Notes for Table 3:

a) CI-HRMS: Calcd:367.2610, Found: 367.2607 (M + H);

b) CI-HRMS: Calcd:384.2400, Found: 384.2393 (M + H);

c) CI-HRMS: Calcd:404.1853, Found: 404.1844 (M + H);

d) CI-HRMS: Calcd:381.1594, Found: 381.1596 (M + H);
Analysis: Calcd: C: 63.07, H, 5.57, N, 22.07, Cl, 9.32;
Found: C: 63.40, H, 5.55, N, 21.96, Cl: 9.15

e) CI-HRMS: Calcd:369.1594, Found: 369.1576 (M + H);

f) CI-HRMS: Calcd:354.2216, Found: 354.2211 (M + H);

g) CI-HRMS: Calcd:410.1072, Found: 410.1075 (M + H);

h) CI-HRMS: Calcd:414.2427, Found: 414.2427(M + H);

i) CI-HRMS: Calcd:368.2372, Found: 368.2372(M + H);

j) CI-HRMS: Calcd:384.1955, Found: 384.1947(M + H);

k) CI-HRMS: Calcd:391.2168, Found: 391.2160(M + H);

l) CI-HRMS: Calcd:335.1984, Found: 335.1961(M + H);

m) CI-HRMS: Calcd:382.0759, Found: 382.0765(M + H);

n) NH_3-CI MS: Calcd: 360, Found: 360 (M + H)+

o) NH_3-CI MS: Calcd: 374, Found: 374 (M + H)+;
NMR ($CDCl_3$, 300 MHz) :δ 7.29 (d, J=8.4Hz, 1H), 7.04 (dd, J=1.8,8Hz, 1H), 6.96 (d, J=1.8Hz, 1H), 6.15 (d, J=10, 1H), 4.19 (m, 1H), 3.81 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.65 (m, 4H), 0.99 (t, J=7.32Hz, 6H)

p) NH_3-CI MS: Calcd: 390, Found: 390 (M + H)+;

NMR ($CDCl_3$, 300 MHz) : δ 7.28 (d, J=8Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.52 (d, J=9Hz, 1H), 4.36 (m, 1H), 3.8 (s, 3H), 3.55 (m, 2H), 3.39 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.76 (m, 2H), 1.01 (t, J=7.32Hz, 3H).

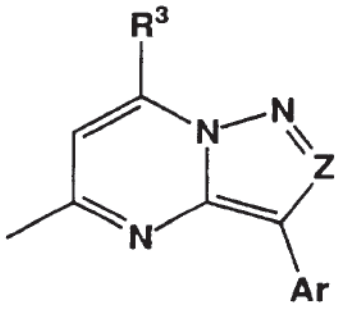
q) CI-HRMS: Calcd: 354.2294, Found: 354.2279 (M + H)+

r) CI-HRMS: Calcd: 340.2137, Found: 340.2138 (M + H)+

s) CI-HRMS: Calcd: 436.1307, Found: 436.1296 (M + H)+

The examples delineated in TABLE 4 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, EtOAc is ethyl acetate.

TABLE 4

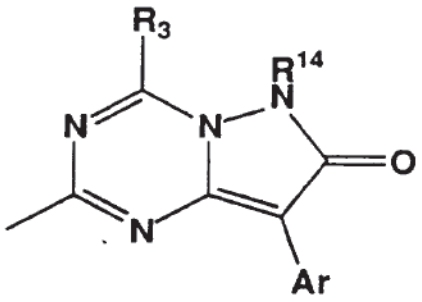


Ex.	Z	R_3	Ar	mp(°C)
631	C-Me	$NHCH(Et)_2$	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$	160-161
632	C-Me	$NHCH(Et)_2$	2-Br-4-MeOPh	110-111
633	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-MeOPh	74-76
634	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-MeOPh	128-130

	635	C-Me	$N(Et)_2$	2-Me-4-ClPh	113-114
	636	C-Me	N(c-Pr)Et	$2,4\text{-}Cl_2Ph$	
	637	C-Me	N(c-Pr)Et	$2,4\text{-}Me_2Ph$	
	638	C-Me	N(c-Pr)Et	$2,4,6\text{-}Me_3Ph$	
5	639	C-Me	N(c-Pr)Et	2-Me-4-MeOPh	
	640	C-Me	N(c-Pr)Et	2-Cl-4-MeOPh	
	641	C-Me	N(c-Pr)Et	2-Cl-4-MePh	
	642	C-Me	N(c-Pr)Et	2-Me-4-ClPh	
	643	C-Me	$NHCH(c\text{-}Pr)_2$	$2,4\text{-}Cl_2\text{-}Ph$	
10	644	C-Me	$NHCH(c\text{-}Pr)_2$	$2,4\text{-}Me_2\text{-}Ph$	
	645	C-Me	$NHCH(c\text{-}Pr)_2$	2-Me-4-Cl-Ph	
	646	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-Me-Ph	
	647	C-Me	$NHCH(c\text{-}Pr)_2$	2-Me-4-OMe-Ph	
	648	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-OMe-Ph	
15	649	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-5-F-OMePh	
	650	C-Me	NEt_2	2-Cl-5-F-OMePh	
	651	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-Cl-5-F-OMePh	
	652	C-Me	$NHCH(Et)_2$	2-Cl-5-F-OMePh	
	653	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-5-F-OMePh	
20	654	C-Me	NEt_2	$2,6\text{-}Me_2\text{-pyrid-3-yl}$	
	655	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	$2,6\text{-}Me_2\text{-pyrid-3-yl}$	
	656	C-Me	$NHCH(Et)_2$	$2,6\text{-}Me_2\text{-pyrid-3-yl}$	
	657	C-Me	$N(CH_2CH_2OMe)_2$	$2,6\text{-}Me_2\text{-pyrid-3-yl}$	
	658	C-OH	$NHCH(CH_2OMe)_2$	$2,4\text{-}Me_2\text{-Ph}$	
25	659	C-OH	NEt_2	$2,4\text{-}Me_2\text{-Ph}$	
	660	C-OH	$N(c\text{-}Pr)CH_2CH_2CN$	$2,4\text{-}Me_2\text{-Ph}$	
	661	C-OH	$NHCH(Et)_2$	$2,4\text{-}Me_2\text{-Ph}$	
	662	C-OH	$N(CH_2CH_2OMe)_2$	$2,4\text{-}Me_2\text{-Ph}$	
	663	$C\text{-}NEt_2$	$NHCH(CH_2OMe)_2$	$2,4\text{-}Me_2\text{-Ph}$	
30	664	$C\text{-}NEt_2$	NEt_2	$2,4\text{-}Me_2\text{-Ph}$	
	665	$C\text{-}NEt_2$	$N(c\text{-}Pr)CH_2CH_2CN$	$2,4\text{-}Me_2\text{-Ph}$	
	666	$C\text{-}NEt_2$	$NHCH(Et)_2$	$2,4\text{-}Me_2\text{-Ph}$	
	667	$C\text{-}NEt_2$	$N(CH_2CH_2OMe)_2$	$2,4\text{-}Me_2\text{-Ph}$	
	668	C-Me	$NHCH(Et)_2$	2-Me-4-CN-Ph	
35	669	C-Me	$N(CH_2CH_2OMe)_2$	2-Me-4-CN-Ph	

The examples in Tables 5 or 6 may be prepared by the methods illustrated in Examples 1A, 1B, 2, 3, 6, 431, 432, 433, 434 or by appropriate combinations thereof. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

Table 5



Ex.	R_{14}	R_3	Ar
670	Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph
671	Me	$NHCHPr_2$	2,4-Cl_2-Ph
672	Me	NEtBu	2,4-Cl_2-Ph
673	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Cl_2-Ph
674	Me	$N(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph
675	Me	NH-3-heptyl	2,4-Cl_2-Ph
676	Me	$NHCH(Et)CH_2OMe$	2,4-Cl_2-Ph
677	Me	NEt_2	2,4-Cl_2-Ph
678	Me	$NHCH(CH_2OEt)_2$	2,4-Cl_2-Ph
679	Me	NH-3-pentyl	2,4-Cl_2-Ph
680	Me	NMePh	2,4-Cl_2-Ph
681	Me	NPr_2	2,4-Cl_2-Ph
682	Me	NH-3-hexyl	2,4-Cl_2-Ph
683	Me	morpholino	2,4-Cl_2-Ph

	684	Me	$N(CH_2Ph)CH_2CH_2OMe$	$2,4\text{-}Cl_2\text{-}Ph$
	685	Me	$NHCH(CH_2Ph)CH_2OMe$	$2,4\text{-}Cl_2\text{-}Ph$
	686	Me	NH-4-tetrahydropyranyl	$2,4\text{-}Cl_2\text{-}Ph$
	687	Me	NH-cyclopentyl	$2,4\text{-}Cl_2\text{-}Ph$
	688	Me	OEt	$2,4\text{-}Cl_2\text{-}Ph$
	689	Me	$OCH(Et)CH_2OMe$	$2,4\text{-}Cl_2\text{-}Ph$
	690	Me	OCH_2Ph	$2,4\text{-}Cl_2\text{-}Ph$
	691	Me	O-3-pentyl	$2,4\text{-}Cl_2\text{-}Ph$
	692	Me	SEt	$2,4\text{-}Cl_2\text{-}Ph$
	693	Me	S(O)Et	$2,4\text{-}Cl_2\text{-}Ph$
	694	Me	SO_2Et	$2,4\text{-}Cl_2\text{-}Ph$
	695	Me	Ph	$2,4\text{-}Cl_2\text{-}Ph$
	696	Me	$2\text{-}CF_3\text{-}Ph$	$2,4\text{-}Cl_2\text{-}Ph$
	697	Me	2-Ph-Ph	$2,4\text{-}Cl_2\text{-}Ph$
	698	Me	3-pentyl	$2,4\text{-}Cl_2\text{-}Ph$
	699	Me	cyclobutyl	$2,4\text{-}Cl_2\text{-}Ph$
	700	Me	3-pyridyl	$2,4\text{-}Cl_2\text{-}Ph$
	701	Me	$CH(Et)CH_2CONMe_2$	$2,4\text{-}Cl_2\text{-}Ph$
	702	Me	$CH(Et)CH_2CH_2NMe_2$	$2,4\text{-}Cl_2\text{-}Ph$
	703	Me	$NHCH(CH_2OMe)_2$	$2,4,6\text{-}Me_3\text{-}Ph$
	704	Me	$NHCHPr_2$	$2,4,6\text{-}Me_3\text{-}Ph$
	705	Me	NEtBu	$2,4,6\text{-}Me_3\text{-}Ph$
	706	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	$2,4,6\text{-}Me_3\text{-}Ph$
	707	Me	$N(CH_2CH_2OMe)_2$	$2,4,6\text{-}Me_3\text{-}Ph$
	708	Me	NH-3-heptyl	$2,4,6\text{-}Me_3\text{-}Ph$
	709	Me	$NHCH(Et)CH_2OMe$	$2,4,6\text{-}Me_3\text{-}Ph$
	710	Me	NEt_2	$2,4,6\text{-}Me_3\text{-}Ph$
	711	Me	$NHCH(CH_2OEt)_2$	$2,4,6\text{-}Me_3\text{-}Ph$
	712	Me	NH-3-pentyl	$2,4,6\text{-}Me_3\text{-}Ph$
	713	Me	NMePh	$2,4,6\text{-}Me_3\text{-}Ph$
	714	Me	NPr_2	$2,4,6\text{-}Me_3\text{-}Ph$
	715	Me	NH-3-hexyl	$2,4,6\text{-}Me_3\text{-}Ph$
	716	Me	morpholino	$2,4,6\text{-}Me_3\text{-}Ph$
	717	Me	$N(CH_2Ph)CH_2CH_2OMe$	$2,4,6\text{-}Me_3\text{-}Ph$
	718	Me	$NHCH(CH_2Ph)CH_2OMe$	$2,4,6\text{-}Me_3\text{-}Ph$
	719	Me	NH-4-tetrahydropyranyl	$2,4,6\text{-}Me_3\text{-}Ph$

720	Me	NH-cyclopentyl	2,4,6-Me_3-Ph
721	Me	OEt	2,4,6-Me_3-Ph
722	Me	OCH(Et)CH_2OMe	2,4,6-Me_3-Ph
723	Me	OCH_2Ph	2,4,6-Me_3-Ph
724	Me	O-3-pentyl	2,4,6-Me_3-Ph
725	Me	SEt	2,4,6-Me_3-Ph
726	Me	S(O)Et	2,4,6-Me_3-Ph
727	Me	SO_2Et	2,4,6-Me_3-Ph
728	Me	CH(CO_2Et)$_2$	2,4,6-Me_3-Ph
729	Me	C(Et)(CO_2Et)$_2$	2,4,6-Me_3-Ph
730	Me	CH(Et)CH_2OH	2,4,6-Me_3-Ph
731	Me	CH(Et)CH_2OMe	2,4,6-Me_3-Ph
732	Me	$CONMe_2$	2,4,6-Me_3-Ph
733	Me	$COCH_3$	2,4,6-Me_3-Ph
734	Me	CH(OH)CH_3	2,4,6-Me_3-Ph
735	Me	C(OH)Ph-3-pyridyl	2,4,6-Me_3-Ph
736	Me	Ph	2,4,6-Me_3-Ph
737	Me	2-Ph-Ph	2,4,6-Me_3-Ph
738	Me	3-pentyl	2,4,6-Me_3-Ph
739	Me	cyclobutyl	2,4,6-Me_3-Ph
740	Me	3-pyridyl	2,4,6-Me_3-Ph
741	Me	CH(Et)CH_2CONMe_2	2,4,6-Me_3-Ph
742	Me	CH(Et)$CH_2CH_2NMe_2$	2,4,6-Me_3-Ph
743	Me	NHCH(CH_2OMe)$_2$	2,4-Me_2-Ph
744	Me	N(CH_2CH_2OMe)$_2$	2,4-Me_2-Ph
745	Me	NHCH(Et)CH_2OMe	2,4-Me_2-Ph
746	Me	NH-3-pentyl	2,4-Me_2-Ph
747	Me	NEt_2	2,4-Me_2-Ph
748	Me	N(CH_2CN)$_2$	2,4-Me_2-Ph
749	Me	NHCH(Me)CH_2OMe	2,4-Me_2-Ph
750	Me	OCH(Et)CH_2OMe	2,4-Me_2-Ph
751	Me	NPr-c-C_3H_5	2,4-Me_2-Ph
752	Me	NHCH(Me)CH_2NMe_2	2,4-Me_2-Ph
753	Me	N(c-C_3H_5)CH_2CH_2CN	2,4-Me_2-Ph
754	Me	N(Pr)CH_2CH_2CN	2,4-Me_2-Ph
755	Me	N(Bu)CH_2CH_2CN	2,4-Me_2-Ph

756	Me	NHCHPr$_2$	2,4-Me$_2$-Ph
757	Me	NEtBu	2,4-Me$_2$-Ph
758	Me	NPr(CH$_2$-c-C$_3$H$_5$)	2,4-Me$_2$-Ph
759	Me	NH-3-heptyl	2,4-Me$_2$-Ph
760	Me	NEt$_2$	2,4-Me$_2$-Ph
761	Me	NHCH(CH$_2$OEt)$_2$	2,4-Me$_2$-Ph
762	Me	NH-3-pentyl	2,4-Me$_2$-Ph
763	Me	NMePh	2,4-Me$_2$-Ph
764	Me	NPr$_2$	2,4-Me$_2$-Ph
765	Me	NH-3-hexyl	2,4-Me$_2$-Ph
766	Me	morpholino	2,4-Me$_2$-Ph
767	Me	N(CH$_2$Ph)CH$_2$CH$_2$OMe	2,4-Me$_2$-Ph
768	Me	NHCH(CH$_2$Ph)CH$_2$OMe	2,4-Me$_2$-Ph
769	Me	NH-4-tetrahydropyranyl	2,4-Me$_2$-Ph
770	Me	NH-cyclopentyl	2,4-Me$_2$-Ph
771	Me	NHCH(CH$_2$OMe)$_2$	2-Me-4-MeO-Ph
772	Me	N(CH$_2$CH$_2$OMe)$_2$	2-Me-4-MeO-Ph
773	Me	NHCH(Et)CH$_2$OMe	2-Me-4-MeO-Ph
774	Me	N(Pr)CH$_2$CH$_2$CN	2-Me-4-MeO-Ph
775	Me	OCH(Et)CH$_2$OMe	2-Me-4-MeO-Ph
776	Me	NHCH(CH$_2$OMe)$_2$	2-Br-4-MeO-Ph
777	Me	N(CH$_2$CH$_2$OMe)$_2$	2-Br-4-MeO-Ph
778	Me	NHCH(Et)CH$_2$OMe	2-Br-4-MeO-Ph
779	Me	N(Pr)CH$_2$CH$_2$CN	2-Br-4-MeO-Ph
780	Me	OCH(Et)CH$_2$OMe	2-Br-4-MeO-Ph
781	Me	NHCH(CH$_2$OMe)$_2$	2-Me-4-NMe$_2$-Ph
782	Me	N(CH$_2$CH$_2$OMe)$_2$	2-Me-4-NMe$_2$-Ph
783	Me	NHCH(Et)CH$_2$OMe	2-Me-4-NMe$_2$-Ph
784	Me	N(Pr)CH$_2$CH$_2$CN	2-Me-4-NMe$_2$-Ph
785	Me	OCH(Et)CH$_2$OMe	2-Me-4-NMe$_2$-Ph
786	Me	NHCH(CH$_2$OMe)$_2$	2-Br-4-NMe$_2$-Ph
787	Me	N(CH$_2$CH$_2$OMe)$_2$	2-Br-4-NMe$_2$-Ph
788	Me	NHCH(Et)CH$_2$OMe	2-Br-4-NMe$_2$-Ph
789	Me	N(Pr)CH$_2$CH$_2$CN	2-Br-4-NMe$_2$-Ph
790	Me	OCH(Et)CH$_2$OMe	2-Br-4-NMe$_2$-Ph
791	Me	NHCH(CH$_2$OMe)$_2$	2-Br-4-i-Pr-Ph

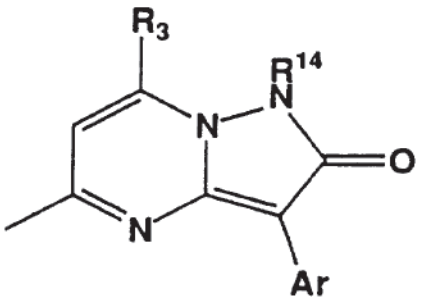
792	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-i-Pr-Ph
793	Me	NHCH(Et)CH_2OMe	2-Br-4-i-Pr-Ph
794	Me	N(Pr)CH_2CH_2CN	2-Br-4-i-Pr-Ph
795	Me	OCH(Et)CH_2OMe	2-Br-4-i-Pr-Ph
796	Me	$NHCH(CH_2OMe)_2$	2-Br-4-Me-Ph
797	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-Me-Ph
798	Me	NHCH(Et)CH_2OMe	2-Br-4-Me-Ph
799	Me	N(Pr)CH_2CH_2CN	2-Br-4-Me-Ph
800	Me	OCH(Et)CH_2OMe	2-Br-4-Me-Ph
801	Me	$NHCH(CH_2OMe)_2$	2-Me-4-Br-Ph
802	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-Br-Ph
803	Me	NHCH(Et)CH_2OMe	2-Me-4-Br-Ph
804	Me	N(Pr)CH_2CH_2CN	2-Me-4-Br-Ph
805	Me	OCH(Et)CH_2OMe	2-Me-4-Br-Ph
806	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph
807	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph
808	Me	$NHCH(CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph
809	Me	$N(CH_2CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph
810	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
811	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
812	Me	$NHCH(CH_2OMe)_2$	2-Br-4-CF_3-Ph
813	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-CF_3-Ph
814	Me	$NHCH(CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph
815	Me	$N(CH_2CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph
816	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph
817	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph
818	Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
819	Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
820	Me	$NHCH(CH_2OMe)_2$	4-(COMe)-2-Br-Ph
821	Me	$N(CH_2CH_2OMe)_2$	4-(COMe)-2-Br-Ph
822	Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl
823	Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl
824	Me	$NHCH(CH_2OMe)_2$	2,4-$(Br)_2$-Ph
825	Me	$N(CH_2CH_2OMe)_2$	2,4-$(Br)_2$-Ph
826	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
827	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph

828	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
829	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
830	Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
831	Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
832	Me	$NHCH(CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
833	Me	$N(CH_2CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
834	Me	$NHCH(CH_2OMe)_2$	2-I-4-i-Pr-Ph
835	Me	$N(CH_2CH_2OMe)_2$	2-I-4-i-Pr-Ph
836	Me	$NHCH(CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph
837	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph
838	Me	NEt_2	2-Br-4-MeO-Ph
839	Me	NH-3-pentyl	2-Br-4-MeO-Ph
840	Me	$NHCH(CH_2OMe)_2$	2-CN-4-Me-Ph
841	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,4,6-Me_3-Ph
842	Me	$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-Br-Ph
843	Me	$NHCH(CH_2OMe)_2$	2,5-Me_2-4-MeO-Ph
844	Me	$N(CH_2CH_2OMe)_2$	2,5-Me_2-4-MeO-Ph
845	Me	NH-3-pentyl	2,5-Me_2-4-MeO-Ph
846	Me	NEt_2	2,5-Me_2-4-MeO-Ph
847	Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MePh
848	Me	$NCH(Et)CH_2OMe$	2-Cl-4-MePh
849	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MePh
850	Me	(S)-$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Cl-4-MePh
851	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,5-Me_2-4-MeOPh
852	Me	NEt_2	2-Me-4-MeOPh
853	Me	OEt	2-Me-4-MeOPh
854	Me	(S)-$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-MeOPh
855	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2-Me-4-MeOPh
856	Me	$NHCH(CH_2CH_2OEt)_2$	2-Me-4-MeOPh
857	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,4-Cl_2-Ph
858	Me	NEt_2	2-Me-4-ClPh
859	Me	NH-3-pentyl	2-Me-4-ClPh
860	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-ClPh
861	Me	$NHCH(CH_2OMe)_2$	2-Me-4-ClPh
862	Me	NEt_2	2-Me-4-ClPh
863	Me	NEt_2	2-Cl-4-MePh

