PCT examination. For the sake of completeness it is pointed out that MTIP in D1 falls within the scope of the current application.

Re Item VII
Certain defects in the international application

1. The reference on page 20, lines 25-26 to "not limit" should be deleted (Art 6 PCT).

Re Item VIII
Certain observations on the international application

1. The prior art documents D1-D6 and D9 have not been cited (Rule 5.1 (a) (ii) PCT).

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(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

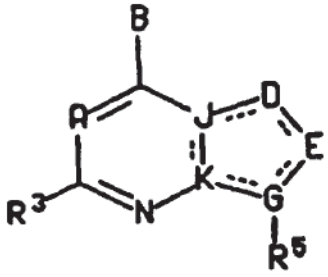
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(54) Title: SUBSTITUTED 6,5-HETERO-BICYCLIC DERIVATIVES

(57) Abstract

This invention relates to compounds of formula (I), wherein the dashed lines represent optional double bonds; A is nitrogen or CR^7; B is $-NR^1R^2$, $-CR^1R^2R^{10}$-$C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$; J and K are each independently nitrogen or carbon and both J and K are not nitrogens; D and E are each selected, independently, from nitrogen, CR^4, C=O, C=S, sulfur, oxygen, CR^4R^6 and NR^8; G is nitrogen or carbon; and their use for the prevention or inhibition of a disorder that can be treated by antagonizing CRF.



(I)

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SUBSTITUTED 6,5- HETERO-BICYCLIC DERIVATIVES

Background of the invention

This invention relates to certain pharmaceutically active substituted 6,5-hetero-bicyclic derivatives, pharmaceutical compositions containing them and methods of administering them to subjects in need of their corticotropin releasing factor antagonist activity.

The substituted heterocyclic derivatives claimed in this case exhibit activity as corticotropin releasing factor (hormone) CRF (CRH) antagonists.

CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. They are also referred to in the following: PCT Patent Application PCT/IB95/00439, which designates the United States and was filed on June 6, 1995 and published on December 14, 1995; PCT Patent Application PCT/IB95/00373, which designates the United States and was filed on May 18, 1995 and published on December 21, 1995; U.S. Patent Application 08/448,539, which was filed in the PCT on Nov. 12, 1993 and entered the U.S. national phase on June 14, 1995; PCT Patent Application WO 95/10506, which was filed on October 12, 1993 and published on April 20, 1995, and U.S. Patent Application 08/481,413, which was filed in the PCT on November 26, 1993 and entered the U.S. national phase on July 24, 1995; U.S. Patent Application 08/254,820, which was filed on April 19, 1995; Provisional U.S. Patent Application 60/008,396, which was filed on December 8, 1995; and Provisional U.S. Patent Application 60/006,333, which was filed on November 8, 1995. All the foregoing patent applications are incorporated herein by reference in their entireties.

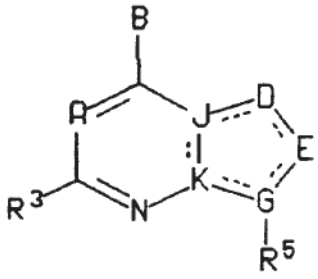
The importance of CRF antagonists is set out in the literature, e.g., P. Black, Scientific American SCIENCE & MEDICINE,1995, p. 16-25; T. Lovenberg et al., Current Pharmaceutical Design, 1995, 1, 305-316; and United States Patent 5,063,245, which is referred to above. A recent outline of the different activities possessed by CRF antagonists is found in M. J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are effective in the treatment of a wide range of stress-related illnesses, mood disorders such as depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, postpartum depression, dysthemia, bipolar disorders and cyclothymia;

chronic fatigue syndrome; eating disorders such as anorexia and bulimia nervosa; generalized anxiety disorder; panic disorder; phobias; obsessive-compulsive disorder, post-traumatic stress disorder, pain perception such as fibromyalgia; headache; gastrointestinal diseases; hemorrhagic stress; ulcers; stress-induced psychotic episodes; fever; diarrhea; post-operative ileus, colonic hypersensitivity; irritable bowel syndrome; Crohn's disease; spastic colon; inflammatory disorders such as rheumatoid arthritis and osteoarthritis; pain; asthma; psoriasis; allergies; osteoporosis; premature birth; hypertension, congestive heart failure; sleep disorders; neurodegenerative diseases such as Alzheimer's disease, senile dementia of the Alzheimer's type, multiinfarct dementia, Parkinson's disease, and Huntington's disease; head trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; spinal cord trauma; psychosocial dwarfism; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone; obesity; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; infertility, cancer; infertility; muscular spasms; urinary incontinence; hypoglycemia and immune dysfunctions including stress induced immune dysfunctions, immune suppression and human immunodeficiency virus infections; and stress-induced infections in humans and animals.

The compounds of this invention are also believed to be inhibitors of CRH binding protein and therefore useful in the treatment of disorders the treatment of which can be effected or facilitated by inhibiting such protein. Examples of such disorders are Alzheimer's disease and obesity.

Summary of the Invention

The present invention relates to compounds of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

J and K are each independently nitrogen or carbon and both J and K are not nitrogens ;

D and E are each selected, independently, from nitrogen, CR^4, C=O, C=S, sulfur, oxygen, CR^4R^6 and NR^8 ;

G is nitrogen or carbon;

the ring containing D, E, G, K, and J in formula I may be a saturated or unsaturated 5-membered ring and may optionally contain one or two double bonds and may optionally contain from one to three heteroatoms in the ring and may optionally have one or two C=O or C=S groups;

R^1 is C_1-C_6 alkyl optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, -O-(C_1-C_4 alkyl), CF_3, -C(=O)O-(C_1-C_4alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, $-NO_2$, -SO(C_1-C_4 alkyl), $-SO_2$(C_1-C_4 alkyl), $-SO_2$NH(C_1-C_4 alkyl) and $-SO_2$N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl),

-COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or -$CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, (C_1-C_2 alkylene)-O-(C_1-C_2 alkyl), (C_1-C_2 alkylene)-OH, or -S(C_1-C_4 alkyl);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C_1-C_2 alkylene)-OH, CF_3, CH_2SCH_3, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl);

R^6 is hydrogen, methyl or ethyl;

R^8 is hydrogen or C_1-C_4 alkyl;

R^5 is phenyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{13} wherein one to three of said substituents may be selected, independently, from fluoro, chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, OH, (C_1-C_4 alkylene)-OH, (C_1-C_4alkylene)-O-(C_1-C_2 alkyl), -CN, -CF_3, -NO_2, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -OCO(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), -S(C_1-C_6 alkyl), (C_1-C_4 alkylene)-S-(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally have one or two double bonds;

R^7 is hydrogen, C_1-C_4 alkyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, -O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -OCF_3, -CF_3, -CH_2OH or -CH_2O(C_1-C_2 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: a) when both J and K are carbon and D is CR^4 and E is nitrogen, then G can not be nitrogen; (b) when both J and K are carbons and D and G are nitrogens, then E can not be CR^4 or C=O or C=S; (c) when both J and K are carbons and D and E are carbons, then G can not be nitrogen; (d) when G is carbon, it must be double bonded to E; and (e) in the ring containing J, K, D, E and G, there can not be two double bonds adjacent to each other.

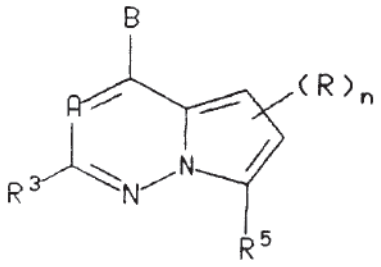
and the pharmaceutically acceptable salts of such compounds.