864	Me	NH-3-pentyl	2-Cl-4-MePh
865	Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MeOPh
866	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MeOPh
867	Me	$NHCH(Et)CH_2OMe$	2-Cl-4-MeOPh
868	Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-Cl-4-MeOPh
869	Me	NEt_2	2-Cl-4-MeOPh
870	Me	NH-3-pentyl	2-Cl-4-MeOPh
871	Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4-MeOPh
872	Me	$NHCH(Me)CH_2CH_2OMe$	2-Cl-4-MeOPh
873	Me	$NHCH(Et)CH_2CH_2OMe$	2-Br-4-MeOPh
874	Me	$NHCH(Me)CH_2CH_2OMe$	2-Br-4-MeOPh
875	Me	$NHCH(Et)CH_2CH_2OMe$	2-Me-4-MeOPh
876	Me	$NHCH(Me)CH_2CH_2OMe$	2-Me-4-MeOPh
877	Me	$NHCH(CH_2OMe)_2$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
878	Me	$N(CH_2CH_2OMe)_2$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
879	Me	$NHCH(Et)CH_2OMe$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
880	Me	$N(c\text{-}Pr)CH_2CH_2CN$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
881	Me	NEt_2	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
882	Me	NH-3-pentyl	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
883	Me	$NHCH(Et)CH_2CH_2OMe$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
884	Me	$NHCH(Me)CH_2CH_2OMe$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
885	Me	$NHCH(CH_2OMe)_2$	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
886	Me	$N(CH_2CH_2OMe)_2$	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
887	Me	$NHCH(Et)CH_2OMe$	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
888	Me	$N(c\text{-}Pr)CH_2CH_2CN$	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
889	Me	NEt_2	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
890	Me	NH-3-pentyl	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
891	Me	$NHCH(CH_2OMe)_2$	$2\text{-Cl-4,6-(MeO)}_2\text{Ph}$
892	Me	$N(CH_2CH_2OMe)_2$	$2\text{-Cl-4,6-(MeO)}_2\text{Ph}$
893	Me	NEt_2	$2\text{-Cl-4,6-(MeO)}_2\text{Ph}$
894	Me	NH-3-pentyl	$2\text{-Cl-4,6-(MeO)}_2\text{Ph}$
895	Me	$NHCH(CH_2OMe)_2$	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$
896	Me	$N(CH_2CH_2OMe)_2$	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$
897	Me	$NHCH(Et)CH_2OMe$	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$
898	Me	NEt_2	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$
899	Me	NH-3-pentyl	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$

	900	Me	$NHCH(Et)CH_2CH_2OMe$	2-Me-4-MeOPh
	901	Me	$NHCH(Me)CH_2CH_2OMe$	2-Me-4-MeOPh
	902	Me	$NHCH(CH_2OMe)_2$	2-MeO-4-MePh
	903	Me	$N(CH_2CH_2OMe)_2$	2-MeO-4-MePh
	904	Me	$NHCH(Et)CH_2OMe$	2-MeO-4-MePh
	905	Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-MeO-4-MePh
	906	Me	NEt_2	2-MeO-4-MePh
	907	Me	NH-3-pentyl	2-MeO-4-MePh
	908	Me	$NHCH(Et)CH_2CH_2OMe$	2-MeO-4-MePh
	909	Me	$NHCH(Me)CH_2CH_2OMe$	2-MeO-4-MePh
	910	Me	$NHCH(CH_2OMe)_2$	2-MeO-4-MePh
	911	Me	$N(CH_2CH_2OMe)_2$	2-MeO-4-MePh
	912	Me	$NHCH(Et)CH_2OMe$	2-MeO-4-MePh
	913	Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-MeO-4-MePh
	914	Me	NEt_2	2-MeO-4-MePh
	915	Me	NH-3-pentyl	2-MeO-4-MePh
	916	Me	$NHCH(CH_2OMe)_2$	2-MeO-4-ClPh
	917	Me	$N(CH_2CH_2OMe)_2$	2-MeO-4-ClPh
	918	Me	$NHCH(Et)CH_2OMe$	2-MeO-4-ClPh
	919	Me	NEt_2	2-MeO-4-ClPh
	920	Me	NH-3-pentyl	2-MeO-4-ClPh

Table 6



Ex.	R14	R3	Ar
921	Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph
922	Me	$NHCHPr_2$	2,4-Cl_2-Ph
923	Me	NEtBu	2,4-Cl_2-Ph
924	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Cl_2-Ph
925	Me	$N(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph
926	Me	NH-3-heptyl	2,4-Cl_2-Ph
927	Me	$NHCH(Et)CH_2OMe$	2,4-Cl_2-Ph
928	Me	NEt_2	2,4-Cl_2-Ph
929	Me	$NHCH(CH_2OEt)_2$	2,4-Cl_2-Ph
930	Me	NH-3-pentyl	2,4-Cl_2-Ph
931	Me	NMePh	2,4-Cl_2-Ph
932	Me	NPr_2	2,4-Cl_2-Ph
933	Me	NH-3-hexyl	2,4-Cl_2-Ph
934	Me	morpholino	2,4-Cl_2-Ph
935	Me	$N(CH_2Ph)CH_2CH_2OMe$	2,4-Cl_2-Ph
936	Me	$NHCH(CH_2Ph)CH_2OMe$	2,4-Cl_2-Ph
937	Me	NH-4-tetrahydropyranyl	2,4-Cl_2-Ph
938	Me	NH-cyclopentyl	2,4-Cl_2-Ph
939	Me	OEt	2,4-Cl_2-Ph
940	Me	$OCH(Et)CH_2OMe$	2,4-Cl_2-Ph
941	Me	OCH_2Ph	2,4-Cl_2-Ph
942	Me	O-3-pentyl	2,4-Cl_2-Ph
943	Me	SEt	2,4-Cl_2-Ph

944	Me	S(O)Et	2,4-Cl_2-Ph
945	Me	SO_2Et	2,4-Cl_2-Ph
946	Me	Ph	2,4-Cl_2-Ph
947	Me	2-CF_3-Ph	2,4-Cl_2-Ph
948	Me	2-Ph-Ph	2,4-Cl_2-Ph
949	Me	3-pentyl	2,4-Cl_2-Ph
950	Me	cyclobutyl	2,4-Cl_2-Ph
951	Me	3-pyridyl	2,4-Cl_2-Ph
952	Me	$CH(Et)CH_2CONMe_2$	2,4-Cl_2-Ph
953	Me	$CH(Et)CH_2CH_2NMe_2$	2,4-Cl_2-Ph
954	Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-Ph
955	Me	$NHCHPr_2$	2,4,6-Me_3-Ph
956	Me	NEtBu	2,4,6-Me_3-Ph
957	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4,6-Me_3-Ph
958	Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-Ph
959	Me	NH-3-heptyl	2,4,6-Me_3-Ph
960	Me	$NHCH(Et)CH_2OMe$	2,4,6-Me_3-Ph
961	Me	NEt_2	2,4,6-Me_3-Ph
962	Me	$NHCH(CH_2OEt)_2$	2,4,6-Me_3-Ph
963	Me	NH-3-pentyl	2,4,6-Me_3-Ph
964	Me	NMePh	2,4,6-Me_3-Ph
965	Me	NPr_2	2,4,6-Me_3-Ph
966	Me	NH-3-hexyl	2,4,6-Me_3-Ph
967	Me	morpholino	2,4,6-Me_3-Ph
968	Me	$N(CH_2Ph)CH_2CH_2OMe$	2,4,6-Me_3-Ph
969	Me	$NHCH(CH_2Ph)CH_2OMe$	2,4,6-Me_3-Ph
970	Me	NH-4-tetrahydropyranyl	2,4,6-Me_3-Ph
971	Me	NH-cyclopentyl	2,4,6-Me_3-Ph
972	Me	OEt	2,4,6-Me_3-Ph
973	Me	$OCH(Et)CH_2OMe$	2,4,6-Me_3-Ph
974	Me	OCH_2Ph	2,4,6-Me_3-Ph
975	Me	O-3-pentyl	2,4,6-Me_3-Ph
976	Me	SEt	2,4,6-Me_3-Ph
977	Me	S(O)Et	2,4,6-Me_3-Ph
978	Me	SO_2Et	2,4,6-Me_3-Ph
979	Me	$CH(CO_2Et)_2$	2,4,6-Me_3-Ph

980	Me	$C(Et)(CO_2Et)_2$	$2,4,6\text{-}Me_3\text{-}Ph$
981	Me	$CH(Et)CH_2OH$	$2,4,6\text{-}Me_3\text{-}Ph$
982	Me	$CH(Et)CH_2OMe$	$2,4,6\text{-}Me_3\text{-}Ph$
983	Me	$CONMe_2$	$2,4,6\text{-}Me_3\text{-}Ph$
984	Me	$COCH_3$	$2,4,6\text{-}Me_3\text{-}Ph$
985	Me	$CH(OH)CH_3$	$2,4,6\text{-}Me_3\text{-}Ph$
986	Me	C(OH)Ph-3-pyridyl	$2,4,6\text{-}Me_3\text{-}Ph$
987	Me	Ph	$2,4,6\text{-}Me_3\text{-}Ph$
988	Me	2-Ph-Ph	$2,4,6\text{-}Me_3\text{-}Ph$
989	Me	3-pentyl	$2,4,6\text{-}Me_3\text{-}Ph$
990	Me	cyclobutyl	$2,4,6\text{-}Me_3\text{-}Ph$
991	Me	3-pyridyl	$2,4,6\text{-}Me_3\text{-}Ph$
992	Me	$CH(Et)CH_2CONMe_2$	$2,4,6\text{-}Me_3\text{-}Ph$
993	Me	$CH(Et)CH_2CH_2NMe_2$	$2,4,6\text{-}Me_3\text{-}Ph$
994	Me	$NHCH(CH_2OMe)_2$	$2,4\text{-}Me_2\text{-}Ph$
995	Me	$N(CH_2CH_2OMe)_2$	$2,4\text{-}Me_2\text{-}Ph$
996	Me	$NHCH(Et)CH_2OMe$	$2,4\text{-}Me_2\text{-}Ph$
997	Me	NH-3-pentyl	$2,4\text{-}Me_2\text{-}Ph$
998	Me	NEt_2	$2,4\text{-}Me_2\text{-}Ph$
999	Me	$N(CH_2CN)_2$	$2,4\text{-}Me_2\text{-}Ph$
1000	Me	$NHCH(Me)CH_2OMe$	$2,4\text{-}Me_2\text{-}Ph$
1001	Me	$OCH(Et)CH_2OMe$	$2,4\text{-}Me_2\text{-}Ph$
1002	Me	$NPr\text{-}c\text{-}C_3H_5$	$2,4\text{-}Me_2\text{-}Ph$
1003	Me	$NHCH(Me)CH_2NMe_2$	$2,4\text{-}Me_2\text{-}Ph$
1004	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	$2,4\text{-}Me_2\text{-}Ph$
1005	Me	$N(Pr)CH_2CH_2CN$	$2,4\text{-}Me_2\text{-}Ph$
1006	Me	$N(Bu)CH_2CH_2CN$	$2,4\text{-}Me_2\text{-}Ph$
1007	Me	$NHCHPr_2$	$2,4\text{-}Me_2\text{-}Ph$
1008	Me	NEtBu	$2,4\text{-}Me_2\text{-}Ph$
1009	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	$2,4\text{-}Me_2\text{-}Ph$
1010	Me	NH-3-heptyl	$2,4\text{-}Me_2\text{-}Ph$
1011	Me	NEt_2	$2,4\text{-}Me_2\text{-}Ph$
1012	Me	$NHCH(CH_2OEt)_2$	$2,4\text{-}Me_2\text{-}Ph$
1013	Me	NH-3-pentyl	$2,4\text{-}Me_2\text{-}Ph$
1014	Me	NMePh	$2,4\text{-}Me_2\text{-}Ph$
1015	Me	NPr_2	$2,4\text{-}Me_2\text{-}Ph$

	1016	Me	NH-3-hexyl	2,4-Me_2-Ph
	1017	Me	morpholino	2,4-Me_2-Ph
	1018	Me	N(CH_2Ph)CH_2CH_2OMe	2,4-Me_2-Ph
	1019	Me	NHCH(CH_2Ph)CH_2OMe	2,4-Me_2-Ph
5	1020	Me	NH-4-tetrahydropyranyl	2,4-Me_2-Ph
	1021	Me	NH-cyclopentyl	2,4-Me_2-Ph
	1022	Me	NHCH(CH_2OMe)$_2$	2-Me-4-MeO-Ph
	1023	Me	N(CH_2CH_2OMe)$_2$	2-Me-4-MeO-Ph
	1024	Me	NHCH(Et)CH_2OMe	2-Me-4-MeO-Ph
10	1025	Me	N(Pr)CH_2CH_2CN	2-Me-4-MeO-Ph
	1026	Me	OCH(Et)CH_2OMe	2-Me-4-MeO-Ph
	1027	Me	NHCH(CH_2OMe)$_2$	2-Br-4-MeO-Ph
	1028	Me	N(CH_2CH_2OMe)$_2$	2-Br-4-MeO-Ph
	1029	Me	NHCH(Et)CH_2OMe	2-Br-4-MeO-Ph
15	1030	Me	N(Pr)CH_2CH_2CN	2-Br-4-MeO-Ph
	1031	Me	OCH(Et)CH_2OMe	2-Br-4-MeO-Ph
	1032	Me	NHCH(CH_2OMe)$_2$	2-Me-4-NMe_2-Ph
	1033	Me	N(CH_2CH_2OMe)$_2$	2-Me-4-NMe_2-Ph
	1034	Me	NHCH(Et)CH_2OMe	2-Me-4-NMe_2-Ph
20	1035	Me	N(Pr)CH_2CH_2CN	2-Me-4-NMe_2-Ph
	1036	Me	OCH(Et)CH_2OMe	2-Me-4-NMe_2-Ph
	1037	Me	NHCH(CH_2OMe)$_2$	2-Br-4-NMe_2-Ph
	1038	Me	N(CH_2CH_2OMe)$_2$	2-Br-4-NMe_2-Ph
	1039	Me	NHCH(Et)CH_2OMe	2-Br-4-NMe_2-Ph
25	1040	Me	N(Pr)CH_2CH_2CN	2-Br-4-NMe_2-Ph
	1041	Me	OCH(Et)CH_2OMe	2-Br-4-NMe_2-Ph
	1042	Me	NHCH(CH_2OMe)$_2$	2-Br-4-i-Pr-Ph
	1043	Me	N(CH_2CH_2OMe)$_2$	2-Br-4-i-Pr-Ph
	1044	Me	NHCH(Et)CH_2OMe	2-Br-4-i-Pr-Ph
30	1045	Me	N(Pr)CH_2CH_2CN	2-Br-4-i-Pr-Ph
	1046	Me	OCH(Et)CH_2OMe	2-Br-4-i-Pr-Ph
	1047	Me	NHCH(CH_2OMe)$_2$	2-Br-4-Me-Ph
	1048	Me	N(CH_2CH_2OMe)$_2$	2-Br-4-Me-Ph
	1049	Me	NHCH(Et)CH_2OMe	2-Br-4-Me-Ph
35	1050	Me	N(Pr)CH_2CH_2CN	2-Br-4-Me-Ph
	1051	Me	OCH(Et)CH_2OMe	2-Br-4-Me-Ph

1052	Me	$NHCH(CH_2OMe)_2$	2-Me-4-Br-Ph
1053	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-Br-Ph
1054	Me	$NHCH(Et)CH_2OMe$	2-Me-4-Br-Ph
1055	Me	$N(Pr)CH_2CH_2CN$	2-Me-4-Br-Ph
1056	Me	$OCH(Et)CH_2OMe$	2-Me-4-Br-Ph
1057	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph
1058	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph
1059	Me	$NHCH(CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph
1060	Me	$N(CH_2CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph
1061	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
1062	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
1063	Me	$NHCH(CH_2OMe)_2$	2-Br-4-CF_3-Ph
1064	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-CF_3-Ph
1065	Me	$NHCH(CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph
1066	Me	$N(CH_2CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph
1067	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph
1068	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph
1069	Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
1070	Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
1071	Me	$NHCH(CH_2OMe)_2$	4-(COMe)-2-Br-Ph
1072	Me	$N(CH_2CH_2OMe)_2$	4-(COMe)-2-Br-Ph
1073	Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl
1074	Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl
1075	Me	$NHCH(CH_2OMe)_2$	2,4-$(Br)_2$-Ph
1076	Me	$N(CH_2CH_2OMe)_2$	2,4-$(Br)_2$-Ph
1077	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
1078	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
1079	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
1080	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
1081	Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
1082	Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
1083	Me	$NHCH(CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
1084	Me	$N(CH_2CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
1085	Me	$NHCH(CH_2OMe)_2$	2-I-4-i-Pr-Ph
1086	Me	$N(CH_2CH_2OMe)_2$	2-I-4-i-Pr-Ph
1087	Me	$NHCH(CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph

1088	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-N(Me)$_2$-6-MeO-Ph
1089	Me	NEt_2	2-Br-4-MeO-Ph
1090	Me	NH-3-pentyl	2-Br-4-MeO-Ph
1091	Me	$NHCH(CH_2OMe)_2$	2-CN-4-Me-Ph
1092	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,4,6-Me$_3$-Ph
1093	Me	$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-Br-Ph
1094	Me	$NHCH(CH_2OMe)_2$	2,5-Me$_2$-4-MeO-Ph
1095	Me	$N(CH_2CH_2OMe)_2$	2,5-Me$_2$-4-MeO-Ph
1096	Me	NH-3-pentyl	2,5-Me$_2$-4-MeO-Ph
1097	Me	NEt_2	2,5-Me$_2$-4-MeO-Ph
1098	Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MePh
1099	Me	$NCH(Et)CH_2OMe$	2-Cl-4-MePh
1100	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MePh
1101	Me	(S)-$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Cl-4-MePh
1102	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,5-Me$_2$-4-MeOPh
1103	Me	NEt_2	2-Me-4-MeOPh
1104	Me	OEt	2-Me-4-MeOPh
1105	Me	(S)-$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-MeOPh
1106	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2-Me-4-MeOPh
1107	Me	$NHCH(CH_2CH_2OEt)_2$	2-Me-4-MeOPh
1108	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,4-Cl$_2$-Ph
1109	Me	NEt_2	2-Me-4-ClPh
1110	Me	NH-3-pentyl	2-Me-4-ClPh
1111	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-ClPh
1112	Me	$NHCH(CH_2OMe)_2$	2-Me-4-ClPh
1113	Me	NEt_2	2-Me-4-ClPh
1114	Me	NEt_2	2-Cl-4-MePh
1115	Me	NH-3-pentyl	2-Cl-4-MePh
1116	Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MeOPh
1117	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MeOPh
1118	Me	$NHCH(Et)CH_2OMe$	2-Cl-4-MeOPh
1119	Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-Cl-4-MeOPh
1120	Me	NEt_2	2-Cl-4-MeOPh
1121	Me	NH-3-pentyl	2-Cl-4-MeOPh
1123	Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4-MeOPh
1124	Me	$NHCH(Me)CH_2CH_2OMe$	2-Cl-4-MeOPh

1125	Me	NHCH(Et)CH_2CH_2OMe	2-Br-4-MeOPh
1126	Me	NHCH(Me)CH_2CH_2OMe	2-Br-4-MeOPh
1127	Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
1128	Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
1129	Me	NHCH$(CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph
1130	Me	N$(CH_2CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph
1131	Me	NHCH(Et)CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
1132	Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,5-$(MeO)_2$Ph
1133	Me	NEt_2	2-Cl-4,5-$(MeO)_2$Ph
1134	Me	NH-3-pentyl	2-Cl-4,5-$(MeO)_2$Ph
1135	Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
1136	Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
1137	Me	NHCH$(CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
1138	Me	N$(CH_2CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
1139	Me	NHCH(Et)CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
1140	Me	N(c-Pr)CH_2CH_2CN	2-Br-4,5-$(MeO)_2$Ph
1141	Me	NEt_2	2-Br-4,5-$(MeO)_2$Ph
1142	Me	NH-3-pentyl	2-Br-4,5-$(MeO)_2$Ph
1143	Me	NHCH$(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
1144	Me	N$(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
1145	Me	NEt_2	2-Cl-4,6-$(MeO)_2$Ph
1146	Me	NH-3-pentyl	2-Cl-4,6-$(MeO)_2$Ph
1147	Me	NHCH$(CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
1148	Me	N$(CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
1149	Me	NHCH(Et)CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
1150	Me	NEt_2	2-Me-4,6-$(MeO)_2$Ph
1151	Me	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph
1152	Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
1153	Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
1154	Me	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
1155	Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh
1156	Me	NHCH(Et)CH_2OMe	2-MeO-4-MePh
1157	Me	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
1158	Me	NEt_2	2-MeO-4-MePh
1159	Me	NH-3-pentyl	2-MeO-4-MePh
1160	Me	NHCH(Et)CH_2CH_2OMe	2-MeO-4-MePh

1161	Me	NHCH(Me)CH_2CH_2OMe	2-MeO-4-MePh
1162	Me	NHCH($CH_2OMe)_2$	2-MeO-4-MePh
1163	Me	N($CH_2CH_2OMe)_2$	2-MeO-4-MePh
1164	Me	NHCH(Et)CH_2OMe	2-MeO-4-MePh
1165	Me	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
1166	Me	NEt_2	2-MeO-4-MePh
1167	Me	NH-3-pentyl	2-MeO-4-MePh
1168	Me	NHCH($CH_2OMe)_2$	2-MeO-4-ClPh
1169	Me	N($CH_2CH_2OMe)_2$	2-MeO-4-ClPh
1170	Me	NHCH(Et)CH_2OMe	2-MeO-4-ClPh
1171	Me	NEt_2	2-MeO-4-ClPh
1172	Me	NH-3-pentyl	2-MeO-4-ClPh

Utility

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

The following is a description of the isolation of cell membranes containing cloned human CRF-R1 receptors for use in the standard binding assay as well as a description of the assay itself.

Messenger RNA was isolated from human hippocampus. The mRNA was reverse transcribed using oligo (dt) 12-18 and the coding region was amplified by PCR from start to stop codons The resulting PCR fragment was cloned into the EcoRV site of pGEMV, from whence the insert was reclaimed using XhoI + XbaI and cloned into the XhoI + XbaI sites of vector pm3ar (which contains a CMV promoter, the SV40 't' splice and early poly A signals, an Epstein-Barr viral origin of replication, and a

hygromycin selectable marker). The resulting expression vector, called phchCRFR was transfected in 293EBNA cells and cells retaining the episome were selected in the presence of 400 μM hygromycin. Cells surviving 4 weeks of selection in hygromycin were pooled, adapted to growth in suspension and used to generate membranes for the binding assay described below. Individual aliquots containing approximately 1 x 10^8 of the suspended cells were then centrifuged to form a pellet and frozen.

For the binding assay a frozen pellet described above containing 293EBNA cells transfected with hCRFR1 receptors is homogenized in 10 ml of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1 μg/l aprotinin, 1 μg/ml leupeptin and 1 μg/ml pepstatin). The homogenate is centrifuged at 40,000 x g for 12 min and the resulting pellet rehomogenized in 10 ml of tissue buffer. After another centrifugation at 40,000 x g for 12 min, the pellet is resuspended to a protein concentration of 360 μg/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 μl capacity. To each well is added 50 μl of test drug dilutions (final concentration of drugs range from 10^{-10} - 10^{-5} M), 100 μl of ^{125}I-ovine-CRF (^{125}I-o-CRF) (final concentration 150 pM) and 150 μl of the cell homogenate described above. Plates are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

Curves of the inhibition of ^{125}I-o-CRF binding to cell membranes at various dilutions of test drug are 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.

A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF.

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.

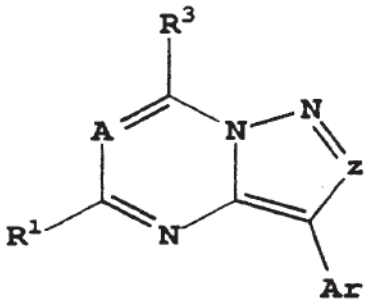
The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

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.

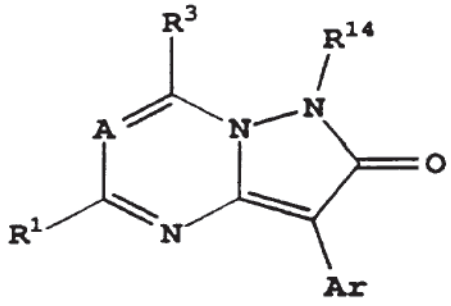
CLAIMS

WHAT IS CLAIMED IS:

1. 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 Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and

pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

A is N or CR;

Z is N or CR^2;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached to an unsaturated carbon atom;

R is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl;

R^1 is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, $-NR^6S(O)_nR^7$, $S(O)_nNR^6R^7$, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is selected from:

-H, OR^7, SH, $S(O)_nR^{13}$, COR^7, CO_2R^7, $OC(O)R^{13}$, NR^8COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^8CO_2R^{13}$, NR^6R^7, $NR^{6a}R^{7a}$, $N(OR^7)R^6$, $CONR^6R^7$, aryl, heteroaryl and heterocyclyl, or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from:

C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, NO_2, halo, CN, C_1-C_4 haloalkyl, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7, R^{6a} and R^{7a} are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-

C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{14} is selected from C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_3-C_8 cycloalkyl, or C_4-C_{12} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, and C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl and C_1-C_6 alkylsulfonyl;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5

substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

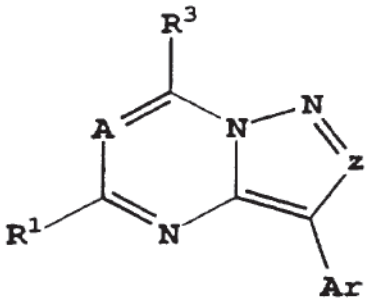
heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2,

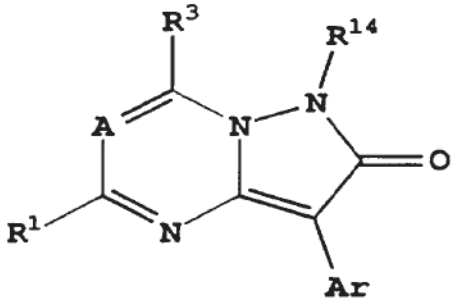
2. A method of claim 1 wherein, in the compound of Formulae (1) or (2), Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

3. A method of claim 1 wherein, in the compound of Formulae (1) or (2), A is N, Z is CR^2, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3, and R^3 is $NR^{6a}R^{7a}$.

4. A compound of Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein:

A is N or CR;

Z is N or CR^2;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached to an unsaturated carbon atom;

R is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl;

R^1 is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

halo, CN, C_1-C_4 haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, $-NR^6S(O)_nR^7$, $S(O)_nNR^6R^7$, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is selected from:

-H, OR^7, SH, $S(O)_nR^{13}$, COR^7, CO_2R^7, $OC(O)R^{13}$, NR^8COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^8CO_2R^{13}$, NR^6R^7, $NR^{6a}R^{7a}$, $N(OR^7)R^6$, $CONR^6R^7$, aryl, heteroaryl and heterocyclyl, or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, NO_2, halo, CN, C_1-C_4 haloalkyl, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7,

or $S(O)_nR^7$, where each such C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R7, R^{6a} and R^{7a} are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{14} is selected from C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_3-C_8 cycloalkyl, or C_4-C_{12} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, and C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl and C_1-C_6 alkylsulfonyl;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano,

OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2,

with the provisos that:

(1) when A is N, Z is CR^2, R^2 is H, R^3 is $-OR^7$ or $-OCOR^{13}$, and R^7 is H, then R^1 is not H, OH or SH;

(2) when A is N, Z is CR^2, R^1 is CH_3 or C_2H_5, R^2 is H, and R^3 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 $N(C_2H_5)_2$, then Ar is not phenyl or m-CH_3-phenyl;

(3) when A is N, Z is CR^2, R^2 is H, and Ar is pyridyl, pyrimidinyl or pyrazinyl, and R^3 is $NR^{6a}R^{7a}$, then R^{6a} and R^{7a} are not H or alkyl;

(4) when A is N, Z is CR^2, and R^2 is $SO_2NR^6R^7$, then R^3 is not OH or SH;

(5) when A is CR and Z is CR^2, then R^2 is not-$NR^6SO_2R^7$ or -$SO_2NR^6R^7$;

(6) when A is N, Z is CR^2 and R^2 is -$NR^6SO_2R^7$ or -$SO_2NR^6R^7$, then R^3 is not OH or SH;

(7) when A is N, Z is CR^2, R^1 is methyl or ethyl, R^2 is H, and R^3 is H, OH, CH_3, C_2H_5, C_6H_5, n-C_3H_7, iso-C_3H_7, SH, SCH_3, $NH(n\text{-}C_4H_9)$, or $N(C_2H_5)_2$, then Ar is not unsubstituted phenyl or m-methylphenyl;

(8) when A is CR, Z is CR^2, R^2 is H, phenyl or alkyl, R^3 is NR^8COR^7 and Ar is phenyl or phenyl substituted with phenylthio, then R^7 is not aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocycly(C_1-C_4 alkyl);

(9) when A is CR, Z is CR^2, R^2 is H or alkyl, Ar is phenyl, and R^3 is SR^{13} or $NR^{6a}R^{7a}$, then R^{13} is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or

(10) when A is CH, Z is CR^2, R^1 is OR^{11}, R^2 is H, R^3 is OR^7, and R^7 and R^{11} are both H, then Ar is not

phenyl, p-Br-phenyl, p-Cl-phenyl, p-$NHCOCH_3$-phenyl, p-CH_3-phenyl, pyridyl or naphthyl;

(11) when A is CH, Z is CR^2, R^2 is H, Ar is unsubstituted phenyl, and R^3 is CH_3, C_2H_5, CF_3 or C_6H_4F, then R_1 is not CF_3 or C_2F_5;

(12) when A is CR, R is H, Z is CR^2, R^2 is OH, and R^1 and R^3 are H, then Ar is not phenyl;

(13) when A is CR, R is H, Z is CR^2, R^2 is OH or NH_2, R^1 and R^3 are CH_3, then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl.

5. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof with the additional provisos that: (1) when A is N, R^1 is H, C_1-C_4 alkyl, halo, CN, C_1-C_{12} hydroxyalkyl, C_1-C_4 alkoxyalkyl or $SO_2(C_1$-C_4 alkyl), R^3 is $NR^{6a}R^{7a}$ and R^{6a} is unsubstituted C_1-C_4 alkyl, then R^{7a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C_3-C_6 cycloalkyl; and (2) A is N, R^1 is H, C_1-C_4 alkyl, halo, CN, C_1-C_{12} hydroxyalkyl, C_1-C_4 alkoxyalkyl or $SO_2(C_1$-C_4 alkyl), R^3 is $NR^{6a}R^{7a}$ and R^{7a} is unsubstituted C_1-C_4 alkyl, then R^{6a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C_3-C_6 cycloalkyl.

6. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

7. A compound of claim 6 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N, Z is CR^2, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3, and R^3 is $NR^{6a}R^{7a}$.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 4.

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

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

11. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N.

12. A compound of Formula (2) of claim 11 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

13. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

14. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

15. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

16. A compound of Formula (1) of claim 11 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2.

17. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

18. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

19. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-; and

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-

C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

20. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, -COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

21. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is selected from:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

22. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15},

CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

23. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

24. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

25. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

26. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

27. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

-C_1-C_4 alkyl, each such C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

28. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

29. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

30. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

31. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents,

-R^3 is $NR^{6a}R^{7a}$ or OR^7 and
-R^1 and R^2 are independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl.

32. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:
-H,
-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,
-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);
R^{7a} is independently selected at each occurrence from:
-H,
-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each

occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

33. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

34. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

-C_1-C_4 alkyl, each such C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

35. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4

haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

36. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

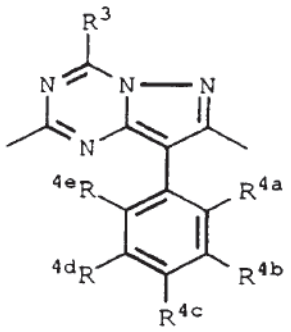
-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

37. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

38. A compound of claim 31 of Formula (50)



FORMULA (50)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, selected from the group consisting of:

a compound of Formula (50) wherein R^3 is $-NHCH(n\text{-}Pr)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)(n\text{-}Bu)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-(n\text{-}Pr)(CH_2cPr)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(n\text{-}Bu)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(Et)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OEt)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(Me)(Ph), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(n-Pr)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)(n-Pr), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -OEt, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CN)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Me)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -OCH(Et)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(n-Pr)(CH_2cPr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Me)($CH_2N(Me)_2$), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(cPr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(n-Bu)(CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2CH_2OMe)(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is morpholino, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NH(c\text{-}Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is CN, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NH(CH_2OMe)(CH_2-iPr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(n-Pr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OEt)(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is NMe2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(CH_2CH_2OMe)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(Et)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(Et)2, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)2, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)2, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NH(Et)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)(CH_2CH_2OH)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2c\text{-}Pr)(n\text{-}Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is CN, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OH)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and

a compound of Formula (50) wherein R^3 is N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H

a compound of Formula (51) wherein R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and

a compound of Formula (51) wherein R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H.

39. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

40. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

41. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein A is CR.

42. A compound of Formula (2) of claim 41 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

43. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

44. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

45. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

46. A compound of Formula (1) of claim 41 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2.

47. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

48. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

49. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

50. A compound of claim 49 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

51. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

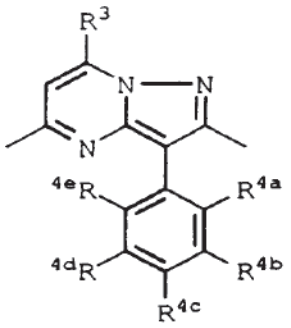
-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents,

-R^3 is $NR^{6a}R^{7a}$ or OR^7 and

-R^1 and R^2 are independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl.

52. A compound of claim 51 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

53. A compound of claim 51 of Formula (51)



FORMULA (51)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:

a compound of Formula (51) wherein R^3 is $-NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(n\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(n\text{-}Bu)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(n-Pr)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NEt_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.

54. A compound of claim 51 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 7-(3-pentylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine.

55. A compound of claim 51 and and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 7-(Diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine.

56. A compound of claim 51 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine.

57. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 4.

58. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 24.

59. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 38.

60. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 39.

61. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 40.

62. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 53.

63. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 54.

64. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 55.

65. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 56.

66. 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

SUBSTITUTE SHEET (RULE 26)

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 claim 4.

67. 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 claim 24.

68. 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

SUBSTITUTE SHEET (RULE 26)

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 claim 38.

69. 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 claim 39.

70. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's

SUBSTITUTE SHEET (RULE 26)

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 claim 40.

71. 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 claim 53.

72. A method of treating affective disorder, anxiety, depression, headache, irritable bowel

SUBSTITUTE SHEET (RULE 26)

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 claim 54.

73. 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 claim 55.

SUBSTITUTE SHEET (RULE 26)

74. 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 claim 56.

SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/13072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 A61K31/505 //(C07D487/04,239:00,231:00), (C07D487/04,251:00,231:00),(C07D487/04,249:00,239:00), (C07D487/04,251:00,249:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 591 528 A (OTSUKA PHARMA CO LTD) 13 April 1994 cited in the application see the whole document ---	1-76
X	EP 0 531 901 A (FUJISAWA PHARMACEUTICAL CO) 17 March 1993 cited in the application see the whole document ---	1-76
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 1997	23. 12. 97

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	Steendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. ɔnal Application No
PCT/US 97/13072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 68, no. 25, 17 June 1968 Columbus, Ohio, US; abstract no. 114635v, TAKAMIZAWA: "7-Haloacylaminopyrazolo(1,5-a)pyrimidines " XP002048048 & JP-A-6716314 see abstract ---	1-76
X	CHEMICAL ABSTRACTS, vol. 67, no. 23, 4 December 1967 Columbus, Ohio, US; abstract no. 108663r, TAKAMIZAWA: "7-Methylaminopyrazolo...." XP002048049 & JP-A-6711753 see abstract ---	1-76
X	CHEMICAL ABSTRACTS, vol. 74, no. 5, 1 February 1971 Columbus, Ohio, US; abstract no. 22872r, TAKAMIZAWA : "7-Aminoalkylaminopyrazolo..." XP002048050 & JP-A-7030335 see abstract ---	1-76
X	DATABASE WPI Section Ch, Week 9142 Derwent Publications Ltd., London, GB; Class B02, AN 91-306726 XP002048051 & JP 03 204 877 A (OTSUKA SEIYAKU KOGYO KK) , 6 September 1991 see abstract ---	1-76
X	US 3 920 652 A (SPRINGER ROBERT H ET AL) 18 November 1975 see the whole document ---	1-76
X	US 3 995 039 A (ROONEY CLARENCE STANLEY ET AL) 30 November 1976 cited in the application see the whole document ---	1-76
X	EP 0 714 898 A (OTSUKA PHARMA CO LTD) 5 June 1996 cited in the application see the whole document --- -/--	1-76

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. ɔnal Application No
PCT/US 97/13072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 503 099 A (OTSUKA PHARMA CO LTD) 16 September 1992 see the whole document ---	1-76
X	DATABASE WPI Section Ch, Week 8618 Derwent Publications Ltd., London, GB; Class B02, AN 86-116678 XP002048052 & JP 61 057 587 A (SHIONOGI & CO LTD) , 24 March 1986 see abstract ---	1-76
A	WO 94 13676 A (PFIZER ;CHEN YUHPYNG L (US)) 23 June 1994 see the whole document ---	1-76
P,A	WO 96 35689 A (NEUROGEN CORP ;YUAN JUN (US); HUTCHISON ALAN (US)) 14 November 1996 see the whole document ---	1-76
E	WO 97 29109 A (JANSSEN PHARMACEUTICA NV ;NEUROCRINE BIOSCIENCES INC (US); CHEN CH) 14 August 1997 see the whole document -----	1-76

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ...nal Application No
PCT/US 97/13072

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0591528 A	13-04-94	AU 651986 B	11-08-94
		AU 8295891 A	17-11-92
		CA 2107479 A	23-10-92
		JP 5070353 A	23-03-93
		WO 9218504 A	29-10-92
EP 0531901 A	17-03-93	AU 2280592 A	11-03-93
		CA 2077732 A	10-03-93
		CN 1070404 A	31-03-93
		HU 65204 A	02-05-94
		JP 7252256 A	03-10-95
		JP 2057962 C	10-06-96
		JP 6287188 A	11-10-94
		JP 7088386 B	27-09-95
		MX 9205145 A	01-04-93
		US 5478827 A	26-12-95
		US 5624931 A	29-04-97
		US 5356897 A	18-10-94
		ZA 9206417 A	15-03-93
		CN 1075965 A	08-09-93
US 3920652 A	18-11-75	AR 193536 A	30-04-73
		AT 330780 B	26-07-76
		BE 786611 A	22-01-73
		BG 19806 A	10-10-75
		DD 99581 A	12-08-73
		DE 2236987 A	01-03-73
		FR 2150771 A	13-04-73
		GB 1359563 A	10-07-74
		LU 65892 A	15-01-73
		NL 7211011 A	20-02-73
		US 4021556 A	03-05-77
		AU 4488372 A	07-03-74
		ZA 7205139 A	25-04-73
US 3995039 A	30-11-76	NONE	
EP 0714898 A	05-06-96	AU 680370 B	24-07-97
		AU 2576595 A	15-01-96
		CA 2169719 A	28-12-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/US 97/13072

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0714898 A		CN 1131948 A	25-09-96
		WO 9535298 A	28-12-95
		JP 8311068 A	26-11-96
		JP 8310951 A	26-11-96
EP 0503099 A	16-09-92	AU 653103 B	15-09-94
		AU 3877593 A	26-08-93
		AU 639615 B	29-07-93
		AU 8626191 A	28-04-92
		CN 1060844 A,B	06-05-92
		WO 9206096 A	16-04-92
		JP 5112571 A	07-05-93
		US 5420128 A	30-05-95
		JP 5000948 A	08-01-93
WO 9413676 A	23-06-94	AU 5666494 A	04-07-94
		CA 2150016 A	23-06-94
		CN 1097758 A	25-01-95
		CZ 9501584 A	17-01-96
		EP 0674641 A	04-10-95
		FI 935585 A	18-06-94
		HU 70505 A	30-10-95
		JP 7509726 T	26-10-95
		NO 952398 A	16-06-95
		NZ 258690 A	29-01-97
		PL 309357 A	02-10-95
		ZA 9309271 A	12-06-95
WO 9635689 A	14-11-96	US 5644057 A	01-07-97
		AU 5679096 A	29-11-96
		CA 2194756 A	14-11-96
		EP 0770080 A	02-05-97
WO 9729109 A	14-08-97	AU 1599197 A	28-08-97

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 #
18/307,718	**05/10/2023 06:23:48 PM ET**	**50535-709.307**

Title of Invention

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9067	FILED BY	Caitlin Newland
PATENT CENTER #	62071239	FILING DATE	-
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Stephen Olshemski

Documents

TOTAL DOCUMENTS: 83

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
IDS_50535-709_307_05-10-2023.pdf		16	-	298 KB
IDS_50535-709_307_05-10-2023-TRAN.LET.pdf	(1-4)	4	Transmittal Letter	147 KB
IDS_50535-709_307_05-10-2023-IDS.pdf	(5-16)	12	Information Disclosure Statement (IDS) Form (SB08)	236 KB
FOR_JP2000302693A_EFS.pdf		14	Foreign Reference	703 KB
FOR_JP2000503661A_ENG_MACH_TRANSL.pdf		13	Foreign Reference	960 KB

FOR_EP2094709B1_EFS.pdf	38	Foreign Reference	1917 KB
FOR_WO2022036123A1_EFS.pdf	51	Foreign Reference	2482 KB
FOR_JP2012504626A_ENG_MACH_TRANSL.pdf	7	Foreign Reference	420 KB
FOR_JP2008533201A_ENG_MACH_TRANSL.pdf	46	Foreign Reference	2173 KB
FOR_JP2002513382A.pdf	31	Foreign Reference	4623 KB
FOR_JP2010504344A_EFS.pdf	32	Foreign Reference	5381 KB
FOR_WO0059908A2_EFS.pdf	118	Foreign Reference	3758 KB
FOR_WO02072202A1_EFS.pdf	56	Foreign Reference	1731 KB
FOR_JP2002501922A_ENG_MACH_TRANSL.pdf	44	Foreign Reference	5432 KB
FOR_WO9413676A1_EFS.pdf	66	Foreign Reference	2768 KB
FOR_WO0123388A2_EFS.pdf	102	Foreign Reference	4008 KB
FOR_WO9729109A1_EFS.pdf	44	Foreign Reference	1877 KB
FOR_WO9808847A1_EFS.pdf	62	Foreign Reference	2326 KB
FOR_WO2010039678A1_EFS.pdf	24	Foreign Reference	695 KB

FOR_WO2005063755A1_EFS.pdf	86	Foreign Reference	2668 KB
FOR_WO2008036579A1_EFS.pdf	60	Foreign Reference	2467 KB
FOR_WO2015112642A1_EFS.pdf	50	Foreign Reference	1718 KB
FOR_WO9803510A1_EFS.pdf	225	Foreign Reference	6901 KB
FOR_WO2019036472A1_EFS.pdf	64	Foreign Reference	3373 KB
NPL_US16639540_OA_16NOV2021.pdf	4	Non Patent Literature	160 KB
NPL_US16388620_OA_25Nov2019.pdf	9	Non Patent Literature	316 KB
FOR_WO2019036503A1_EFS.pdf	78	Foreign Reference	4057 KB
NPL_US16639540-OA-07-11-2022.pdf	9	Non Patent Literature	508 KB
FOR_WO2021016208A1_EFS.pdf	70	Foreign Reference	3692 KB
NPL_US17063592_OA_7DEC2021.pdf	13	Non Patent Literature	461 KB
FOR_WO2006102194A1_EFS.pdf	205	Foreign Reference	8462 KB
NPL_US17078054_OA_14DEC2020.pdf	13	Non Patent Literature	469 KB
NPL_US17359414_OA_16N	14	Non Patent Literature	470 KB

OV2021.pdf			
NPL_US17359411_OA_6JAN2022.pdf	17	Non Patent Literature	582 KB
NPL_US17586228-OA-06-10-22.pdf	16	Non Patent Literature	533 KB
NPL_Varma_Excipientsusedinthe_2016.pdf	12	Non Patent Literature	134 KB
NPL_WO-03-20-2009-PCT-US2007-078605.pdf	8	Non Patent Literature	761 KB
NPL_WO-04-02-2011-PCT-US2009-058722.pdf	6	Non Patent Literature	600 KB
NPL_ZHANG_D-LevelEssay_2009.pdf	18	Non Patent Literature	992 KB
NPL_US17720074.pdf	59	Non Patent Literature	2681 KB
NPL_DO-A-GENERAL-METHOD-COPPER-CATALYZED-15185-15192-2008.pdf	48	Non Patent Literature	1800 KB
NPL_DO-COPPER-CATALYZED-ARYLATION-2008-1128-1129.pdf	7	Non Patent Literature	288 KB
FOR_JP2017503030A_EFS.pdf	52	Foreign Reference	20122 KB
NPL_DO-COPPER-CATALYZED-ARYLATION-HETEROCYCLE-12404-12405.pdf	7	Non Patent Literature	263 KB
NPL_EP18846043-ESR-02-	11	Non Patent Literature	499 KB

10-21.pdf			
NPL_ESCOBAR-MORREALE-Polycystic-ovary-270-284.pdf	15	Non Patent Literature	828 KB
NPL_DAVE_Overviewofpharmaceutical_2008.pdf	52	Non Patent Literature	5745 KB
NPL_Fuqua_DurationofSuppression_712549.pdf	8	Non Patent Literature	431 KB
NPL_Gennaro.pdf	4	Non Patent Literature	154 KB
NPL_Gehlert_JournalofNeuroscience_2718-2726.pdf	9	Non Patent Literature	793 KB
NPL_GILLIGAN-DISCOVERY-181-189.pdf	9	Non Patent Literature	135 KB
NPL_Hodgetts_DiscoveryofN-1_4187-4206.pdf	20	Non Patent Literature	1652 KB
NPL_US18078649.pdf	81	Non Patent Literature	12319 KB
NPL_ISR-04-08-2010-PCT-US2009-058722.pdf	3	Non Patent Literature	279 KB
NPL_ESR-12-22-2020-EP18846689-0.pdf	7	Non Patent Literature	5716 KB
NPL_ISR-WO-02-20-2023-PCT-US2022-050436.pdf	15	Non Patent Literature	266 KB
NPL_KHADILKAR-Can-polycystic-297-302.pdf	6	Non Patent Literature	713 KB
NPL_Lee-Attenuatedforms_866-871.pdf	6	Non Patent Literature	908 KB

NPL_MAJO-FACILE-PALLADIUM-620.pdf	5	Non Patent Literature	131 KB
NPL_ISR-WO-11-25-2020-PCT-US2020-042820.pdf	10	Non Patent Literature	1515 KB
NPL_CHEN-DESIGN-4787-4798.pdf	12	Non Patent Literature	16642 KB
NPL_HE-4-1-3-DIMETHOXYPROP-449-456.pdf	8	Non Patent Literature	8654 KB
NPL_MALVERN-BASIC-GUIDE-PARTICLE-CHARACTERIZATION-2012.pdf	26	Non Patent Literature	4968 KB
NPL_Bornstein_DiagnosisandTreatment_364-389.pdf	26	Non Patent Literature	18340 KB
NPL_NOA-03-09-2021-US17078054.pdf	5	Non Patent Literature	7369 KB
NPL_NOA-04-04-2022-US17359411.pdf	3	Non Patent Literature	2409 KB
NPL_NOA-03-04-2022-US17359414.pdf	8	Non Patent Literature	9145 KB
NPL_NOA-04-28-2022-US17359411.pdf	3	Non Patent Literature	2374 KB
NPL_NOA-03-25-2022-US17063592.pdf	7	Non Patent Literature	8638 KB
NPL_NOA-03-22-2022-US17359411.pdf	7	Non Patent Literature	8854 KB
NPL_PCT-US2021-045780-	9	Non Patent Literature	400 KB