When the ring containing D, E, G, K and J is a 5-membered heteroaromatic ring, it may be, e.g., pyrazolo, imidazolo, thieno, furano, thiazolo, oxazolo, triazolo or thiadiazolo.

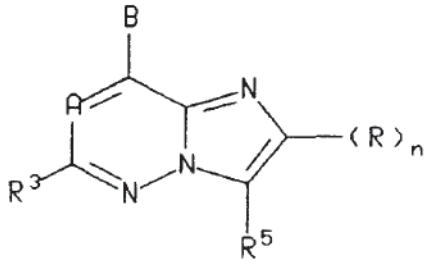
The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, unless otherwise indicated, means -O-alkyl, where "alkyl" is defined as above.

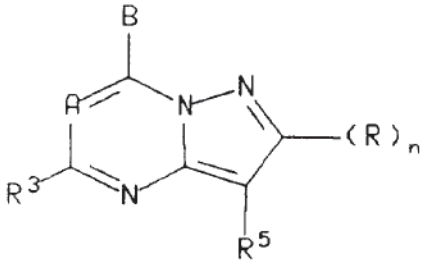
Examples of more specific embodiments of formula I are the following, wherein $(R)_n$ represents from zero to two substituents, wherein such substitutents are as defined above in the definition of formula I.



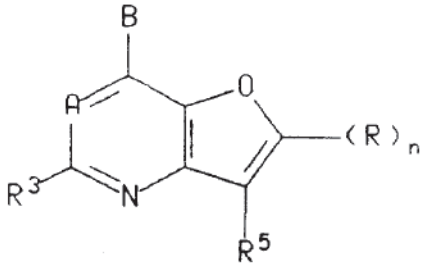
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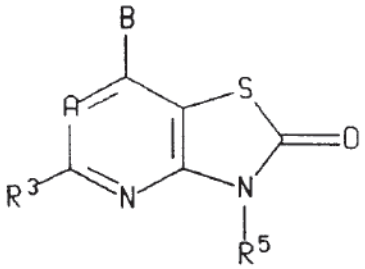
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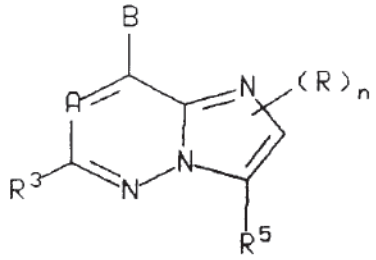
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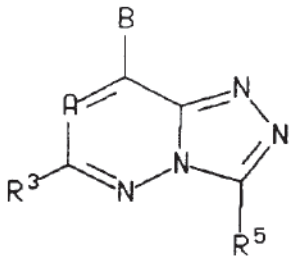
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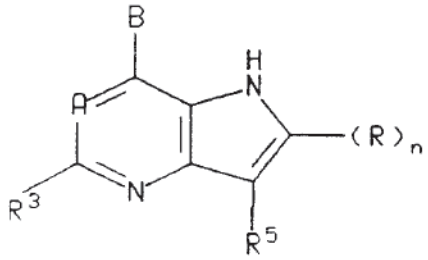
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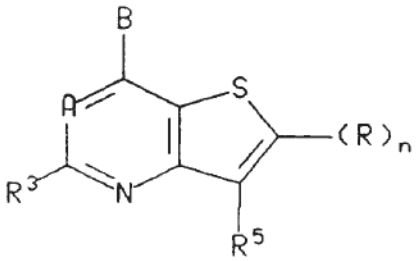
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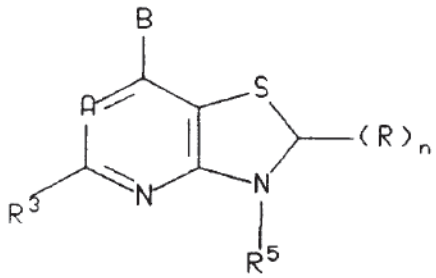
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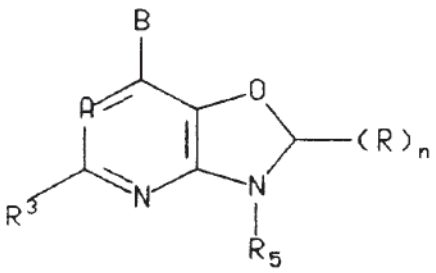
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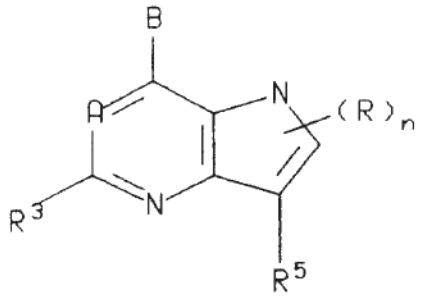
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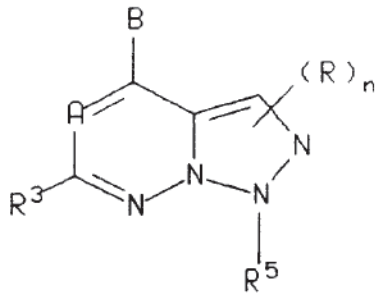
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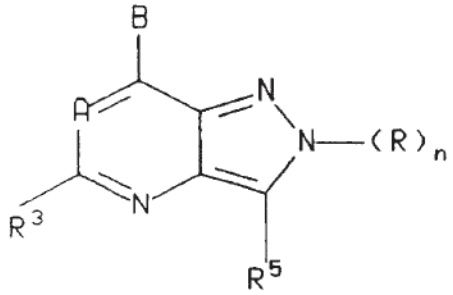
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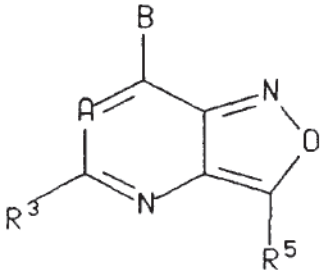
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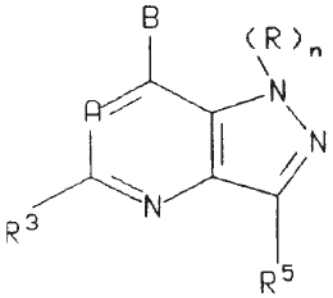
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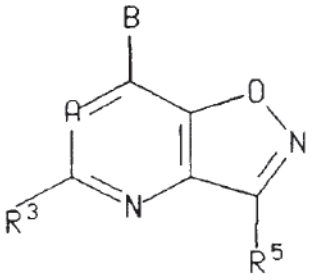
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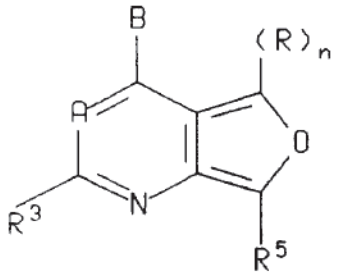
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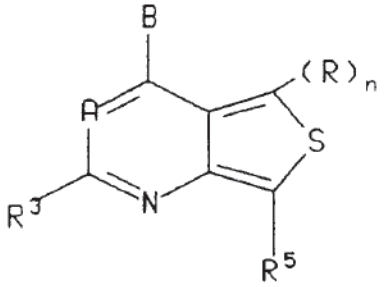
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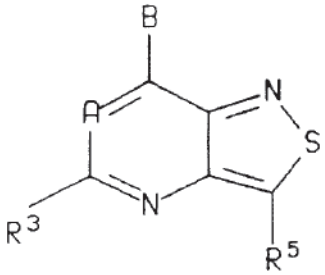
I-W