ISRWO-17Dec2021.pdf			
NPL_NOA-03-28-2023-US17720074.pdf	7	Non Patent Literature	8863 KB
NPL_O-REILLY-11-oxygenated-840-848.pdf	9	Non Patent Literature	936 KB
NPL_PCTUS2018046707_ISRWO.pdf	8	Non Patent Literature	393 KB
NPL_PCTUS2018046760_ISRWO_24OCT2018.pdf	12	Non Patent Literature	1153 KB
NPL_ROSENFIELD-The-pathogenesis-467-520.pdf	54	Non Patent Literature	1250 KB
NPL_SARAFOGLOU-TILDACERFONT-IN-ADULTS-4666-4679.pdf	22	Non Patent Literature	869 KB
NPL_OA-08-26-2022-US17720074.pdf	9	Non Patent Literature	6808 KB
NPL_THAKRAL_SaltDisproportionationin_4141-4151.pdf	11	Non Patent Literature	1289 KB
NPL_Turcu_Signledosestudy_1174-1180.pdf	7	Non Patent Literature	1066 KB
NPL_NOA-05-27-2011-US12377733.pdf	9	Non Patent Literature	9306 KB
NPL_US16388620_OA_15July2019.pdf	8	Non Patent Literature	262 KB
NPL_NOA-09-30-2020-US16388620.pdf	7	Non Patent Literature	8959 KB
NPL_US18-310463.pdf	60	Non Patent Literature	8542 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
IDS_50535-709_307_05-10-2023.pdf	B076677B56C331CA1BDB82799941DDCA7D928B2142C6FE32ECC30DFBFBBC2B8BCC3E971957293F3198644ECEC4DFE51E71C420CCAAAC5478A3AB0D7E92DF4502
IDS_50535-709_307_05-10-2023-TRAN.LET.pdf	6C8621C5B368A4AF84CC21DF2A10A491A7807BBEDAADCFB345670B94663174FE414AB17F948FA8C35AE1081A0044752E214B98B1C5CF167080F8838F170618B9
IDS_50535-709_307_05-10-2023-IDS.pdf	9466EF92F5CEE70BC2E4A95AAE375399B310504D8464C97B11746A486D68FB6F73E43C5F39789BA5F0E730C6DADDF1EFC53B14D8BBA62182CB64CF207B2F497F
FOR_JP2000302693A_EFS.pdf	17CA02BFD75626DF9722FA274C06182C23E6C396D8BC858D3292AA182E51F0B650E88CABDD048607AD29E2D7D01A1A45A81C415C412FFAF70CC01B59DDA9387D
FOR_JP2000503661A_ENG_MACH_TRANSL.pdf	D590F368FE0D09DFDAE9993767F94F7718A8C2D83BE5B42B7F7F3A75AFD03674FD82B0BC4D590CE96616526A38B58446843ABAF0943152736CCF5698C04DE342
FOR_EP2094709B1_EFS.pdf	49AD77ABE98D09ED13470AAB516EE6FAFCF28AB986CB6B6FF826CBB7BF1F7D7DFB333886082E5F1AE045D4FAE37A7F625C7ACFBE78F9674BA234E97059E05F28
FOR_WO2022036123A1_EFS.pdf	AF164B6FFA2B010656B54A4A891311CAF5751D6F8CFEE036400F34E0CEA2FEA4CEADC9E7B0AFA840B9325700848813DB9DE999028A611CF7B68BE1E11612DCFC
FOR_JP2012504626A_ENG_MACH_TRANSL.pdf	90E7F56ED879ECAC18DA86E6DCD0485914550F354DB18185313BA2F640AFC1EFE2D37EE43B48FA097F0040C06BBA49E43ED23CB125BC0C6BE0B153A9B6A69E03
FOR_JP2008533201A_ENG_MACH_TRANSL.pdf	8EC204231E5E9BE7C2E97F95A168EA6A772C986DB92DA1AB0702D80B80666B3951F7EAE9A8E097860A94DE2C8E09282560A93DC6136181D0C9883C18A8A8BE6C

FOR_JP2002513382A.pdf	A80E3561E75D239069C8E239B92E5D162C5EBAC9EB5E375EB E5F4A12CE2C88C7E3690BA117077B9C9AA1B425F7626A09CA 0E5AA682C0A0DA898A0831EC51CA97
FOR_JP2010504344A_EFS.pdf	DC0666839B2BB8C39A298273CCC01593AEB32B377FDCB5C9 49F6B5DDBEB2561B5A30BC74552A1F540AC926276D43234DB EE940ECA5BE5A89244936582F7000EA
FOR_WO0059908A2_EFS.pdf	195662FF7C7820D70AB1E031EEB9BAE09890633DE729A2AA4 E0FA3D2683FE3F58E494C1160C8F92B7A200962D5DAF52AB0 BAFB3A5653B1A7FDAE05E1F7C7DB93
FOR_WO02072202A1_EFS.pdf	93EDB8711526F937C1D0BF3762EBC767213004E9616517F3B2 C2F77A3117F1524AAFAC2A87E462797408C576F2B25BDAA48 C850A822C8010A138650CE1D7B531
FOR_JP2002501922A_ENG_MACH_TRANSL.pdf	F77FA88C019DE12E9C6154784FC3F491D65FE82E1985B835B4 FA504F902500232970A9DF0C521097E0A14731A5A5012194658 FFE14D2A33DD816C99D531C7962
FOR_WO9413676A1_EFS.pdf	45C523F505033DA20F1F3C1B7B532B55D77EA50F615F3293D1 C29C031326BA6ADC4F5944112DF1B4B2F0C14F173331E4F20 B51983179552AFBC2197BC6BE477B
FOR_WO0123388A2_EFS.pdf	AE9E85E19968EF8EBB32560A861DA73E0F1865B84CAFB9498 2731AF96542B4F8235C7983085C6B6FBE772AD2E712DB006A7 5C03427D1A0C8F684932682FB480F
FOR_WO9729109A1_EFS.pdf	54040854B0614CC8D9B7FF5FD07B72194E906E35883CA31A4 D0D0BC46B3D74D8EBDB0D9D1D111A8F1C26E3B799565DD74 D9D376EF4D18A1DFB5ED4AA6831D8DB
FOR_WO9808847A1_EFS.pdf	D075EBAA89876E646552B832699223FCB621E5036AB566DC19 DCEBDBD0576C622418F0D3703E3039143851C796D146B627E 70F111C3304E1E306044C92956EF5
FOR_WO2010039678A1_EFS.pdf	EDBD2530FFA7DAC52253F42B16FD66E194BF1E3BB72BDBC1 4CEB93AB9088D399F720AF252436F3CBBC9A087A5FCFA1EC D75C500AF82076FD1F7A868A8560165F

FOR_WO2005063755A1_EFS.pdf	80111ECCB9945636435A5BD276FBC87A68CB9192FD3968F1243CB71E26CACEA8180A33FE5D79DF32589FAD06845D4CD55F710F932F37D42872153E1FFD545B03
FOR_WO2008036579A1_EFS.pdf	4FF01A21135811282E9F25F5D8FAC7BB1E77FEA8783F9C364EE8A788EAAD3A07B735E0C0AEF06E517B28A370F9469A14D03A044E66610E076E3CA1A2208D107B
FOR_WO2015112642A1_EFS.pdf	A55EFF1D161A2ADEA8BB1DA46AE9CEE32474E7E2C4871D9C46394219E78E04A5F9D96BBAA45A5E4465B92A07B3F13CD9C1BDEF8096E0A9173A539385ED8BE4FC
FOR_WO9803510A1_EFS.pdf	2ECE8F336F946ACB461225998028B8FB6748DCBDDE8F092E7B133C02200C93679930F179C7C262CD296D47CB31DD409B9CEBC88757B06D6321C5B766AA51D2B2
FOR_WO2019036472A1_EFS.pdf	5710AF7DA13BB41769F63E18C559470BC69D13E48BB52EA12546306530D8BBF95117920 2C01AF5641C2700A8B3F8FBDF32BD019F651311133BB93A0076E8FF19
NPL_US16639540_OA_16NOV2021.pdf	A214FBC391C987EEB90F0D198CB1DA0BA4627D1C49F0C4442C9911FA1E433DEEE4F3982865F6308B56D16A913CABAECC0BB76A4D2B8DE24E4C6708E5C1C3E7E7
NPL_US16388620_OA_25Nov2019.pdf	D95829824895C5C2D237779F371BB49C55D059A0207B45D24E8CEE27D4FF27C9BB347663BE6698331CADBF31E0602BB3244FAC1D000AB8C70E8F6504F899822C
FOR_WO2019036503A1_EFS.pdf	7AAE80F99D4332954550F25CBC3E4C9110161D3779CBEBC683DED4BD81A679C4349027C00C9738EB7A949176277DA2BDE001085E9EE8C83E883755C8CF85829
NPL_US16639540-OA-07-11-2022.pdf	855A686ED6842CA0B64FCE8C8F9F91A2F9D56600D313969A21161CB214D76275EBB2F4A7B5D734683AEA9E99A1C91056280AF8EB967ECEA6F9D98090C38A0FB7
FOR_WO2021016208A1_EFS.pdf	9A24D080452744C904C5C7875F75F051BE599EDDB27143F50D0A9FB4099B0320E5FADC4E7316F1B16068252D229B1F3208BC6B09013BAEA41E3421C26D2A8366

NPL_US17063592_OA_7DEC2021.pdf	54CF3C1FE30A64186BF15FF63AFB15389AB46AF20C8783481F1FEC04267DF42692CF95DDBEA429D3323053629F8BB08FE2487FC935710A48E66C2BB3784897F1
FOR_WO2006102194A1_EFS.pdf	7CEBE207BF375A884A19C09384E90E9E8A09D58963C163E1497BF51D4832C5850198E7EA306385F56B49C6BBD9222873F0FDEB81A4FA54F351099A548BA774F8
NPL_US17078054_OA_14DEC2020.pdf	0FA72606EF4481C05B20DA645D00A397C691411336C1D5F1235A38CFCB604E04019BB77819BB176479C404A29FD11773B11D4E4D142A820B1AC86F56217F73B2
NPL_US17359414_OA_16NOV2021.pdf	D247B135C2C9CA565371B3BDE31C8094025DC2C6E511DAEC5E782799960126E3A5FDD581B196F295EEA2C6122AEE7672B9097BA9F1F25A76A9AF8DBE93551BD1
NPL_US17359411_OA_6JAN2022.pdf	8C118934D77D26B1F50483E17328A299F5A63E98AF3405851A23D76FF89AE502AACFADA332717CF0293B7ED8F18BDFB7010CA61A7E633ED8FD19EFB53E3654C2
NPL_US17586228-OA-06-10-22.pdf	DF75840EBE9D2B7C24393E20FB058D1401D4DBC262A6A5DFB94458D008171C14479A69EED38E6CBB679C3A096319A65000AF940B37120D0D3D3CFD9671486FC8
NPL_Varma_Excipientsusedinthe_2016.pdf	CB254E459D2440D2308A73E36E5702675C384D696F5FB585F0B59F28E2278499B70667F6A2E87FF54AD8545BB8EE289BD6392D86B6AA00968723958AA9ADC17B
NPL_WO-03-20-2009-PCT-US2007-078605.pdf	B951083ED2F86EF3E6C5DFC848B4D0CB700D58243304FAECF3E85BB9CC30595C529669060AE5F4E099EA90588CEC07D0544B9EEA2847C13DB7024F12CCB82CCE
NPL_WO-04-02-2011-PCT-US2009-058722.pdf	F0A7BA3FAEB7667074E74283125A2682CE2DFBE042AFA1A663194B5395095F01BC3C5645C1FF83E8CBE20BC401D0D1DE927B0FA7DE320BFBCDFF72864ED90383
NPL_ZHANG_D-LevelEssay_2009.pdf	B58D2231ACF3514985D7E15E41DC44218D1F7084726E301BD916F6A269B7D07A6C253288F532749E6FFE365BCE8FE7E11FB95851D91BFBE04867C6DB59F77AE6

NPL_US17720074.pdf	C00F6C2088CBD511ECF15C1B427581DC0010801AA0526F5F268A462FF20E8BC264BA835D85ABA37B9ADCB5A0EF7E37A1B5112074B558C39475620D9CD932E3E1
NPL_DO-A-GENERAL-METHOD-COPPER-CATALYZED-15185-15192-2008.pdf	2338D068E04EC6490A2B4EB365008D3137EA0D013649788DF53C964F17626E4971C5CB952D2658A1D73565C2B119433A53B7121DCFB565F15A16122FBD293107
NPL_DO-COPPER-CATALYZED-ARYLATION-2008-1128-1129.pdf	34B180F33359EEBF187DA124F9099D724129F62C633010503C4DCE9AE0A9001CBCA3FF7DFA30BD071BF3501A289D9EFF2BE93D186FB17E7EF5A96C6AFCE1C3C4
FOR_JP2017503030A_EFS.pdf	0AA3814BAFDD9492B58E9614A949FF9F0FD6EF907437FEA43049B2D484846571FF8EDC3B82D3F30D981ED548F214D182AE38E74A84821B14EB5AA50F1E02B5F1
NPL_DO-COPPER-CATALYZED-ARYLATION-HETEROCYCLE-12404-12405.pdf	D31AA539CCBD26CBDA37AB4A290D61F4E4A8289930317F47DF7D4439225B2E55B2A3139EAB3E4F66364E243C6B3BF664551AAA14819C43E0144D7C38051F6F57
NPL_EP18846043-ESR-02-10-21.pdf	45AA5FF6668F42FEDCCDB3C15E50D3E014234CA7E811EA24AD0FA68ADA540B1E8A6B5E025143BC26B9D32BABA30C9257CDAD13BEDEA8E866F67A7D4E14010628
NPL_ESCOBAR-MORREALE-Polycystic-ovary-270-284.pdf	F009F7E538CB6348DF1D63F8FD8D869EE62A3DF95987AEAC4CE98FA726AFB5A683FE7022FA3D2429776A645866178F99C0C00E4A034A0497A333EFC4E320278C
NPL_DAVE_Overviewofpharmaceutical_2008.pdf	8F0D0FCE13993D9E3201CA27B60C2CD51399D26C0EEE33E7035E10B2521E65A39825B79B433DA690FC7458458F912AFB1A9ACEE66711775A90C9800590F27056
NPL_Fuqua_DurationofSuppression_712549.pdf	64228387F8C1180CF2AFA6C9FAEE82FCA1BF57002B1701405D6230E0C29374798EB1DBC4A0B6C3F1A1D27DEA84ED1A17148C5B4E7976500ADA9210A32CE16649
NPL_Gennaro.pdf	01A486C9361677812887C0295698056E393CE0AD472FBEBF58B9A99DBBCA93830F5847F8930D9A685E581C2261950FB5B5907E7DE728C0DA8ABC8F37FD9E3163

NPL_Gehlert_JournalofNeuroscience_2718-2726.pdf	E7998E735B29EAAA3A115C18D753875F168D8E5184A31B9CC75F0FFA42729BC570397D22AA9458DB993C0E520A228C545A1DBBF09E4118D6C593257AFCFAB921
NPL_GILLIGAN-DISCOVERY-181-189.pdf	C8A45BF69C47F6B7D061B54460A1D34B2779C807A0777469ADFC377B353C2AB2A21A4FEC381003BD40C7BF63C78AB1E0B04E5E445605E6B597C9227BEF230F00
NPL_Hodgetts_DiscoveryofN-1_4187-4206.pdf	D3703A3063B1FAC7E4D90750987F273859CDDB03809F56F342DEE5126DDF9599B4EDA5CCF663D00BC4AC00CC791E74C27E83ADDC99C0F9587F631825DFA6580E
NPL_US18078649.pdf	4B2E1ADB75010E15156D29D5AF45134BABE9B9296E570A90B19901D867ADC65DBA1E4CC3AE4278AD3BCE4FD05A425D9094BD7B4D5589870C537102CA879552BC
NPL_ISR-04-08-2010-PCT-US2009-058722.pdf	DF5D07B638EDCDDDBC8D17E9CC84872C7ECBA837FFC15FAABFD00D8936ADA3E60EB0467A7435DF4420B351D283ABE13C2DF6A232A57657CBE342D112D05E63A4
NPL_ESR-12-22-2020-EP18846689-0.pdf	446A2000A5AB2DBB317B1D0769CC72DD62BA2DDE6FEC4FF43EFC47A4BA833E47B222985AE85BE3C67F964018E885A5BDB2113A8DAFF3CD01767B7BF4C293908F
NPL_ISR-WO-02-20-2023-PCT-US2022-050436.pdf	3AD67FA1F4F04C5E190A6D9C4CEDE38615077867E49B8AB0CE1372A8343ABB87DFA4529BCF456827780E10163260C027F3F58E99DDA04A77550C7F468E20BAB2
NPL_KHADILKAR-Can-polycystic-297-302.pdf	5B0D4479ED0EAAA9ED3285DCC2481CE11E7A7E56F93CCCEA0C4822DDF3E249D6F50F544A0B0FB6A725FB8BC6B10DE39D91495C32B98A7513E101A3B96334C0F1
NPL_Lee-Attenuatedforms_866-871.pdf	2A02348744CAD8C3359CE6E7939E8398788C1B3A7B36A83A1745F120B5691C4800A25E69FA4CEA615B40600FF904A5D5C710B00E90D9D13B1D6FCD923AF9A9A6
NPL_MAJO-FACILE-PALLADIUM-620.pdf	48D129B9D55077603785EEDC4C56B47F4D04305A9A281D96933226A71469BAC8DAAEA68F8B697CEBA03063FE314B4CE69E5B992F0C29AD5284FFE68510F408B1

NPL_ISR-WO-11-25-2020-PCT-US2020-042820.pdf	7ECD72FDDAC3B422A12DB88306989D2B4CD34B518EBA15E2F79DC767EFF6C42699DD775CF6857223D835B114624D7C28BF23632BDAD79CAD9E427EE0C3E3CC1D
NPL_CHEN-DESIGN-4787-4798.pdf	EC0279C249BD9643BC82E493CE48CE0E0FFFD4F579FBF451AA901786A963E756D828E3351277CEA9D13676228992571695290180DE3EEE0D546340AA4B73959E
NPL_HE-4-1-3-DIMETHOXYPROP-449-456.pdf	CA45957E558182D346B4522EC0CA4C8962119C596857A346C1CF5208DE2DAAFD392478333ADA4DA5BD5F7E01A3A6A2866976C1CA74DD1FC313380F5A5D28B2D0
NPL_MALVERN-BASIC-GUIDE-PARTICLE-CHARACTERIZATION-2012.pdf	ABCD942C772A779A7A59C033593638D6EA9DC9D6B041976359CB5DD1E149FBE157205D42299C9E51BB7D7421943C6F2392BF9D820EC72DB903E8DD58A073A233
NPL_Bornstein_DiagnosisandTreatment_364-389.pdf	F9D532C427920C527929A0256EE2E25F6F3A9268E8E236FB4D27DD83E8C9CDEE66EAFEAA8468E1ECD21ECBF98A0A37AAEF646F01272FF6AF224ECEA71909CCB1
NPL_NOA-03-09-2021-US17078054.pdf	1EFAC3F09B291A173D70E55FBE956EBFF2598403EF12EBCD224A8A11FC235390D815F441A0F1D13EE91AC81225F0894C874347285C0766BFB9EEA5E17FA4934A
NPL_NOA-04-04-2022-US17359411.pdf	E85C9C56E7EB2A068F99AE2135E57499D5AC596A192CAE43D4492100CB90405F91F760D582795B600DC35FF34712A8F6627E2FD905EF5DEB8DA966E47D0E7E8E
NPL_NOA-03-04-2022-US17359414.pdf	6BC4E00055F2912F184BD7DFC1D15AE08CB2E7B976B82576D4448CF7B581D1834A9E6E2A08309D4A6550B7B3CB3FAB5B32A1460996CC0238295B1E4106F11F21
NPL_NOA-04-28-2022-US17359411.pdf	55968F2D94FAF6A1B351614BA1BACD1B0F59A76826D3613D848D01E2CD62CCC2CF392812DCF98710C08393EC1C05140F16A4A6227B2C9EA5367137C0B112AFA7
NPL_NOA-03-25-2022-US17063592.pdf	1AEFC187A6590D2A1B3ABCB4CA3538F32006C0308ED1FD6F2B47EE00B16811C9A69E12FA31CC82A627C9EEE4ACE37DA2180F8E668E7A7CA513A5EE5C5929BB58

NPL_NOA-03-22-2022-US17359411.pdf	4E3C7E413987F10CE91BA6AC6FB3A3723B16BB61E11A9076D6F7B334B662256E79072BEE5B0F64980AACD07641D3C75E928F367BBF5BE91E2FF9525830485DB4
NPL_PCT-US2021-045780-ISRWO-17Dec2021.pdf	D2C0F8F4DFDBD698E288F56A751DC1D1302C1BB22513FA50C3436F604F04C65506B74CD8346A7064F811696297378F2DE09387EBE62394776783A56C98BD35B9
NPL_NOA-03-28-2023-US17720074.pdf	3E6F5AC1859317C04A5D52BFDF698B35F7D424C1812AE5261F35F5144F9583CEF770B2F97C65A9019D7D75F2E7A73E52F3055B0E0ABD777E35C7048B1F8E9387
NPL_O-REILLY-11-oxygenated-840-848.pdf	20F629306F60692FBA58CC6A774C3A3B66E426E3AF464B503BF3FE155ECD460656C96CF1095F99366351B87AC1D561594DE4CB889F1BB481F30128AAB5685E85
NPL_PCTUS2018046707_ISRWO.pdf	B5364FCA9EB925081F89F43B9A6E4A53F1ABE1CECF2FE37A5967FF589ACEFCEF1CB0C88C8A9B14DF2701D2B2C62BF993B51CE127C7BE3182EFD4B6C56840DD4E
NPL_PCTUS2018046760_ISRWO_24OCT2018.pdf	921CA3E6F66AAF40BC7CE3534535582C47174503944935EE5CDF82B800F4B6D8652ADD07C1A15C0D98C9304E6EB329628EE3CBFC2EFA1BAEC5504760A8C1E2E1
NPL_ROSENFIELD-The-pathogenesis-467-520.pdf	F7DCF7F46D5D87B4FD00F6CA2E736C4C0B372FA10DB9568EAB4C9418D2A93AEC2B27CC92117A5532665E865D759A5F5C0D21C1F5AF53AC22E00A67BC62CE6B0E
NPL_SARAFOGLOU-TILDACERFONT-IN-ADULTS-4666-4679.pdf	7C62E4A9CEC14A77CF49AD2975D6018F760AD3AB5DC874528DF763D31C387BD0E74919D28DD1323790E0D333760EF1A705002919CF92A7A1A695FCAFCC28F3EE
NPL_OA-08-26-2022-US17720074.pdf	7BB9B5D2E8D3BDE0B9CEFB30572C75B0C42AA8E2E6C4CDF55AC16D970022E7CA2A6875FF95E038043BE6EE0AD2FD614782663A63E0F3E360D65CB621348ADA6B
NPL_THAKRAL_SaltDisproportionationin_4141-4151.pdf	22B9E2C369129C08859ADC1C10467227419973B4E70E739B9A274CA920296849A13CE5099851E5FD2DAEC57FA7BD30B2910BD2DA7789A304A768EC1C811176DD

NPL_Turcu_Signledosestudy_1174-1180.pdf	1588E6A9F50112CF3D92F3EB0798C963CA03DED28504132E86980C9B15BC302A4471373C0A9AD8CCEB50E853022293B9822FC88703BA4552928A1B19A9CEF573
NPL_NOA-05-27-2011-US12377733.pdf	899D787DD6AD4EBA463A55FD4D1586BE49CA6577D7E7518A3E8C6987877783A65F109853BE3C1E43A3FCAEE51D6A3044D342CB9D454F9944B1C209C38E9446DE
NPL_US16388620_OA_15July2019.pdf	9B3FBC139242CEF752798434CA085BE15B2B19556E08D80610C1D6CEDDFD9D4FAB9754DD15CBC0A128A54090BF9D90AD066A159A83B3F96E06BD373DDF254ABC
NPL_NOA-09-30-2020-US16388620.pdf	2C4A4054799DE05A0D1A8EF3C508F15D44AA7B5AA50EF2F3D1343EDADE1A24AC8AB2834DE484EB81F629300600D580C43AC5C84C7920075653CE317FF97A06D2
NPL_US18-310463.pdf	C651F2BE24F0A9E4CE80925AF669340346BEA7DD759FF386F0AA15558368C2E39970850C452641A021C123A12703F2B0DC63435BBD39F816D3BB42DC8F82DCCF

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.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 February 2019 (21.02.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/036472 A1

(51) International Patent Classification:
C07D 471/04 (2006.01)

(21) International Application Number:
PCT/US2018/046707

(22) International Filing Date:
14 August 2018 (14.08.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/545,393 14 August 2017 (14.08.2017) US

(71) Applicant: **SPRUCE BIOSCIENCES, INC.** [US/US]; 548 Market Street, Suite 74589, San Francisco, CA 94105 (US).