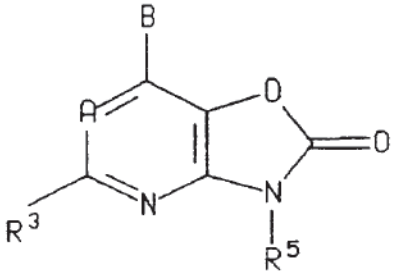
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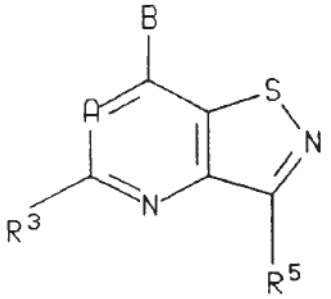
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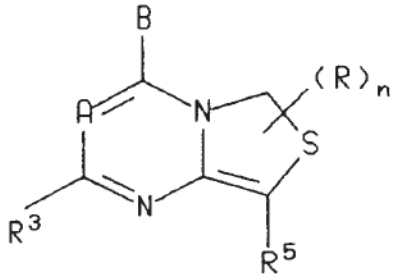
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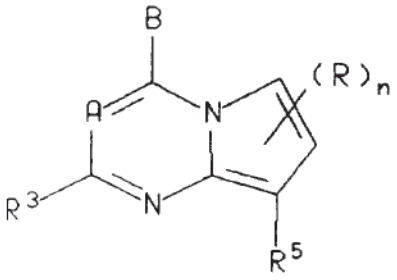
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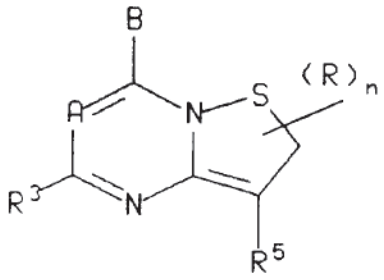
I-X



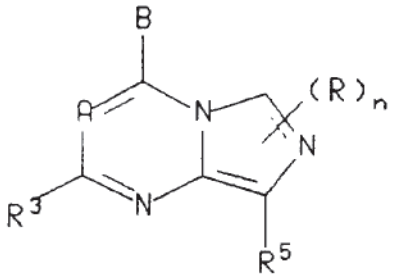
I-B′



I-Y



I-Z



I-A'

More specific embodiments of this invention include compounds of the above formula I wherein B is $-CHR^1R^2$, $-NR^1R^2$, $-NHCHR^1R^2$, $-OCHR^1R^2$ or $-SCHR^1R^2$, and R^1 is C_1-C_6 alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3 or C_1-C_4 alkoxy group and which may optionally contain one double or triple bond; and R^2 is benzyl or C_1-C_6 alkyl, which may optionally contain one double or triple bond, wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl may optionally be substituted with one fluoro, CF_3, C_1-C_2 alkyl, C_1-C_2 alkoxy or chloro group.

Other more specific embodiments of this invention include compounds of formula I wherein R^3 is methyl, ethyl, chloro or methoxy; R^4 and R^6 are selected from hydrogen, methyl and ethyl; R^5 is di- or tri-substituted phenyl, pyridyl, or pyrimidyl, in which the two or three substitutents on said phenyl, pyridyl or pyrimidyl are selected, independently, from C_1-C_4 alkyl, -O-(C_1-C_4 alkyl), (C_1-C_2 alkyl)-O-(C_1-C_4 alkyl), $-CF_3$, $-OCF_3$, -CHO, -(C_1-C_4 alkyl)-OH, cyano, chloro, fluoro, bromo and iodo, wherein each of the forgoing C_1-C_4 alkyl groups may optionally contain one double or triple bond;

Other more specific embodiments of this invention include compounds of the formula I wherein B is or contains an NR^1R^2 or $CR^1R^2R^{10}$ moiety which forms a saturated or unsaturated 5-membered carbocyclic ring wherein one of the ring carbons may optionally be replaced by a sulfur or oxygen atom.

Other more specific embodiments of this invention include compounds of the formula I wherein A is nitrogen or CR^7 and R^7 is hydrogen or methyl.

Other more specific embodiments of this invention include compounds of the formula I wherein B is $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$.

Other more specific embodiments of this invention include compounds of the formula I wherein A is CH, J and K are carbon and D, E, and G are nitrogen;

Other more specific embodiments of this invention include compounds of the formula I wherein J and D are nitrogen, K and G are carbon, and E is CH, CCH_3, or CC_2H_5.

Other more specific embodiments of this invention include compounds of the formula I wherein B contains a $-NR^1R^2$ or $-CR^1R^2R^{10}$ moiety that is a saturated or unsaturated three to five membered ring.

Other more specific embodiments of this invention include compounds of the formula I wherein J and K are carbon, and D–E–G is O-C(CH_3)=C, O-CH=C,

S-C(CH_3)=C, S-CH=C, N(CH_3)-C(CH_3)=C, N(CH_3)-CH=C, O-N=C, S-N=C, N(CH_3)-N=C, O-CH_2N, S-CH_2N, or NH-C(C_1-C_2alkyl)=C.

Examples of preferred compounds of the formula I:

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-propyl-amine;

[6-bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]-pyridin-7-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]-pyridin-7-yl]-amine;

[6-bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-methyl-amine; and

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]-pyridine.

Other compounds of formula I include the following:

4-(1-ethyl-propoxy)-2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]-pyrimidine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

[3-(4-bromo-2,6-dimethyl-phenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

3-(4-bromo-2,6-dimethyl-phenyl)-7-(1-ethyl-propoxy)-5-methyl-pyrazolo[1,5-a]-pyrimidine;

[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-diethyl-amine;

[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-ethyl-propyl-

amine;

[8-(4-chloro-2,6-dimethyl-phenyl)-2,7-dimethyl-pyrrolo[1,2-a]pyrimidin-4-yl]-ethyl-propyl-amine;

[8-(4-chloro-2,6-dimethyl-phenyl)-2,7-dimethyl-pyrrolo[1,2-a]pyrimidin-4-yl]-diethyl-amine;

[8-(4-chloro-2,6-dimethyl-phenyl)-2,6-dimethyl-pyrrolo[1,2-a]pyrimidin-4-yl]-diethyl-amine;

[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-diethyl-amine;

[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-ethyl-propyl-amine;

butyl-[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-ethyl-amine;

[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-(1-ethyl-propyl)-amine;

[8-(4-chloro-2,6-dimethyl-phenyl)-2,6-dimethyl-pyrrolo[1,2-a]pyrimidin-4-yl]-(1-ethyl-propyl)-amine;

8-(4-chloro-2,6-dimethyl-phenyl)-4-(1-ethyl-propoxy)-2,6-dimethyl-pyrrolo[1,2-a]-pyrimidine;

4-(1-ethyl-propoxy)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]-pyrimidine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidine;

(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-amine;

butyl-ethyl-[2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-a]pyrimidin-4-yl]-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-2H-isothiazolo[2,3-a]-pyrimidin-7-yl]-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-2H-isothiazolo[2,3-a]-pyrimidin-7-yl]-amine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-2H-isothiazolo[2,3-a]-pyrimidine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-imidazo[1,5-a]-

pyrimidine;

(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-imidazo[1,5-a]pyrimidin-4-yl]-amine;

[2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-imidazo[1,5-a]pyrimidin-4-yl]-(1-ethyl-propyl)-amine;

4-(1-ethyl-propoxy)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-imidazo[1,5-a]-pyrimidine;

4-(1-ethyl-propoxy)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-6,7-dihydro-imidazo [1,5-a]pyrimidine;

4-(1-ethyl-propoxy)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-thiazolo[3,4-a]-pyrimidine;

4-(1-ethyl-propoxy)-2-methyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]pyridazine;

4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]-pyridazine;

4-(1-ethyl-propoxy)-2,6-dimethyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]; pyridazine;