(72) Inventors: **HOWERTON, Alexis**; 548 Market Street, Suite 74589, San Francisco, CA 94105 (US). **GERBER, Hal**; 548 Market Street, Suite 74589, San Francisco, CA 94105 (US). **KARABORNI, Sami**; 548 Market Street, Suite 74589, San Francisco, CA 94105 (US).

(74) Agent: **DELANEY, Simren**; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA 94304 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

WO 2019/036472 A1

(54) Title: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

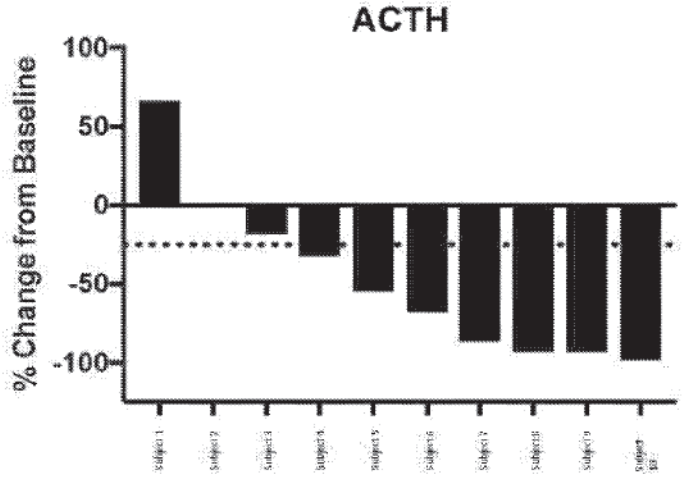


FIG. 2

(57) Abstract: The present invention provides novel pharmaceutical compositions comprising 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5- a)pyrimidine and methods of using the same for the treatment of Congenital adrenal hyperplasia (CAH).

[Continued on next page]

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

CROSS-REFERENCE

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/545,393, filed August 14, 2017, which is incorporated herein by reference in its entirety.

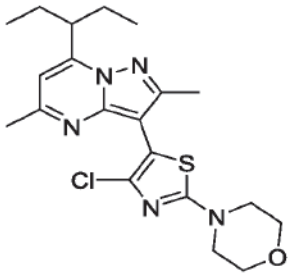
BACKGROUND OF THE INVENTION

[0002] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

SUMMARY OF THE INVENTION

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

[0004] In one aspect, the present disclosure provides a pharmaceutical composition in the form of a capsule comprising Compound 1:



or a pharmaceutically acceptable salt or solvate thereof.

[0005] In one embodiment, the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical

composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0006] In one embodiment, the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 100 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0007] In one embodiment, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

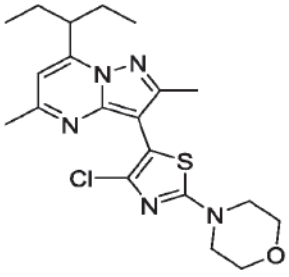
[0008] In one embodiment, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles. In one embodiment, the average size of the microparticles is between about 1 μm and about 20 μm. In one embodiment, the average size of

the microparticles is between about 5 μm and about 15 μm. In one embodiment, the average size of the microparticles is less than about 10 μm.

[0009] In one embodiment, the capsule is a hard gelatin capsule. In one embodiment, the capsule is a soft gelatin capsule. In one embodiment, 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.

[0010] In one embodiment, the pharmaceutical composition is free of additional excipients. In one embodiment, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0011] In one aspect, the present disclosure provides a pharmaceutical composition in the form of a tablet comprising Compound 1:



or a pharmaceutically acceptable salt or solvate thereof.

[0012] In one embodiment, the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0013] In one embodiment, the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 100 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 100 mg and about 300

mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0014] In one embodiment, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0015] In one embodiment, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles. In one embodiment, the average size of the microparticles is between about 1 μm and about 20 μm. In one embodiment, the average size of the microparticles is between about 5 μm and about 15 μm. In one embodiment, the average size of the microparticles is less than about 10 μm.

[0016] In one embodiment, the tablet is made by compression, molding, or extrusion. In one embodiment, he tablet is made by hot-melt extrusion. In one embodiment, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0017] In one embodiment, the pharmaceutical composition is stable for at least 1 month at 25 °C. In one embodiment, the pharmaceutical composition is stable for at least 3 months at 25 °C. In one embodiment, the pharmaceutical composition is stable for at least 6 months at 25 °C. In one embodiment, the pharmaceutical composition is stable for at least 9 months at 25 °C. In one embodiment, the pharmaceutical composition is stable for at least 12 months at 25 °C.

INCORPORATION BY REFERENCE

[0018] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0020] FIG. 1 shows Compound 1 in patients with CAH following 14-days of once daily dosing at each level;

[0021] FIG. 2 demonstrates the attenuation of ACTH across different subjects due to the administration of Compound 1;

[0022] FIG. 3 demonstrates the reduction in 17-OHP due to the administration of Compound 1;

[0023] FIG. 4 demonstrates the reduction of Androstenedione due to the administration of Compound 1;

[0024] FIG. 5 demonstrates the percentage release of Manufacturing Formulae A-1, A-2 and A-3 in 0.1N HCL + 1.0% SDS, media at 50 rpm and 900 mL using USP-II (Paddle);

[0025] FIG. 6 demonstrates the percentage release of Manufacturing Formulae B-1, B-2 and B-3 in 0.1N HCL + 1.0% SDS, media at 50 rpm and 900 mL using USP-II (Paddle); and

[0026] FIG. 7 demonstrates the percentage release of Manufacturing Formulae C-1, C-2 and C-3 in 0.1N HCL + 1.0% SDS, media at 50 rpm and 900 mL using USP-II (Paddle).

DETAILED DESCRIPTION OF THE INVENTION

[0027] 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.

[0028] CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors. A more discrete septallhypothalmic distribution and the availability of alternative endogenous ligands suggest a different functional role for the CRF2 receptor. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF 1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism. In other cases, CRF2 agonism produces similar effects to those reported for CRF 1 antagonists or CRF 1 gene deletion. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well.

[0029] Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous Cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which Cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment include Cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

[0030] The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient Cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of Addisonian syndrome due to under-treatment. Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione, testosterone, renin activity, and electrolytes.

[0031] Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance. A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the

aforementioned adverse outcomes. Treatment of CAH includes efforts to normalize the Cortisol deficiency with glucocorticoids (usually hydrocortisone in children but often more potent agents with narrow therapeutic indices, such as dexamethasone, in adults) and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for Cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] In one embodiment, the CRF receptor antagonist useful for the treatment of CAH is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine.

Certain Definitions

[0036] 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.

[0037] 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.

[0038] The term "about" is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value.

[0039] 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."

[0040] 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.

[0041] "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.

[0042] 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.

[0043] The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as Compound 1, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for

determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[0044] The term "supraphysiologic" amount" describes hormones levels that are elevated compared to average levels found in healthy individuals.

[0045] The term "physiologic amount" describes average hormone levels found in healthy individuals.

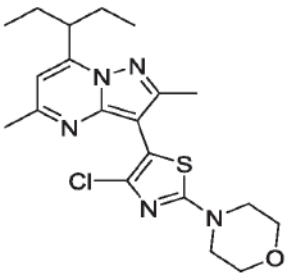
[0046] A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical 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).

[0047] 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.

[0048] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Compound

[0049] Disclosed herein is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine (or alternatively 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine), a pharmaceutically acceptable salt, and/or a solvate thereof:



. In some embodiments, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine is referred to as Compound 1. In some embodiments, 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine is referred to as Compound 1.

Pharmaceutical Compositions

[0050] Poorly soluble drugs may be difficult to formulate using technologies such as high shear wet granulation. Optimum delivery of poorly soluble drugs may require complex technologies such as solid solutions or amorphous dispersions (for example hot melt extrusion or spray drying), nano-formulations or lipid-based formulations. Hydrophobic drug substances which may be considered poorly soluble according to USP criteria may also be difficult to granulate with water and other excipients as most excipients for immediate-release formulations may be water soluble or water-swellable.

[0051] Making a small 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 difficult, and at a certain drug load, it may become impossible.

[0052] In one embodiment, the pharmaceutical compositions described herein may be for a pediatric population. Hence, it may be necessary to maintain the pharmaceutical composition as small as possible to facilitate swallowing of pills and therefore increase patient compliance. In some embodiments, tablet weights are less than 400 mg. In some embodiments, tablet weights are less than 300 mg. In some embodiments, where dose strength is 200 mg, the drug load in the tablet is higher than 50%. In some embodiments, where dose strength is 200 mg, the drug load in the tablet is higher than 66%. In some embodiments, where dose strength is 200 mg, the drug load is as high as possible.

[0053] Disclosed herein is a pharmaceutical composition comprising Compound 1, a pharmaceutically acceptable salt, and/or a solvate thereof.

Dosage Form

[0054] In some embodiments, the pharmaceutical compositions described herein are provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of Compound 1 that is suitable for administration to an animal, preferably mammal, subject in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

[0055] 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.

[0056] 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

[0057] 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.

[0058] 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.

[0059] In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients. In some embodiments, the capsule is free of additional excipients.

[0060] 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

[0061] Insoluble drugs may be difficult to formulate using standard technologies such as high shear wet granulation. Optimum delivery of insoluble 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 insoluble 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 insoluble 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.

[0062] In some embodiments, the pharmaceutical composition is formulated as a tablet.

[0063] In some embodiments, the tablet is made by compression, molding, or extrusion, optionally with one or more pharmaceutically acceptable excipient. In some embodiments, compressed tablets are prepared by compressing Compound 1 in a free-flowing form, optionally mixed with pharmaceutically acceptable excipients. In some embodiments, molded tablets are made by molding a mixture of the powdered Compound 1 moistened with an inert liquid diluent. In some embodiments, the tablet is prepared by hot-melt extrusion. In some embodiments, extruded tablets are made by forcing a mixture comprising Compound 1 through an orifice or die under controlled conditions. In some embodiments, the tablet is coated or scored. In some embodiments, the tablet is formulated so as to provide slow or controlled release of Compound 1. In some embodiments, a tablet is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the tablet has a dose strength of up to 200 mg. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus II.

[0064] In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg, more than about 150 mg, more than about 200 mg, or more than about 250 mg. In some embodiments, the tablet size is less than about 1000 mg for a dose strength of more than about

50 mg. In some embodiments, the tablet size is less than 800 mg for a dose strength of more than about 100 mg. In some embodiments, the tablet size is less than 600 mg for a dose strength of more than about 150 mg. In some embodiment, the tablet size is less than 400 mg for a dose strength of more than about 200 mg. In some embodiments, the tablet size is less than 400 mg for a dose strength of 200 mg.

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

[0065] In some embodiments, the tablet is produced at a commercial scale.

[0066] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[0067] In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some

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

Pharmaceutically Acceptable Excipients

[0068] 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.

[0069] 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, carxylate 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 hosphate, dibasic calcium phosphate or tribasic calcium phosphate).
- Co-processed diluents.
- Compression aids .
- Anti-tacking agents such as silicon dioxide and talc.

Amounts

[0070] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg

of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 1 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0071] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically

acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0072] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0073] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 400

mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0074] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 70 mg

of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. . In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0075] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0076] In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0077] In some embodiments, the pharmaceutical composition comprises about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

Particle size

[0078] In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises Compound 1, or a pharmaceutically acceptable salt or solvate thereof, in the form of microparticles. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 100 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 50 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 30 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 20 μm. In some

embodiments, microparticles of Compound 1 have an average size from about 5 μm to about 15 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 3 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 4 μm to about 9 μm.

[0079] In some embodiments, microparticles of Compound 1 have an average size less than about 100 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 80 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 60 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 50 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 40 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 30 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 20 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 10 μm.

Pharmacokinetics

[0080] In some embodiments, Compound 1 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, Compound 1 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, Compound 1 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, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

[0081] In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

Stability

[0082] The pharmaceutical compositions described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein

refers to pharmaceutical compositions having about 95% or greater of the initial Compound 1 amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of Compound 1. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable pharmaceutical compositions have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable pharmaceutical compositions have about 5% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 4% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 3% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 2% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 1% w/w total impurities or related substances.

[0083] At refrigerated condition, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±5 °C. In some embodiments, refrigerated condition is about 0 °C, about 0.1 °C, about 0.2 °C, about 0.3 °C, about 0.4 °C, about 0.5 °C, about 0.6 °C, about 0.7 °C, about 0.8 °C, about 0.9 °C, about 1 °C, about 1.1 °C, about 1.2 °C, about 1.3 °C, about 1.4 °C, about 1.5 °C, about 1.6 °C, about 1.7 °C, about 1.8 °C, about 1.9 °C, about 2 °C, about 2.1 °C, about 2.2 °C, about 2.3 °C, about 2.4 °C, about 2.5 °C, about 2.6 °C, about 2.7 °C, about 2.8 °C, about 2.9 °C, about 3 °C, about 3.1 °C, about 3.2 °C, about 3.3 °C, about 3.4 °C, about 3.5 °C, about 3.6 °C, about 3.7 °C, about 3.8 °C, about 3.9 °C, about 4 °C, about 4.1 °C, about 4.2 °C, about 4.3 °C, about 4.4 °C, about 4.5 °C, about 4.6 °C, about 4.7 °C, about 4.8 °C, about 4.9 °C, about 5 °C, about 5.1 °C, about 5.2 °C, about 5.3 °C, about 5.4 °C, about 5.5 °C, about 5.6 °C, about 5.7 °C, about 5.8 °C, about 5.9 °C, about 6 °C, about 6.1 °C, about 6.2 °C, about 6.3 °C, about 6.4 °C, about 6.5 °C, about 6.6 °C, about 6.7 °C, about 6.8 °C, about 6.9 °C, about 7 °C, about 7.1 °C, about 7.2 °C, about 7.3 °C, about 7.4 °C, about 7.5 °C, about 7.6 °C, about 7.7 °C, about 7.8 °C, about 7.9 °C, about 8 °C, about 8.1 °C, about 8.2 °C, about 8.3 °C, about 8.4 °C, about 8.5 °C, about 8.6 °C, about 8.7 °C, about 8.8 °C, about 8.9 °C, about 9 °C, about 9.1 °C, about 9.2 °C, about 9.3 °C, about 9.4 °C, about 9.5 °C, about 9.6 °C, about 9.7 °C, about 9.8 °C, about 9.9 °C, or about 10 °C. At accelerated conditions, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6

months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, or at least 24 month. Accelerated conditions for the pharmaceutical compositions described herein include temperatures that are at or above ambient levels (e.g. 25±5 °C). In some instances, an accelerated condition is at about 40±2 °C. In some instances, an accelerated condition is at about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C, or about 60 °C. Accelerated conditions for the pharmaceutical compositions described herein also include relative humidity (RH) that are at or above ambient levels (55±10% RH). In other instances, an accelerated condition is above about 65% RH, about 70% RH, about 75% RH, or about 80% RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40±2 °C at 75±5% RH humidity.

[0084] In some embodiments, the pharmaceutical compositions are stable at about 5±5 °C to about 25±5 °C for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 °C for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 °C for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5±5 °C for at least 24 months. In one embodiment, the pharmaceutical compositions are stable at about 25±5 °C for at least 24 months.

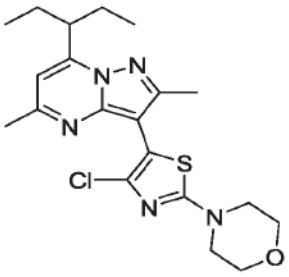
Methods of Use

[0085] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH. In some embodiments, the methods described herein result in the reduction of a hormone level. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17α-hydroxy progesterone (17-OHP), dehydroepiandrosterone, androstenediol, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein result in the reduction of 17α-hydroxy progesterone (17-OHP). In some embodiments, the methods described herein result in the reduction of adrenocorticotropic hormone (ACTH), also known as corticotropin.

[0086] Also disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising:

(i) measuring a hormone level in the subject in need thereof;

(ii) administering Compound 1:



or a pharmaceutically acceptable salt or solvate thereof;

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

[0087] In some embodiment, the hormone is 17α-Hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, or androstenedione.

[0088] In some embodiment, the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL. In some embodiment, the hormone is 17-OHP, and the pre-determined range is less than about 400 ng/dL, less than about 350 ng/dL, less than about 300 ng/dL, less than about 250 ng/dL, or less than about 200 ng/dL.

[0089] In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL. In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL, below about 90 pg/mL, or below about 80 pg/mL.

[0090] In some embodiment, the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL. In some embodiment, the hormone is testosterone and the pre-determined range is less than about 76 ng/dL, less than about 70 ng/dL, less than about 65 ng/dL, less than about 60 ng/dL, less than about 55 ng/dL, less than about 50 ng/dL, less than about 45 ng/dL, less than about 40 ng/dL, less than about 35 ng/dL, less than about 30 ng/dL, less than about 25 ng/dL, less than about 20 ng/dL, or less than about 15 ng/dL.

[0091] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 200 ng/dL in males. In some embodiment, the hormone is androstenedione and the pre-determined range is less than about 200 ng/dL, less than about 150 ng/dL, less than about 100 ng/dL, less than about 50 ng/dL, or less than about 30 ng/dL in males

[0092] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 150 ng/dL in females. In some embodiment, the hormone is androstenedione and the pre-determined range is less about 150 ng/dL, less about 100 ng/dL, less about 50 ng/dL, or less about 40 ng/dL in females.

[0093] In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a month, twice a month, three times a month, once a week, twice a week, three times a week, once every two days, once a day, twice a day, three times a day, or four

times a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof twice a day.

[0094] In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, about 100 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

[0095] In some embodiments, less than about 2000 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1200 mg Compound 1, or a pharmaceutically

acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1000 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 800 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 600 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 500 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 400 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 300 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 200 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day.

[0096] 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.

[0097] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

[0098] 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.

[0099] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

[0100] 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.

[0101] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

Combination Therapy

[0102] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; and a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0103] In some embodiments, the methods described herein reduce the amount of a glucocorticoid administered from a supraphysiologic amount to a physiologic amount.

[0104] In some embodiments, the methods described herein reduce the symptoms associated with high-dose glucocorticoid therapy. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.

[0105] In some embodiments, the amount of glucocorticoid administered is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 80, or about 90% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the amount of glucocorticoid administered is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0106] In some embodiments, the amount of glucocorticoid administered is reduced by about 1% to about 90%, about 1% to about 60%, about 1% to about 30%, about 1% to about 10%, about 10% to about 50%, about 10% to about 40%, about 10% to about 30%, about 15% to about 25%, about 20% to about 30%, about 5% to about 25%, about 20% to about 50%, about 30% to about 60%, or about 40% to about 70% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0107] In some embodiments, the glucocorticoid is administered at a dose between about 0.1 mg/day and about 25 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 20 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 15 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 12 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 9 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 8 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 7 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 6 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 5 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 4 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 3 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 2 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 3 mg/day and about 13 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 8 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 9 mg/day and about 12 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 9 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 10 mg/day.

[0108] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered in one pharmaceutical composition. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently in separate pharmaceutical compositions.

[0109] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 24 hours. In some embodiments, Compound 1, or a pharmaceutically

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

[0110] In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

[0111] In some embodiments, the glucocorticoid is hydrocortisone and the dose administered is less than the recommended dose of 15-25 mg/day.

[0112] In some embodiments, the glucocorticoid is prednisone and the dose administered is less than the recommended dose of 5-7.5 mg/day.

[0113] In some embodiments, the glucocorticoid is prednisolone and the dose administered is less than the recommended dose of 4-6 mg/day.

[0114] In some embodiments, the glucocorticoid is dexamethasone and the dose administered is less than the recommended dose of 0.25-0.5 mg/day.

[0115] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; a glucocorticoid; and optionally a mineralcorticoid. In some embodiments, the mineralocorticoid is fludrocortisone and the dose is less than the recommended dose of 0.05-0.2 mg/day.

EXAMPLES

[0116] 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.

[0117] All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples,

or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

Example 1: Pharmaceutical Composition

[0118] The pharmaceutical composition is manufactured as size 1 white hard gelatin capsules containing 200 mg of Compound 1 micronized to and average size of 10 microns or less. The pharmaceutical composition contains no additional excipients.

Example 2: Stability of the Pharmaceutical Composition

Stability Data Summary

[0119] A summary of the pharmaceutical composition stability studies is provided in Table 1. The pharmaceutical composition is a Compound 1 neat-filled into size 0 capsules with no added excipients, in 3 strength configurations: 1-mg, 5-mg, and 50-mg. The capsules were blister packaged in a polyvinyl chloride (PVC)-based film.

[0120] Under long term and accelerated conditions, no significant trend was observed in the three lots for any of the attributes evaluated throughout the course of the stability study.

Table 1. Summary of Stability

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

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

Stability Protocols

[0121] The stability protocol for various pharmaceutical compositions is provided in Table 2, 3, and 4.