4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]-pyridazine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]pyridazin-4-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[2-methyl-7-(2,4,6-trimethyl-phenyl)-pyrrolo[1,2-b]pyridazin-4-yl]-amine;

[2,6-dimethyl-3-(2,4,6-trimethyl-phenyl)-imidazo[1,2-b]pyridazin-8-yl]-(1-ethyl-propyl)-amine;

8-(1-ethyl-propoxy)-2,6-dimethyl-3-(2,4,6-trimethyl-phenyl)-imidazo[1,2-b]-pyridazine;

8-(1-ethyl-propoxy)-6-methyl-3-(2,4,6-trimethyl-phenyl)-imidazo[1,2-b]pyridazine;

(1-ethyl-propyl)-[6-methyl-3-(2,4,6-trimethyl-phenyl)-imidazo[1,2-b]pyridazin-8-yl]-amine;

(1-ethyl-propyl)-[2-methyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-amine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-(1-ethyl-propyl)-amine;

4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]-pyridazine-b]pyridazine;

butyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-ethyl-amine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-ethyl-propyl-amine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-imidazo[1,5-b]pyridazin-4-yl]-diethyl-amine;

diethyl-[6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-amine;

ethyl-[6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-propyl-amine;

butyl-ethyl-[6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-amine;

(1-ethyl-propyl)-[6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]-pyridazin-8-yl]-amine;

8-(1-ethyl-propoxy)-6-methyl-3-(2,4,6-trimethyl-phenyl)-[1,2,4]triazolo[4,3-b]-pyridazine;

7-(1-ethyl-propoxy)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]-pyridine;

7-(1-ethyl-propoxy)-1,2,5-trimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]-pyridine;

(1-ethyl-propyl)-[1,2,5-trimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]-pyridin-7-yl]-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

butyl-[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-ethyl-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-ethyl-propyl-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-diethyl-amine;

ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-

propyl-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-amine;

diethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-amine;

[3-(4-bromo-2,6-dimethyl-phenyl)-5-methyl-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

[3-(4-chloro-2,6-dimethyl-phenyl)-5-methyl-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

3-(4-chloro-2,6-dimethyl-phenyl)-7-(1-ethyl-propoxy)-5-methyl-3H-[1,2,3]triazolo[4,5-b]pyridine;

3-(4-bromo-2,6-dimethyl-phenyl)-7-(1-ethyl-propoxy)-5-methyl-3H-[1,2,3]triazolo[4,5-b]pyridine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,5-b]pyridine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,5-b]pyridin-7-yl]-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isoxazolo[4,5-b]pyridin-7-yl]-amine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isoxazolo[4,5-b]pyridine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-thieno[3,2-b]pyridine;

7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-thieno[3,2-b]pyridine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-thieno[3,2-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-thieno[3,2-b]pyridin-7-yl]-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-furo[3,2-b]pyridin-7-yl]-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-furo[3,2-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-furo[3,2-b]pyridine;

7-(1-ethyl-propoxy)- 5-methyl-3-(2,4,6-trimethyl-phenyl)-furo[3,2-b]pyridine;

4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-6H-pyrrolo[3,4-b]-pyridine;

4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-6H-pyrrolo[3,4-b]-

pyridine;

(1-ethyl-propyl)-[2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-6H-pyrrolo[3,4-b]pyridin-4-yl]-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-2-thia-4-aza-inden-7-yl]-(1-ethyl-propyl)-amine;

7-(1-ethyl-propoxy)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-2-thia-4-aza-indene;

4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-furo[3,4-b]pyridine;

[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-furo[3,4-b]pyridin-4-yl]-(1-ethyl-propyl)-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-2H-pyrazolo[4,3-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-2H-pyrazolo[4,3-b]-pyridine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,3-b]pyridine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,3-b]pyridin-7-yl]-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-7-yl]-amine;

diethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl]-amine;

ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl]-propyl-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-7-yl]-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-diethyl-amine;

butyl-[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-amine;

butyl-ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

ethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;

diethyl-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

[3-(4-chloro-2,6-dimethyl-phenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