Table 2. Stability Protocol

Test	Acceptance Criteria	Time (months)			
		T_0	1	3	6
Appearance	Size 0 blue capsule containing yellow powder, blister pack and foil backing intact	X	A,B	A,B	A,B
Assay	Report (% Label Claim)	X	A,B	A,B	A,B
Related Substances	Report RRT and % each individual species and total	X	A,B	A,B	A,B
Disintegration	Report	X	A,B	A,B	A,B

RRT = relative retention time
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

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

Test	Acceptance Criteria	Time (months)			
		T_0	1	3	6
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	A,B	A,B	A,B
Assay (%LC)	90.0 – 110.0	X	A,B	A,B	A,B
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	A,B	A,B	A,B
Disintegration (min)	NMT 15	X	A,B	A,B	A,B
Water Activity	Report result	X	A,B	A,B	A,B

LC = label claim; NMT = not more than
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

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

Test	Acceptance Criteria	Time (months)					
		T_0	1	3	6	9	12
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	B	A,B	A,B	A	A
Assay (%LC)	90.0 – 110.0	X	B	A,B	A,B	A	A
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	 ≤1.0 ≤2.0	X	B	A,B	A,B	A	A
Disintegration (min)	NMT 15	X	B	A,B	A,B	A	A
Water Activity	Report result	X	n/a	n/a	n/a	A	A
Microbial Enumeration Total Aerobic Microbial Count (CFU/g) Total Combined Yeast and Mold (CFU/g) Count	NMT 2000 CFU/g NMT 200 CFU/g	X	n/a	n/a	n/a	A	A
Test for Specified Microorganisms *E. coli* (/g)	Absent	X	n/a	n/a	n/a	A	A

CFU = colony forming units; LC = label claim; n/a = not applicable; NMT = not more than
X-testing performed at the time study was initiated
A-samples stored under long term conditions of 25 ± 2 °C/60 ± 5 % RH
B-samples stored under accelerated conditions of 40 ± 2 °C/75 ± 5 % RH

[0122] The supportive data demonstrate that the pharmaceutical composition is stable for a minimum of 6 months (end of study). No adverse trends were observed under long term and accelerated conditions. The assay results were consistent through the entire study and no new related substances species were observed during the stability study. The reported stability results for lots stored in a blister packaging configuration are considered supportive for the updated packaging configuration of a 30-mL HDPE bottle, induction seal, and a child resistant cap. There are no excipients in either configuration and both configurations provide protection from light.

Example 3: Phase 1 Clinical Studies

[0123] Compound 1 has been investigated in 2 Phase 1 studies in healthy adult volunteers.

[0124] Study 1 was the first-in-human study that investigated the safety, tolerability, and PK of single-escalating doses of Compound 1, given orally, to healthy adult subjects. Safety and tolerability assessments were made over a wide range of single oral doses, and dose escalation did not proceed until safety data from the preceding doses had been reviewed. The data from this study were used for the selection of doses for Study 2.

[0125] The 2-part multiple-dose study, Study 2, determined the safety and tolerability of repeated daily doses of Compound 1 and investigated the effects on biomarkers of relevance for the treatment of alcohol dependence. Part B investigated the interaction of Compound 1 with midazolam (a cytochrome P450 3A4 [CYP3A4] substrate), determining whether Compound 1 significantly inhibited the metabolism of drugs that are metabolized by CYP3A4.

[0126] In Study 1, Compound 1 was administered to healthy adult subjects as a single PO dose of 2, 10, 50, 150, 400, or 800 mg in the fed state and 150 mg in the fasted state. Absorption occurred moderately late, achieving peak C_{max} between 4 to 6 hours following dosing in the fed state.

[0127] Table 5 provides a summary of the PK parameters at each dose level. When Compound 1 was given in the fed state, median time to reach maximum plasma concentration (T_{max}) occurred between 4 and 6 hours. The median T_{max} was 10.05 hours when Compound 1 was given in the fasted state at 150 mg and ranged between 6 and 12 hours, suggesting possible delayed absorption in the fasted state. Mean half-life ($t_{1/2}$) after a single PO dose (fed and fasted state) was between 31 and 44 hours, ranging from 11 to 101 hours. Apparent volume of distribution (V_z/F) was large and appeared highly variable with greatest variability observed at the 2 highest dose levels of 400 mg and 800 mg.

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

PK Parameters	Geometric Mean (CV%)					
	Analyte = Plasma Compound 1					
	2 mg	**10 mg**	**50 mg**	**150 mg**	**400 mg**	**800 mg**
N	6	6	6	6	6	6
C_{max} (ng/mL)	0.867 (53)	3.01 (87)	19.5 (39)	93.4 (22)	207 (92)	382 (110)
T_{max}[a] (h)	6.00 (4.00-6.00)	4.00 (2.00 -6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	6.00 (4.00 - 6.00)
$t_{1/2}$b (h)	NC (NC)	NC (NC)	31 (10.8-53.4)	29.2 (20.0 - 41.5)	44.2 (20.2 - 101)	41.9 (24.1 - 67.8)
$AUC_{0\text{-tlast}}$ (ng•h/mL)	NC (NC)	NC (NC)	152 (60)	891 (26)	2300 (103)	4390 (100)

$AUC_{0-\infty}$ (ng•h/mL)	NC (NC)	NC (NC)	165 (64)	956 (25)	2580 (93)	4850 (95)
CL/F (L/h)	NC (NC)	NC (NC)	302 (64)	157 (25)	155 (93)	165 (95)
V_z/F (L)	NC (NC)	NC (NC)	13500 (45)	6620 (38)	9890 (212)	9970 (144)
V_{ss}/F (L)	NC (NC)	NC (NC)	8080 (36)	4600 (33)	6580 (152)	6820 (120)

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

a Median (range)

b Geometric mean (range)

[0128] As part of this single-dose escalation study, a food effect PK investigation was performed to examine Compound 1 exposures in both the fed and fasted states at the 150-mg dose level. A total of 6 subjects were administered 150 mg Compound 1 in each of these 2 dosing groups. Of these 6 subjects, 4 subjects received Compound 1 at the same dose in both fed and fasted states. The administration of Compound 1 in the fasted state resulted in a much flatter mean concentration-time (i.e., with significantly lower absorption) profile when compared against the mean profile at the same dose, given within 5 minutes after a standardized breakfast meal. The mean $AUC_{0-\infty}$, and C_{max} values for a 150-mg dose in the fed state was approximately 3- and 11-fold greater than that of the fasted state, respectively. Table 6 provides a summary of the PK parameters at the 150-mg dose level under both fed and fasted state conditions.

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

Pharmacokinetic Parameters	**Geometric Mean (CV %)**	
	Analyte = Plasma Compound 1	
	150 mg Fed	**150 mg Fasted**
N	6	6
C_{max} (ng/mL)	93.4 (22)	8.22 (83)
T_{max}[a] (h)	4.00 (3.00 – 6.00)	10.05 (6.00 – 12.00)
$t_{1/2}$[b] (h)	29.2 (20.0 – 41.5)	38.4 (24.2 – 88.5)
$AUC_{0-tlast}$ (ng•h/mL)	891 (26)	288 (48)
$AUC_{0-\infty}$ (ng•h/mL)	956	331

	(25)	(44)
CL/F (L/h)	157 (25)	454 (44)
V_Z/F (L)	6620 (38)	25100 (81)
V_{SS}/F (L)	4600 (33)	25200 (68)

AUC = area under the plasma concentration-time curve; CL/F = apparent total body clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; N = number of subjects; NC = not calculable; PK = pharmacokinetic; T_{max} = time to reach maximum plasma concentration; t1/2 = elimination half-life; $V_{ss}F$ = apparent volume of distribution at steady state during the terminal phase after extravascular administration; V_z/F = apparent volume of distribution during the terminal phase after extravascular administration.

a Median (range)

b Geometric mean (range)

[0129] PK parameters $AUC_{0-\infty}$ and C_{max} were analyzed separately for dose proportionality for Compound 1 from 50 to 800 mg when administered in the fed state. The analysis results suggested that for every doubling of dose, $AUC_{0-\infty}$ can be expected to increase 1.74 times more than what would be expected under dose proportionality. C_{max} appeared more than dose proportional but the formal test was inconclusive as the 90% confidence interval were partially within the 0.8 – 1.25 interval. Dose proportionality across administered doses in the fed state could not be concluded on the basis of $AUC_{0-\infty}$ or C_{max}.

[0130] PK were also evaluated in the multiple-dose, dose-escalation study, Study 2. In Part A of the study, subjects were divided into 3 cohorts and received 50, 150, or 200 mg Compound 1 or placebo for 14 consecutive days (at least 6 subjects received Compound 1 and 2 subjects received placebo in each cohort). Blood concentrations of Compound 1 were close to steady-state levels after 2 weeks of dosing and the accumulation ratio was between 2.51 to 3.65. Part B investigated the interaction of Compound 1 with midazolam (a CYP3A4 substrate), thereby determining whether this compound significantly inhibited the metabolism of drugs that are metabolized by CYP3A4 serial blood samples were collected to determine plasma concentrations of study drug after a single dose of Compound 1 had been administered and at steady state. All dosing occurred in the fed state. An assessment of diurnal cortisol levels, plus when under conditions of glucose clamp, were also carried out both prior to and during the dosing period.

[0131] Overall concentration time profiles of Compound 1 showed that absorption was moderately delayed with C_{max} achieved at a median of 5 hours following oral dosing. Consistent with the single-dose study (Study 1), concentrations appeared to decline in a bi-exponential

manner, characterized by a rapid decrease within the first 24 hours. Following multiple daily dosing for 2 weeks, the $t_{1/2}$ of Compound 1 exceeded 100 hours; therefore, an accumulation ratio of Compound 1 was between 2.51 to 3.65 (see Table 7). The T_{max} appeared to be consistent across doses. Overall half-lives, weight normalized CL/F and V/F were consistent for 150 and 200 mg. However, the values for these latter 2 parameters were almost doubled at the 50-mg dose level. Variability (CV%) for apparent clearance and volume of distribution were large and not reduced with weight-normalization.

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

	Geometric Mean (CV%)					
	50 mg Day 1	**150 mg Day 1**	**200 mg Day 1**	**50 mg Day 14**	**150 mg Day 14**	**200 mg Day 14**
N	**8**	**9**	**7**	**8**	**9**	**6**
C_{max} (ng/mL)	22.7 (59)	127 (52)	143 (62)	50.3 (56)	222 (58)	314 (93)
T_{max} [a] (hr)	4.52 (3.00 – 10.00)	5.00 (5.00 - 6.00)	5.00 (2.00 - 5.00)	5.00 (3.00 - 5.00)	5.00 (3.00 - 5.03)	5.00 (3.00 - 5.00)
Effective $t_{1/2}$ [b] (hr)	NC NC	NC NC	NC NC	37.7 (27.4)	32.7 (29.7)	52.0
$AUC_{0-\infty}$ (ng•hr/mL)	NC NC	NC NC	NC NC	980 (53.8)	4680 (104)	5660 (122)
AUC_{0-24h} (ng•hr/mL)	97.6 (58)	590 (56)	559 (55[c])	273 (56)	1480 (66)	2040 (98)
C_{avg} (ng/mL)	NC NC	NC NC	NC NC	11.4 (56)	61.7 (66)	85.0 (98)
CL_{aa}/F (L/hr)	NC NC	NC NC	NC NC	183 (56)	101 (66)	98 (98)
WT-norm						
Cl_{aa}/F (L/hr/kg)	NC NC	NC NC	NC NC	2.88 (46.9)	1.42 (72.9)	1.50 (89.9)
Vz/F (L)	NC NC	NC NC	NC NC	33500 (90)	17600 (59)	16300 (76)
Vss/F (L)	NC NC	NC NC	NC NC	12900 (91)	6170 (40)	5080 (78)
WT-norm						
Vss/F (L/kg)	NC NC NC	NC NC NC	NC NC NC	204 (71.3) 2.80	86.5 (41.0) 2.51	77.4 (68.6) 3.65
R_A	NC	NC	NC	(27.4)	(29.7)	(34.4)

AUC = area under the plasma concentration-time curve; CL/F = apparent clearance; C_{max} = maximum plasma concentration; RA = accumulation ratio calculated as Day 14 AUC_{0-24}/Day 1 AUC_{0-24}; t1/2 = terminal half-life; effective t1/2 = half-life calculated by accumulation ratio; Tmax = time to maximum plasma concentration; Vss/F = volume of distribution at steady state; Vz/F = volume of distribution at terminal phase; WT-norm = weight normalized

[a] Median (range).

[b] Geometric mean (range).

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

[0132] Table 8 presents the results of the dose proportionality assessment for the AUC_{0-24} and C_{max} over the tested dose range. For AUC_{0-24} and C_{max}, the adjusted mean slope at Day 1 and Day 14 were all above the value of 1, suggesting a slightly more than proportional increase of AUC_{0-24} and C_{max} values with increasing doses.

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

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

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

Safety

[0133] The safety of Compound 1 was evaluated in 2 Phase 1 studies in healthy adult volunteers (Study 1 and Study 2). In both studies, adverse events (AEs), clinical laboratory tests, vital signs (supine blood pressure and pulse rate), and electrocardiograms (ECGs) were evaluated. Overall, in Study 1, Compound 1 was well-tolerated. Compound 1, when administered as multiple doses up to 200 mg, was generally well tolerated in the healthy subject population studied.

[0134] In Study 1, the effects upon biomarkers of relevance for the treatment of alcohol dependence were investigated. Five clusters of an Addiction Research Center Inventory Questionnaire (ARCI-49) were used to compare the effect of Compound 1 vs. placebo: Morphine-Benzedrine Group Scale measuring euphoria; Lysergic-Acid-Diethylamide Group Scale estimating dysphoric and somatic changes; Pentobarbital-Chlorpromazine-Alcohol Group Scale measuring sedation; Benzedrine Group (BG) Scale measuring intellectual efficiency and energy; Amphetamine Group Scale measuring effects of d-amphetamine, respectively. No

systematic pattern or dose-response for the change from baseline or for the difference over placebo in each cluster was observed.

[0135] In summary, single, oral doses up to 800 mg and multiple doses up to 200 mg of Compound 1 were well-tolerated by healthy male and female subjects.

Example 4: Phase 2 Multiple-Dose, Dose-Escalation Clinical Studies

[0136] Cohort A of the Phase 2 Study includes a 6-week, multiple-dose, dose escalation study of Compound 1 for the treatment of adults with classic CAH. After screening, eligible patients will be enrolled into a 6-week treatment period followed by a 4-week washout/safety follow-up period.

[0137] This cohort will be conducted in approximately 9 patients, who will receive Compound 1 daily for up to 6 weeks. Compound 1 will be administered as an oral daily dose. Patients will undergo titration of Compound 1 through three escalating dosage strengths at 2-week intervals. Patients will have overnight PK/PD assessments performed at baseline, which include an pre-dose overnight assessment and a post-dose overnight assessment for PK/PD following administration of the first dose. At the end of each 2-week dosing period, patients will return for single overnight visits for steady-state PK/PD assessments. A follow-up outpatient visit will occur 30 days after their last dose. Upon completion of the initial cohort (Cohort A), the study will proceed to a multiple ascending dose (MAD) design with up to 3 sequential cohorts (Cohorts B, C, and D) to further evaluate the safety, PK, and PD of various SPR001 dosing regimens and to identify an optimal dose regimen. Each cohort will undergo a 2-week run-in period, a 2-week treatment period, and a 30-day washout and safety follow-up period. During the run-in period, which will occur during screening, subjects will document in a paper diary each dose of glucocorticoid medication taken, the time of each meal, and the time they went to bed and woke up each day, to ensure compliance with background glucocorticoid regimens and the stability of their daily routine.

[0138] Patients in Cohort B will receive study drug at 200 mg BID, with a dose in the morning and a dose in the evening, either with a meal or consumption of a standardized snack. For Cohorts C and D, the dose level and the frequency and timing of dosing will be determined based on interim data from the previous cohorts. However, the dose level of each successive cohort will be capped at twice the daily dose level of the previous cohort.

Study Design

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2
- Interventional Study Model: Sequential Assignment

- Number of Cohorts: Up to 4
- Masking: No masking
- Allocation: Non-Randomized
- Enrollment: Up to approximately 27 [Anticipated]

Arms and Interventions

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

Outcome Measures

Primary Outcome Measure:

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

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

Secondary Outcome Measure:

3. To explore the dose(s) of Compound 1 that cause pharmacodynamics changes in plasma concentrations of ACTH, androstenedione, and testosterone, as measured by the absolute and percent change from baseline by dose.

4. To determine pharmacokinetics of Compound 1 in subjects with CAH.

5. To explore potential relationships between pharmacodynamics and pharmacokinetics.

Exploratory

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

Eligibility

- Minimum Age: 18 Years
- Maximum Age:
- Sex: All

- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

Results:

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

[0139] With respect to patient-level response to Compound 1, 80% showed reduced ACTH (see FIG. 2). Generally, attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of patient subjects demonstrated reduction in ACTH. 70% of subject demonstrated more than 25% reduction in ACTH. 40% of subjects were in the normal range after treatment.

[0140] A reduction of 17-OHP demonstrates "control" of the disease based on Standard guidelines. This allows for steroid taper. 80% of subjects demonstrated reduction in 17-OHP (see FIG. 3). 50% of subjects demonstrated more than 25% reduction in 17-OHP. 50% of subjects were within the guideline range (1200 ng/dL) after treatment.

Compound 1 attenuates morning rise in A4 which indicates an ability to control excess androgen production and associated symptoms (see FIG. 4). 100% of subjects demonstrated reduction in Androstenedione (at various doses). 60% of subjects demonstrated more than 25% reduction in Androstenedione. 50% of subjects were within normal reference range after treatment.

Example 5: Formulation Development

[0141] The objectives of this experiment was to (1) evaluate different formulations to obtain a Compound 1 200 mg immediate release core tablet; (2) evaluate dissolution profiles of

Compound 1 tablets in wet granulation process and in granulation with Gelucire 48/16 and/or Vitamin E TPGS; and (3) evaluate dissolution of the tablets/capsules in various bio-relevant media and sink conditions to compare dissolution of API in capsule.

Experimental Outcomes

[0142] The formulation of Compound 1 tablets were performed in two phases.

[0143] In the first phase of manufacturing, two immediate release trial formulations were manufactured. The first trial involved granulation of Compound 1 using Gelucire (10%) and included fillers and disintegrants. No surfactant was used in his formulation. The granules were final belnded and compressed at a tablet weight of 500 mg. No issues were observed in granulation and compression. The second trial involved wet granulation with HPC as the binder with fillers and disintegrants. Sodium lauryl sulphate was used as a surfactant at a concentration of 1%. The granules were softer when compared to the first trial and the final blend had poor flow. The filler in the extra granular portion was increased to improve flow and weight variation during compression. The tablets were compressed at 600 mg tablet weight. The first and second trial batches were tested for dissolution in different bio-relevant media – SGF (simulated gastric fluid), SIF (simulated intestinal fluid), FaSSIF (fasted state simulated intestinal fluid) and FeSSIF (fed state simulated intestinal fluid).

[0144] In the second phase of manufacturing, two additional formulations with Gelucire and Vitamin E TPGS at a percentage of 8% and with high concentration of sodium lauryl sulphate were manufactured. The percentage of the surfactant was increased to 7%. The tablets were compressed at 570 mg tablet weight. No issues were observed in the manufacturing process. Further development included manufacturing with high concentration of Gelucire (25%). Due to the high concentration of the Gelucire in the formulation, the granules could not be compressed and were manually filed into size 0 capsules.

[0145] Further development of wet granulation process was recommended as the flow was poor and particle size of granules was not optimum. The granules from the wet granulation formulation also showed weight variation during compression.

[0146] The release in SIF and FaSSIF was very low, ranging from between 0.5% to 3% at 60 minutes for the Gelucire and HPC formulations. The release in SGF and FeSSIF was higher and ranged from 11-16% in 60 minutes. The higher release in SGF and FeSSIF may have been due to the presence of surfactants in the media. However, the dissolution in the bio-relevant media did not show improvement with the lipid excipients or high concentration of surfactants. The release in SIF and FeSSIF was below 2%, in SGF approximately 15% and 10% in FeSSIR at 60 minutes. Dissolution showed no improvement with high concentration of Gelucire in the capsule formulation. A comparison of the dissolution of API in capsule and the different

formulations did not show any improvement in dissolution. An animal pK study was also prformed with the wet granulation formulation and the Gelucire formulation. The dissolution and pK studies indicate that the current formulation approach may not be suitable to improve bioavailability of Compound 1 or minimize the food effect. A different formulation approach was recommended for Compound 1 in Phase 2/3 studies.

Example 6: Preliminary Tablet formulation

[0147] The objective of the general experiments were to develop, manufacture and commercialize a small tablet or capsule for a drug substance that is insoluble (solubility less than 0.002 mg/ml in water and at all physiological pHs ranging from 1.2 to 7.5) and a dose strength up to 200 mg. Tablet should be immediately released in a dissolution medium using USP apparatus I or II.

Success criteria

1. A tablet size less than 400 mg for a dose strength of 200 mg
2. More than 70% dissolved in 60 minutes in conventional dissolution media.

General Manufacturing Procedure

[0148] 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.

[0149] A granulation was developed with a minimum amount and number of excipients. The granulation consisted of at least 90% Compound 1 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.

[0150] Two blends were granulated. One blend had 95% Compound 1, 1% sodium lauryl sulfate, and 4% HPC-EXF. The second blend had 91% Compound 1, 1% sodium lauryl sulfate (surfactant and wetting agent), 6% PVP (water soluble binder) and 2% Ac-di-sol (water-swellable super-disintegrant).

[0151] The granulation consisting of HPC-EXF (binder) was further blended with SiO_2 (flow aid and anti-tacking agent), ac-di-sol (water swellable disintegrant) and magnesium stearate (lubricant). Different levels of MCC were added to the tablets (0, 10 and 20% levels). All three formulations (90%, 81% and 71% DL) dissolved quickly, and there were no significant changes during accelerated stability in open dish conditions. The granulation with PVP as a binder was repeated three times. The first granulation consisted of 93% Compound 1, 6% PVP and 1%

SLS. This formulation demonstrated inferior manufacturing features (granular flow) however the tablets had acceptable dissolution. No further stability was conducted.

[0152] The second granulation (identical to first) had acceptable manufacturing features (good flow and compression) however dissolution was somewhat slower and there were significant changes during on stability in very stressful conditions.

[0153] The third granulation consisted of 91% Compound 1, 6% PVP, 1% SLS and 2% Ac-di-sol as intra-granular super-disintegrant. The granulation was further blended with SiO_2 (flow aid and anti-tacking agent), ac-di-sol (water swellable disintegrant) and magnesium stearate (lubricant). Different levels of MCC were added to the tablets (0, 10 and 20% levels). All three formulations (86%, 77% AND 68% DL) all dissolved quickly.

[0154] This demonstrated a successful tablet of Compound 1 with water solubility less than 0.002 mg/ml, while maintaining a drug load above 50% and resulting in acceptable dissolution in a conventional dissolution media (1% SLS and USP apparatus II). The tablet was manufactured using a conventional high shear wet granulation method.

Table 10. Summary of Compound 1 solubility in different aqueous media (n=2, 24 hours at room temperature)

Aqueous media	Equilibrium pH	Solubility mg/mL	Standard Deviation (n=2)	Description
Water	7.78	0.0003	0.0000	insoluble
0.1N HCl	1.06	0.0018	0.0000	insoluble
0.01N HCl	2.06	0.0004	0.0000	Insoluble
0.001N HCl	3.36	0.0003	0.0000	Insoluble
pH 4.5 Acetate (USP)	4.65	0.0005	0.0000	Insoluble
pH 6.0 Phosphate (USP)	6.08	0.0002	0.0000	Insoluble
pH 7.5 Phosphate (USP)	7.57	0.0006	0.0000	Insoluble
0.1N NaOH	11.65	0.0002	0.0000	Insoluble
SGF	2.25	0.0204	0.0001	Insoluble
FaSSIF	6.73	0.0036	0.0000	Insoluble
FaSSIF	5.16	0.0104	0.0000	insoluble

Example 7: Tablet Formulation A

[0155] Three formulations were prepared using wet granulations with common granules and PVP K30 as a binder (see Table 11). The granules were diluent with MCC PH102 with 95%, 85% and 75% drug loads respectively.

Table 11. Manufacturing Formulae A

Material	A-1		A-2		A-3	
	%w/w	mg/tablet	%w/w	mg/tablet	%w/w	mg/tablet
Common Granular						
Compound 1	93	200.00	93	200.00	93	200.00
Povidone Compendial [plasdoneK-29/32]	6	12.90	6	12.90	6	12.90
Kolliphor® SLS fine	1	2.15	1	2.15	1	2.15
Extra Granular						
Common granules	95	215.05	85	215.05	75	215.05
Microcrystalline Cellulose PH102	-	0.00	10	25.30	20	57.35
Croscarmellose Sodium, Compendial	3	6.79	3	7.59	3	8.60
Silica Dioxide (Aerosil200Pharma)	1	2.26	1	2.53	1	2.87
LIGAMEDMF-2-V Magnesium Stearate	1	2.26	1	2.53	1	2.87
Target Tablet Weight (mg)		226.37		253.00		286.73

[0156] Compound 1, Povidone and sodium lauryl sulfate were mixed to produce a dry mixture. Water was added to the dry mixture and subjected to a wet granulation at an impeller speed of about 550 – 560 rpm. The wet granules were then sifted and dried. The dry granules were dry-sieved after which the granules were compressed into tablets.

[0157] In process control tests, each tablet was satisfactory. Dissolution results of A-1 and A-3 showed similar curves whereas A-2 was slightly slower than the other two in the first few points (see table 12 and FIG. 5).

Table 12. Dissolution for Manufacturing Formulae A

Dissolution in 0.1N HCl + 1.0% SDS, media at 50 rpm and 900 ml using USP-II (Paddle)			
Time points (Minutes)	A-1	A-2	A-3
5 minutes	48.4	35.0	46.7
10 minutes	58.3	48.2	56.4
15 minutes	65.2	55.9	62.2
20 minutes	70.4	61.3	65.9
30 minutes	78.1	68.3	71.9
45 minutes	85.6	77.4	79.3
60 minutes	91.5	84.1	85.1

90 minutes	98.5	92.6	91.9
120 minutes	100.5	97.2	95.6

Example 8: Tablet Formulation B

[0158] Three formulations were prepared using wet granulation with common granules and PVP K30 as a binder (see Table 13). The granules were diluent with MCC PH102 with 95%, 85% and 75% drug loads respectively.

Table 13. Manufacturing Formulae B

Material	B-1		B-2		B-3	
	%w/w	mg/tablet	%w/w	mg/tablet	%w/w	mg/tablet
Common Granular						
Compound 1	93	200.00	93	200.00	93	200.00
Povidone Compendial [plasdoneK-29/32]	6	12.90	6	12.90	6	12.90
Kolliphor® SLS fine	1	2.15	1	2.15	1	2.15
Extra Granular						
Common granules	95	215.05	85	215.05	75	215.05
Microcrystalline Cellulose PH102	-	0.00	10	25.30	20	57.35
Croscarmellose Sodium, Compendial	3	6.79	3	7.59	3	8.60
Silica Dioxide (Aerosil200Pharma)	1	2.26	1	2.53	1	2.87
LIGAMEDMF-2-V Magnesium Stearate	1	2.26	1	2.53	1	2.87
Target Tablet Weight (mg)		226.37		253.00		286.73

[0159] Compound 1, Povidone and sodium lauryl sulfate were mixed to produce a dry mixture. Water was added to the dry mixture and subjected to a wet granulation at an impeller speed of about 600 – 610 rpm. The wet granules were then sifted and dried. The dry granules were dry-sieved after which the granules were compressed into tablets.

[0160] Dissolution results showed slower dissolution than previous tablets which may be caused by more granules and more hardness (see table 14 and FIG. 6).

Table 14. Dissolution for Manufacturing Formulae B

Dissolution in 0.1N HCl + 1.0% SDS, media at 50 rpm and 900 ml using USP-II (Paddle)			
Time points (Minutes)	B-1	B-2	B-3
5 minutes	9.4	13.7	20.4
10 minutes	21.2	33.3	47.0
15 minutes	28.6	47.8	56.4
20 minutes	34.7	54.3	61.9
30 minutes	41.8	62.0	68.2
45 minutes	49.5	70.1	74.4
60 minutes	56.3	75.8	78.8

90 minutes	66.9	84.0	84.3
120 minutes	74.8	89.5	87.4

Example 9: Tablet Formulation C

[0161] Three formulations were prepared using wet granulation with common granules, PVP K30 as a binder, and 2% Croscarmellose Sodium Intragranular (see Table 15).

Table 15. Manufacturing Formulae C

Material Name	C-1		C-2		C-3	
	%w/w	Mg/tablet	%w/w	Mg/tablet	%w/w	Mg/tablet
Common Granular						
C07102401-F	91	200	91	200	91	200
Povidone Compendial [plasdoneK-29/32]	6	13.2	6	13.2	6	13.2
Kolliphor® SLS Fine	1	2.2	1	2.2	1	2.2
Croscarmellose Sodium, Compendial	2	4.4	2	4.4	2	4.4
Extra Granular						
Common granules	95	219.78	85	219.78	75	219.78
Microcrystalline Cellulose PH102	-	-	10	25.86	20	58.61
Croscarmellose Sodium, Compendial	3	6.94	3	7.76	3	8.79
Silica Dioxide(Aerosil200Pharma)	1	2.31	1	2.59	1	2.93
LIGAMEDMF-2-V Magnesium Stearate	1	2.31	1	2.59	1	2.93
Target Tablet Weight (mg)		231.36		258.60		293.06

[0162] Compound 1, Povidone, croscarmellose sodium and sodium lauryl sulfate were mixed to produce a dry mixture. Water was added to the dry mixture and subjected to a wet granulation at an impeller speed of about 600 – 610 rpm. The wet granules were then sifted and dried. The dry granules were dry-sieved after which the granules were compressed into tablets.

[0163] Dissolution results showed faster dissolution than other tablets which may be caused by the additional quantity of croscarmellose sodium (see Table 16 and FIG. 7).

Table 16. Dissolution for Manufacturing Formulae C

Dissolution in 0.1N HCl + 1.0% SDS, media at 50 rpm and 900 ml using USP-II (Paddle)			
Time points (Minutes)	1806DFP2555-02A	1806DFP2555-02B	1806DFP2555-02C
5 minutes	26.3	25.1	26.2
10 minutes	66.3	62.7	65.8
15 minutes	79.9	81.7	77.8
20 minutes	85.4	89.3	83.6
30 minutes	90.6	94.9	88.5
45 minutes	94.2	98.3	92.4
60 minutes	95.4	99.6	94.1

90 minutes	95.3	100.2	95.0
120 minutes	95.5	100.4	95.7
250RPM/5min	95.6	100.5	98.0

Example 10: Tablet Formulation D

[0164] Two formulations were prepared using wet granulation (see Table 17).

Table 17. Manufacturing Formulae D

Material Name	D-1			D-2		
	%w/w	mg/tablet	Batch formula	%w/w	Mg/tablet	Batch formula
C07102401-F	71.25	200.000	570.00	77.35	200.000	546.00
Klucel(TM)EXF PHARM Hydroxypropyl cellulose	3.00	8.421	24.00	-	-	-
Povidone Compendial [plasdoneK-29/32]	-	-	-	5.10	13.187	36.00
Kolliphor® SLS Fine	0.75	2.105	6.00	0.85	2.198	6.00
Croscarmellose Sodium, Compendial	-	-	-	1.70	4.396	12.00
Extra granular material						
Microcrystalline Cellulose PH102	20.00	56.140	160.00	10.00	25.856	70.59
Croscarmellose Sodium, Compendial	3.00	8.421	24.00	3.00	7.757	21.18
Silica Dioxide (Aerosil200 Pharma)	1.00	2.807	8.00	1.00	2.586	7.06
LIGAMEDMF-2-V Magnesium Stearate	1.00	2.807	8.00	1.00	2.586	7.06
Target Tablet Weight (mg)		280.701	800.00		258.566	705.89

[0165] Compound 1, Povidone, croscarmellose sodium and sodium lauryl sulfate were mixed to produce a dry mixture. Water was added to the dry mixture and subject to a wet granulation at an impeller speed of about 600 – 610 rpm. The wet granules were then sifted and dried. The dry granules were dry-sieved after which the granules were compressed into tablets.

[0166] The release profile of Formulation D-1 and D2 were similar to previous formulations with no significant changes (see Table 18).

Table 18. Dissolution for Manufacturing Formulae C

Dissolution in 0.1N HCl + 1.0% SDS, media at 50 rpm and 900 ml using USP-II (Paddle)		
Time points (Minutes)	D-1	D-2
5 minutes	18.7	30.6
10 minutes	43.8	72.1
15 minutes	56.9	85.1
20 minutes	65.2	91.5
30 minutes	73.9	96.4
45 minutes	81.9	99.9
60 minutes	87.1	101.3

90 minutes	92.4	102.3
120 minutes	95.6	-
250RPM/5min	99.4	100.9

[0167] Both formulations had a faster relief profile in SGF media (see Table 19).

Table 19. Dissolution for Manufacturing Formulae C in SGF media

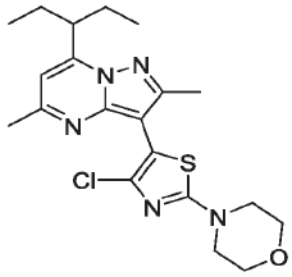
Dissolution in SGF, media at 60 rpm and 900 ml using USP-II (Paddle)			
Time points (Minutes)	D-1	D-2	Capsule with Compound 1
5 minutes	10.8	7.0	0.3
10 minutes	18.4	11.0	1.9
15 minutes	21.3	11.8	4.2
20 minutes	23.4	12.2	6.5
30 minutes	24.4	12.4	9.4
45 minutes	26.1	12.8	13.6
60 minutes	25.7	13.0	15.1
90 minutes	27.9	13.1	15.5
120 minutes	28.2	13.2	15.2
250RPM/5min	28.0	13.2	15.8

[0168] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition in the form of a capsule comprising Compound 1:

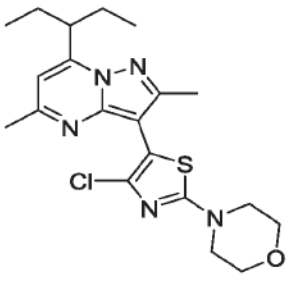


or a pharmaceutically acceptable salt or solvate thereof.

2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
3. The pharmaceutical composition of claim 1 or 2, wherein the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
4. The pharmaceutical composition of any one of claims 1 to 3, wherein the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
5. The pharmaceutical composition of any one of claims 1 to 4, wherein the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
6. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
7. The pharmaceutical composition of any one of claims 1 to 4, wherein the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
8. The pharmaceutical composition of any one of claims 1 to 4, wherein the pharmaceutical composition comprises between about 100 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
9. The pharmaceutical composition of any one of claims 1 to 4, wherein the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

10. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
11. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
12. The pharmaceutical composition of any one of claims 1 to 4, wherein the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
13. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
14. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
15. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
16. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
17. The pharmaceutical composition of any one of claims 1 to 6, wherein the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
18. The pharmaceutical composition of any one of claims 1 to 6, wherein the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
19. The pharmaceutical composition of any one of claims 1 to 6, wherein the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
20. The pharmaceutical composition of any one of claims 1 to 6, wherein the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

21. The pharmaceutical composition of any one of claims 1 to 6, wherein the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
22. The pharmaceutical composition of any one of claims 1-21, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles.
23. The pharmaceutical composition of claim 22, wherein the average size of the microparticles is between about 1 μm and about 20 μm.
24. The pharmaceutical composition of claim 22 or 23, wherein the average size of the microparticles is between about 5 μm and about 15 μm.
25. The pharmaceutical composition of any one of claims 22 to 24, wherein the average size of the microparticles is less than about 10 μm.
26. The pharmaceutical composition of any one of claims 1 to 25, wherein the capsule is a hard gelatin capsule.
27. The pharmaceutical composition of any one of claims 1 to 25, wherein the capsule is a soft gelatin capsule.
28. The pharmaceutical composition of any one of claims 1 to 27, 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.
29. The pharmaceutical composition of any one of claims 1 to 28, wherein the pharmaceutical composition is free of additional excipients.
30. The pharmaceutical composition of any one of claims 1 to 28, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.
31. A pharmaceutical composition in the form of a tablet comprising Compound 1:



or a pharmaceutically acceptable salt or solvate thereof.
32. The pharmaceutical composition of claim 31, wherein the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

33. The pharmaceutical composition of claim 31 or 32, wherein the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
34. The pharmaceutical composition of any one of claims 31 to 33, wherein the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
35. The pharmaceutical composition of any one of claims 31 to 34, wherein the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
36. The pharmaceutical composition of any one of claims 31 to 35, wherein the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
37. The pharmaceutical composition of any one of claims 31 to 34, wherein the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
38. The pharmaceutical composition of any one of claims 31 to 34, wherein the pharmaceutical composition comprises between about 100 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
39. The pharmaceutical composition of any one of claims 31 to 34, wherein the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
40. The pharmaceutical composition of any one of claims 31 to 35, wherein the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
41. The pharmaceutical composition of any one of claims 31 to 35, wherein the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
42. The pharmaceutical composition of any one of claims 31 to 34, wherein the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
43. The pharmaceutical composition of any one of claims 31 to 35, wherein the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

44. The pharmaceutical composition of any one of claims 31 to 35, wherein the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

45. The pharmaceutical composition of any one of claims 31 to 35, wherein the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

46. The pharmaceutical composition of any one of claims 31 to 35, wherein the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

47. The pharmaceutical composition of any one of claims 31 to 36, wherein the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

48. The pharmaceutical composition of any one of claims 31 to 36, wherein the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

49. The pharmaceutical composition of any one of claims 31 to 36, wherein the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

50. The pharmaceutical composition of any one of claims 31 to 36, wherein the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

51. The pharmaceutical composition of any one of claims 31 to 36, wherein the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. The pharmaceutical composition of any one of claims 31 to 50, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles.

52. The pharmaceutical composition of claim 51, wherein the average size of the microparticles is between about 1 μm and about 20 μm.

53. The pharmaceutical composition of claim 51 or 52, wherein the average size of the microparticles is between about 5 μm and about 15 μm.

54. The pharmaceutical composition of any one of claims 51 to 53, wherein the average size of the microparticles is less than about 10 μm.

55. The pharmaceutical composition of any one of claims 31 to 54, wherein the tablet is made by compression, molding, or extrusion.

56. The pharmaceutical composition of claim 55, wherein the tablet is made by hot-melt extrusion.

57. The pharmaceutical composition of any one of claims 31 to 56, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

58. The pharmaceutical composition of any one of claims 1 to 57, wherein the pharmaceutical composition is stable for at least 1 month at 25 °C.

59. The pharmaceutical composition of any one of claims 1 to 58, wherein the pharmaceutical composition is stable for at least 3 months at 25 °C.

60. The pharmaceutical composition of any one of claims 1 to 59, wherein the pharmaceutical composition is stable for at least 6 months at 25 °C.

61. The pharmaceutical composition of any one of claims 1 to 60, wherein the pharmaceutical composition is stable for at least 9 months at 25 °C.

62. The pharmaceutical composition of any one of claims 1 to 61, wherein the pharmaceutical composition is stable for at least 12 months at 25 °C.

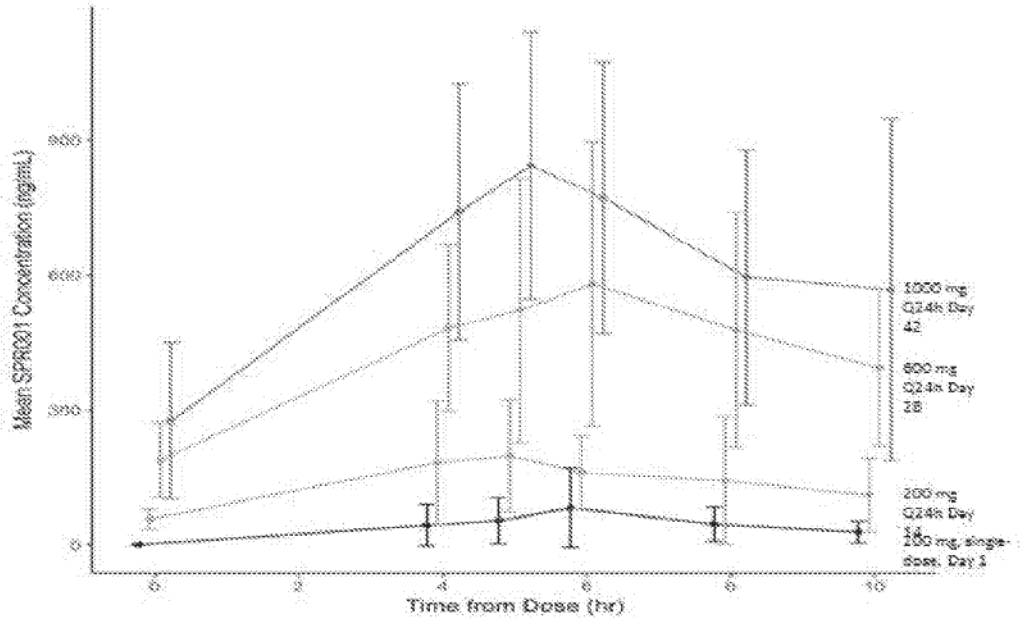

Mean SPR001 Concentration (ng/mL)
Time from Dose (hr)
1000 mg Q24h Day 42
600 mg Q24h Day 28
200 mg Q24h Day 14
100 mg, single dose, Day 1

FIG. 1

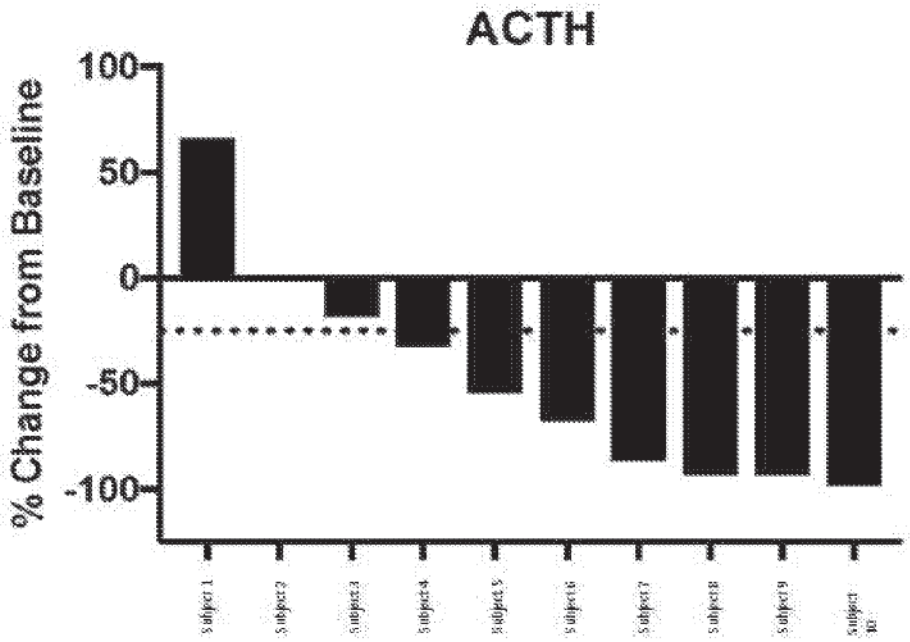

ACTH
% Change from Baseline
100
50
0
-50
-100
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
Subject 9
Subject 10

FIG. 2

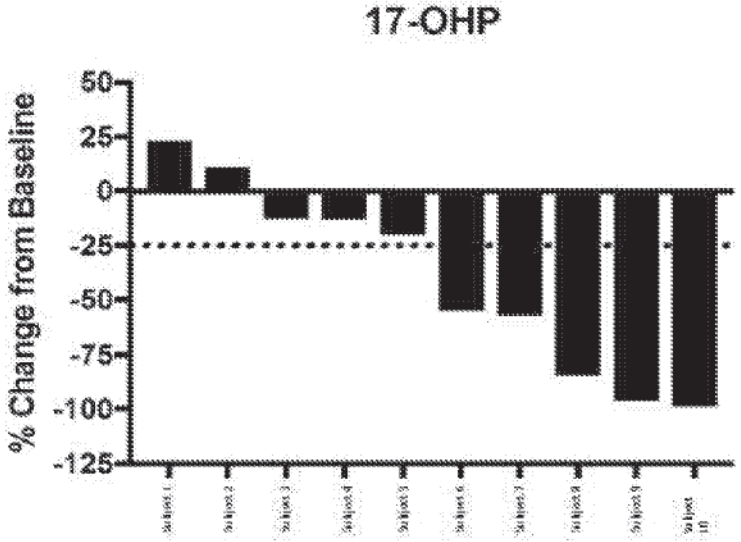

17-OHP
% Change from Baseline
50
25
0
-25
-50
-75
-100
-125

FIG. 3

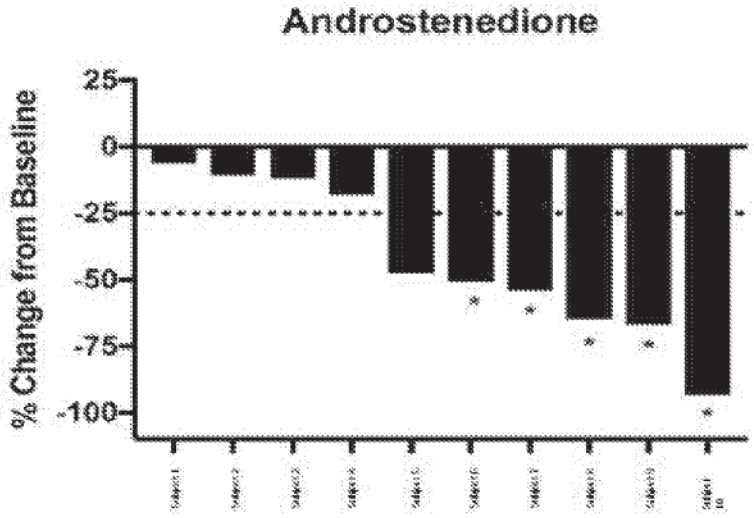

Androstenedione
% Change from Baseline
25
0
-25
-50
-75
-100
*

FIG. 4

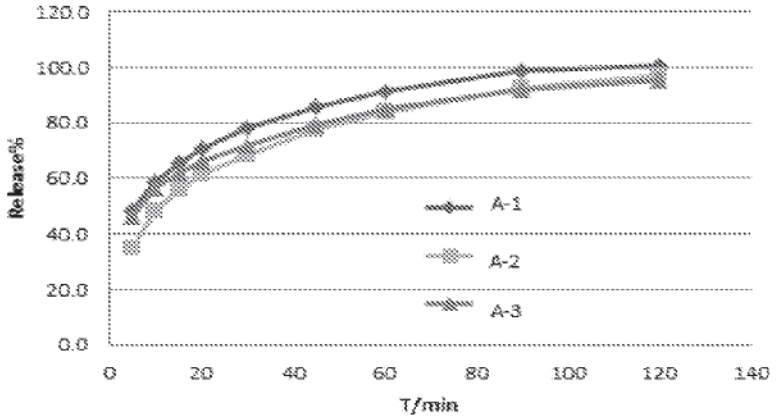

120.0
100.0
80.0
60.0
40.0
20.0
0.0
Release%
A-1
A-2
A-3
0
20
40
60
80
100
120
140
T/min

FIG. 5

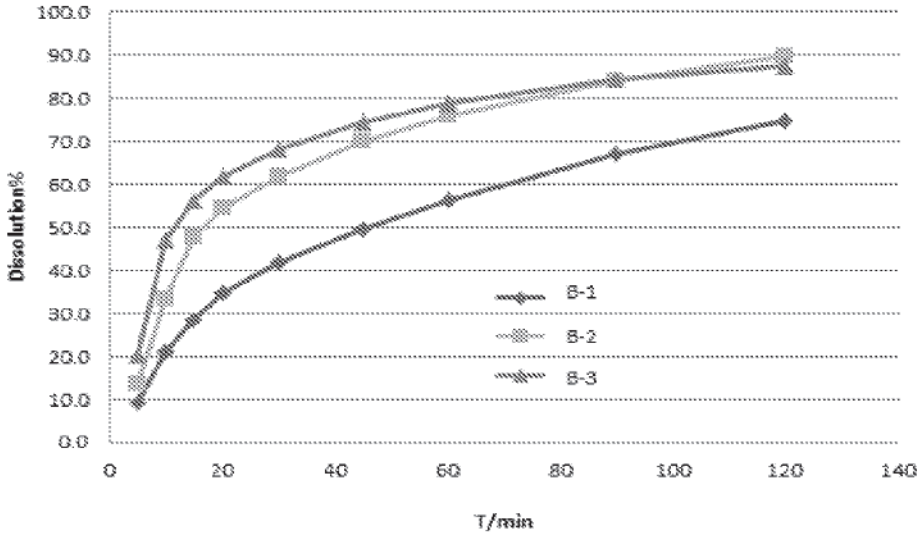

100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Dissolution%
B-1
B-2
B-3
0
20
40
60
80
100
120
140
T/min

FIG. 6

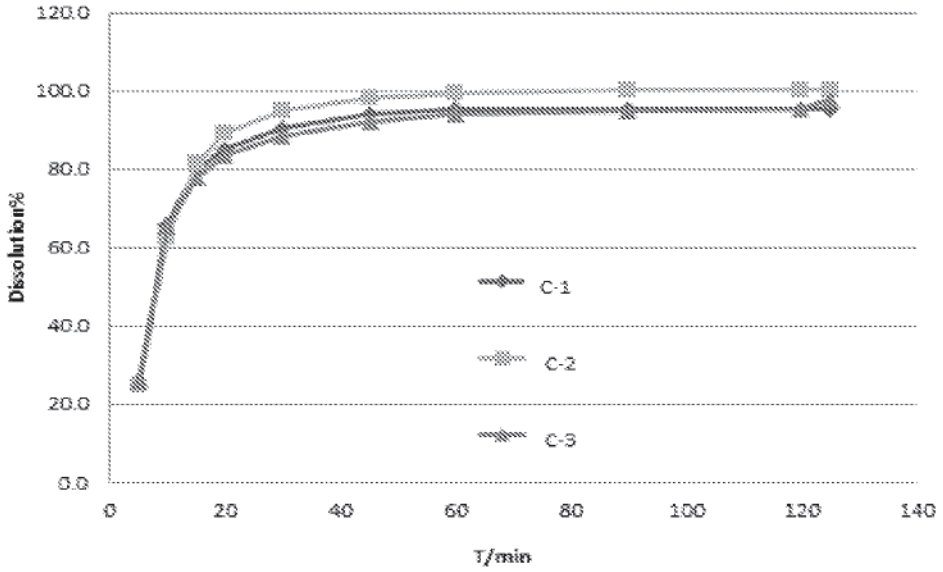

120.0
100.0
80.0
60.0
40.0
20.0
0.0
Dissolution%
0
20
40
60
80
100
120
140
T/min
C-1
C-2
C-3

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/46707

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 471/04 (2018.01)
CPC - A61P 35/00, C07D 471/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0222339 A1 (Chen et al.) 02 September 2010 (02.09.2010); Abstract, para[0055], para[0056], para[0144]	1-3, 31-33
A	US 2011/0166345 A1 (Rizzo et al.) 07 July 2011 (07.07.2011); entire document	1-3, 31-33
A	US 2010/0022560 A1 (Chen et al.) 28 January 2010 (28.01.2010); entire document	1-3, 31-33
A	Hodgetts et al. 'Discovery of N-(1-Ethylpropyl)-[3-methoxy-5-(2-methoxy-4-trifluoromethoxyphenyl)-6-methyl-pyrazin-2-yl]amine 59 (NGD 98-2): An Orally Active Corticotropin Releasing Factor-1 (CRF-1) Receptor Antagonist', Journal of Medicinal Chemistry, 07 May 2011 (07.05.2011), Vol.54, pages4187-4206; entire document	1-3, 31-33

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 October 2018	24 OCT 2018

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/46707

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

3. ☒ Claims Nos.: 4-30, 34-62
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

(43) International Publication Date
14 July 2005 (14.07.2005)

PCT

(10) International Publication Number
WO 2005/063755 A1

(51) International Patent Classification[7]: C07D 487/04, A61K 31/495

(21) International Application Number: PCT/IB2004/004234

(22) International Filing Date: 20 December 2004 (20.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/532,031 22 December 2003 (22.12.2003) US

(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).

(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.

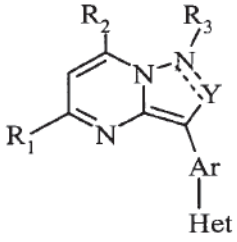
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, 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:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

WO 2005/063755 A1

(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

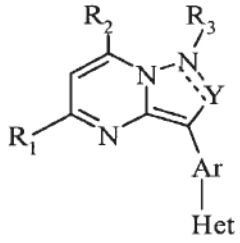
application WO 98/54093 described certain pyrazolopyrimidine compounds as tyrosine kinase inhibitors.

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.

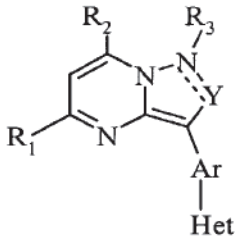
The CRF receptor antagonists of this invention may have utility over a wide range of therapeutic applications, and may be used to treat a variety of disorders or illnesses, including stress-related disorders. Such methods include administering a pharmaceutically effective amount of a CRF receptor antagonist 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.

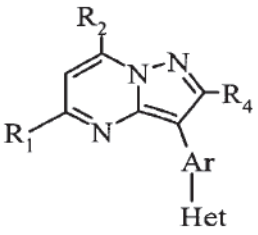
"Mono- or di(alkyl)amino represents an amino substituted with one alkyl or with two alkyls, respectively.

"Mono- or di(alkyl)aminoalkyl" represents an alkyl substituted with a mono- or di(alkyl)amino.

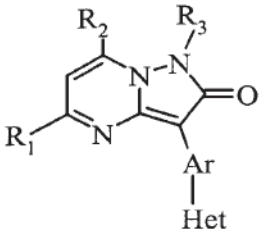
"Alkylsulfonyl or alkylsulfinyl" represents an alkyl substituted with a ($-S(=O)_2-$) or ($-S(=O)-$) functionality, respectively.

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).

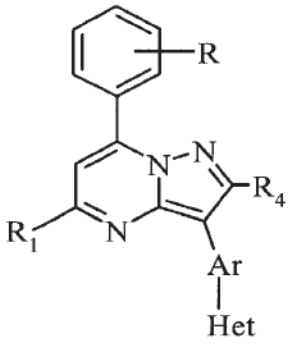


(II)



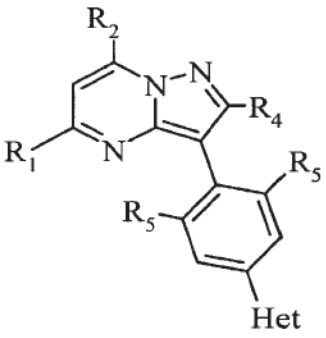
(III)

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)-.

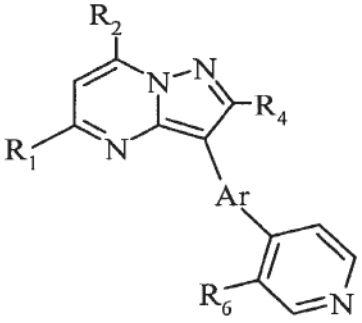


(IV)

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)



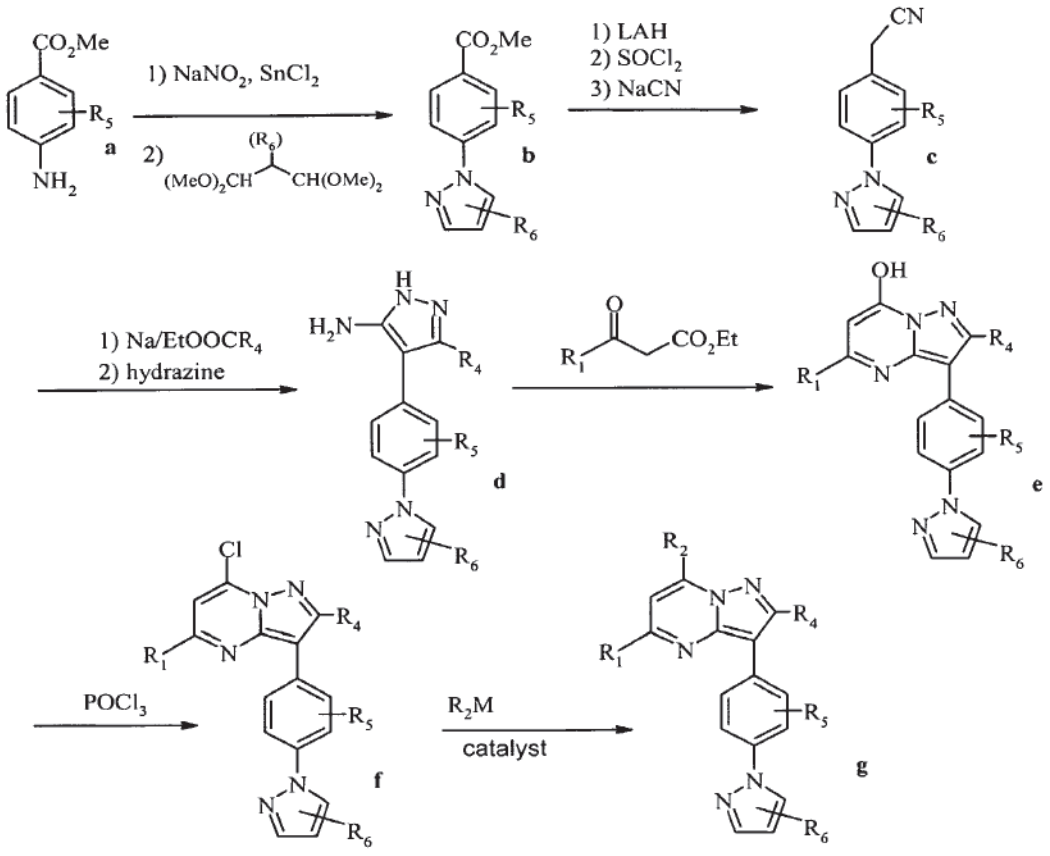
(VI)

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

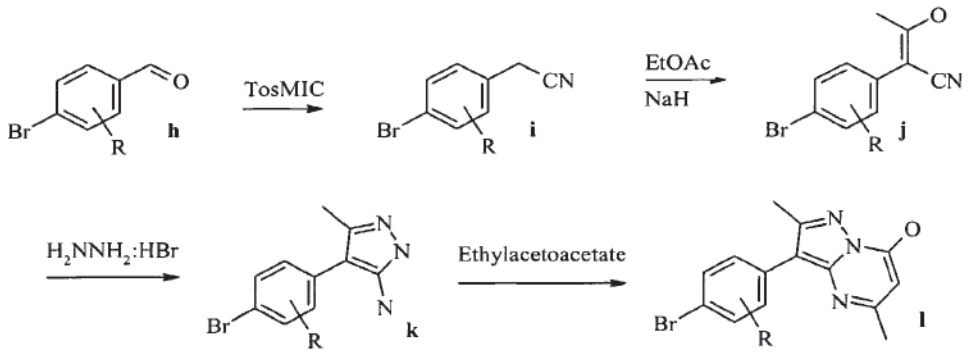


The amino functionality of 4-aminobenzoate **a** may be condensed with an, optionally, substituted malonaldehyde to give the corresponding 4-pyrazol-1-yl benzoate **b**. After reaction with LAH, $SOCl_2$, and NaCN to give conversion to the pyrazolophenylacetonitrile compound **c**, reaction with Na/ethyl 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).

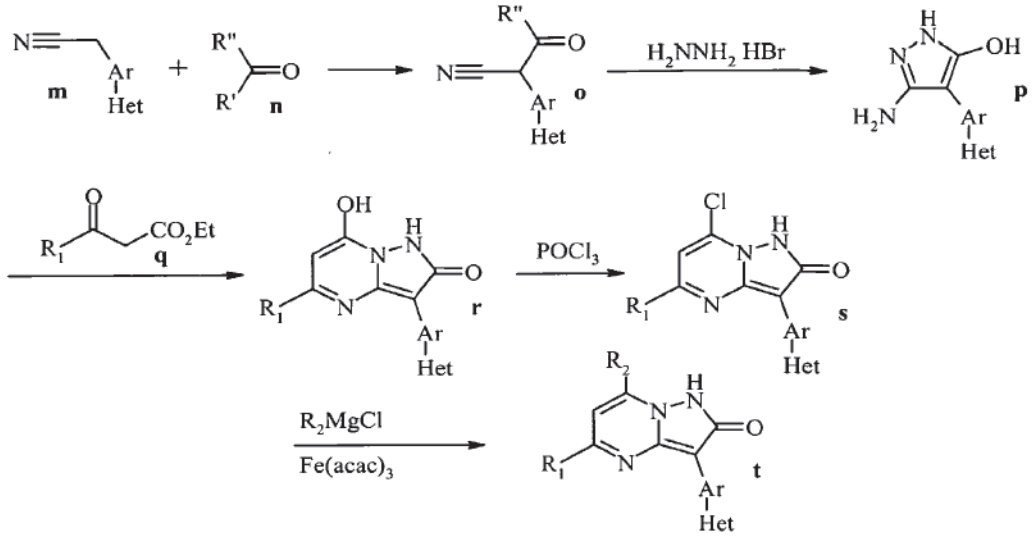
The R_2 groups thus installed may be further manipulated or reacted, using standard methods known to those skilled in the art (for example oxidation/reduction, hydrolysis, and the like), to provide further examples of the invention.

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

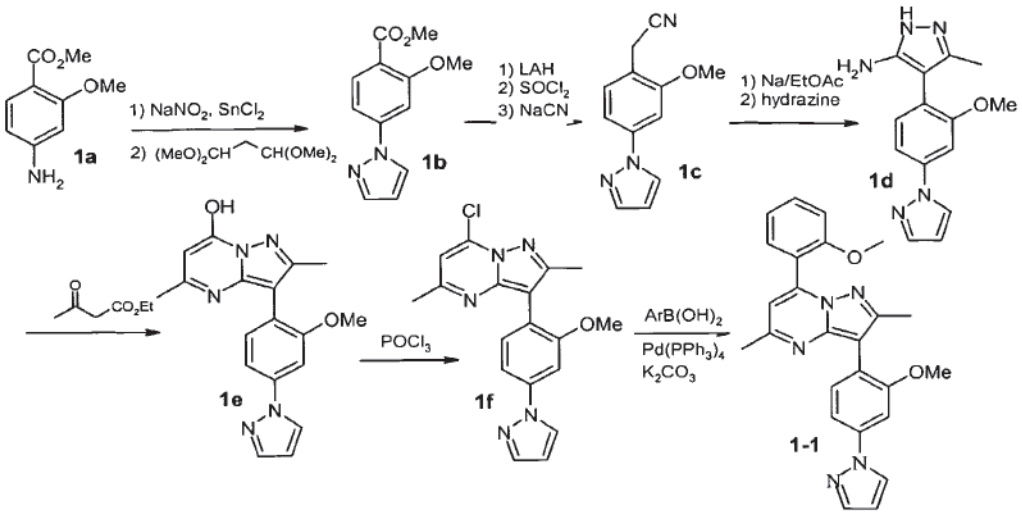
THF: tetrahydrofuran

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.

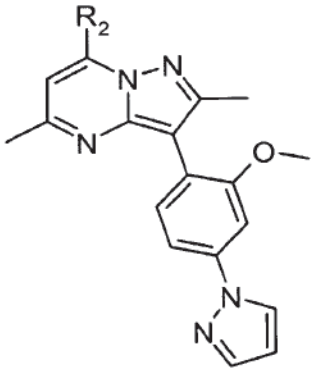
Step 1E:

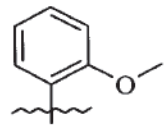
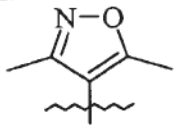
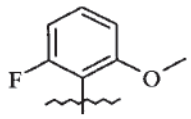
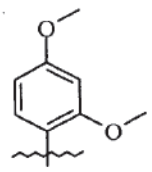
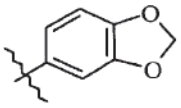
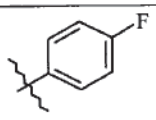
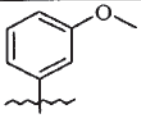
To a suspension of **1e** (2.1 g, 6.3 mmol) in acetonitrile was added $POCl_3$ (2.2 mL, 24.1 mmol,) and this mixture was refluxed for 5 hr, decanted to ice-water, and extracted with EtOAc to yield Cmpd **1f** (1.88 g) after chromatographic purification.

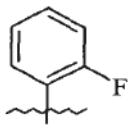
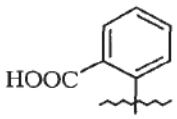
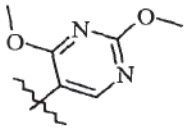
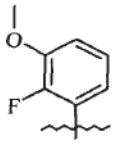
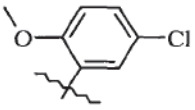
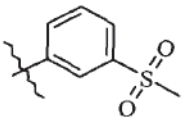
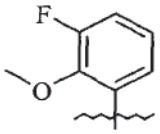
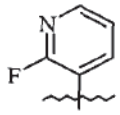
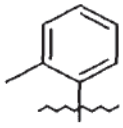
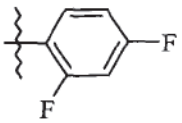
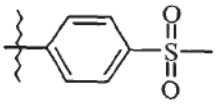
Step 1F:

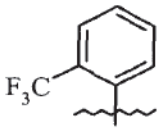
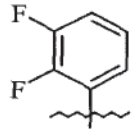
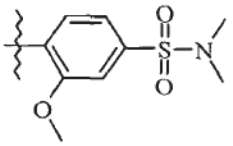
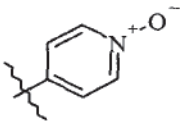
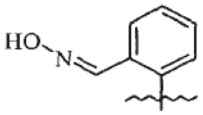
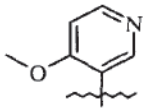
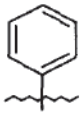
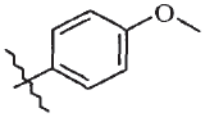
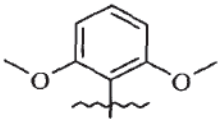
A mixture of Cmpd **1f** (1.0 mmol), 2-methoxyphenylboronic acid (1.2 mmol), K_2CO_3 (2.0 mmol) and $Pd(PPh_3)_4$ (0.05 mmol) was heated in 1,4-dioxane/H_2O (2:1) at 110 °C overnight. After evaporation of solvent, the mixture was extracted between $CHCl_3$/H_2O, and the organic phase was dried and evaporated to dryness. Cmpd **1-1** (402 mg) was obtained after column chromatography. Depending on the

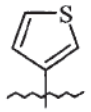
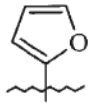
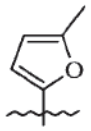
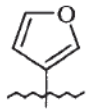
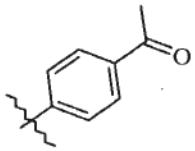
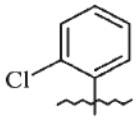
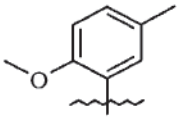
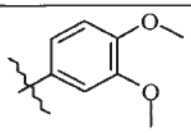
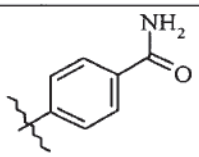
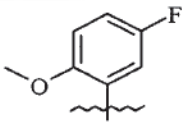
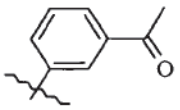
aryl functionality in the arylboronic acid reagent, the compounds listed in the following table were synthesized and purified by preparative LC-MS:

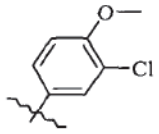
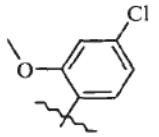
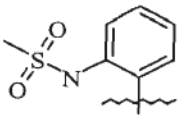
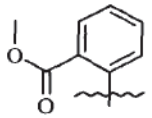
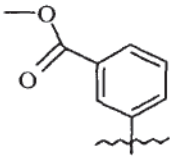
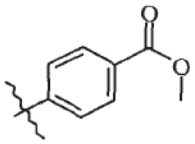
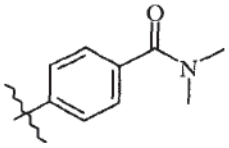
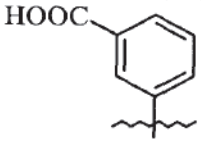
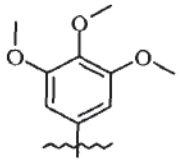
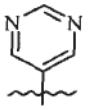


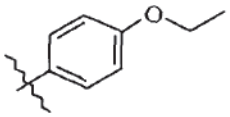
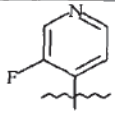
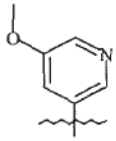
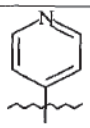
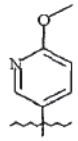
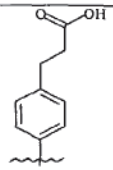
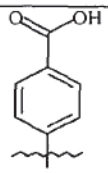
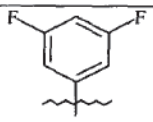
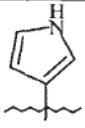
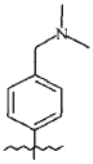
Cmpd	R_2	MW	MS	t_R	HPLC Method
1-1		425.49	425	1.315	4
1-2		414.47	414	1.586	4
1-3		443.48	443	1.335	4
1-4		455.52	455	1.32	4
1-5		439.47	439	1.353	4
1-6		413.45	413	1.25	4
1-7		425.49	425	1.317	4

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