[3-(4-chloro-2,6-dimethyl-phenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

3-(4-chloro-2,6-dimethyl-phenyl)-7-(1-ethyl-propoxy)-5-methyl-pyrazolo[1,5-a]-pyrimidine;

8-(4-chloro-2,6-dimethyl-phenyl)-4-(1-ethyl-propoxy)-2-methyl-pyrazolo[1,5-a]-[1,3,5]triazine;

(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-amine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]-triazine;

4-(1-ethyl-propoxy)-2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]-triazine;

[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-(1-ethyl-propyl)-amine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrazolo[4,3-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

7-(1-ethyl-propoxy)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrazolo[4,3-b]-pyridine;

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,5-b]-pyridine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isothiazolo[4,5-b]pyridin-7-yl]-amine;

1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(1-ethyl-propoxy)-1H-pyrrolo[3,2-b]pyridine;

1,5-dimethyl-3-(2,6-dimethyl-4-chloro-phenyl)-7-(1-ethyl-propoxy)-1H-pyrrolo[3,2-b]pyridine;

2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(1-ethyl-propoxy)-1H-pyrrolo[3,2-b]pyridine;

2,5-dimethyl-3-(2,6-dimethyl-4-chloro-phenyl)-7-(1-ethyl-propoxy)-1H-pyrrolo[3,2-b]pyridine;

7-(1-cyclopropylmethyl-propoxy)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine;

7-(1-cyclopropylmethyl-propoxy)-1,5-dimethyl-3-(2,6-dimethyl-4-chloro-phenyl)-1H-pyrrolo[3,2-b]pyridine;

1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(tetrahydro-furan-3-yloxy)-1H-pyrrolo[3,2-b]pyridine;

1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(S)-(tetrahydro-furan-3-yloxy)-1H-pyrrolo[3,2-b]pyridine;

1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-7-(1-propyl-butoxy)-1H-pyrrolo[3,2-b]pyridine;

7-sec-butylsulfanyl-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine;

cyclopropylmethyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-b]pyrimidin-4-yl]-propyl-amine;

2-[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-ylamino]-butan-1-ol;

1,5-dimethyl-7-thiazolidin-3-yl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine;

[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-ethyl-(2,2,2-trifluoro-ethyl)-amine;

cyclopropylmethyl-[1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-propyl-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isoxazolo[4,5-b]pyridin-7-yl]-amine; and

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-isoxazolo[4,5-b]-pyridine.

This invention also relates to a pharmaceutical composition for the treatment, prevention or inhibition of (a) 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, or (b) 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, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, nicotine, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; 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; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., 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; multiinfract dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; and hypoglycemia in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in the treatment of such disorder, and a pharmaceutically acceptable carrier.

The invention also relates to a method for the treatment, prevention or inhibition of (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitator by CRF, or (b) 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, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders;

cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; 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; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., 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, nicotine, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; and hypoglycemia in a mammal, including a human, comprising administering to a subject in need of said treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder.

This invention also relates to a method of treating or preventing a disorder or condition, the treatment or prevention of which can be effected or facilitated by inhibiting CRH binding protein, in a mammal, including a human, comprising administering to said mammal a CRH binding protein inhibiting amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

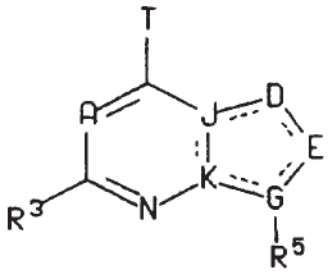
This invention also relates to a pharmaceutical composition for treating or preventing a disorder or conditon, the treatment or prevention of which can be effected or facilitated by inhibiting CRH binding protein in a mammal, including a human, comprising a CRH binding protein inhibiting amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

This invention includes all optical isomers and other stereoisomers of compounds of the formula I. When such compounds contain one or more chiral

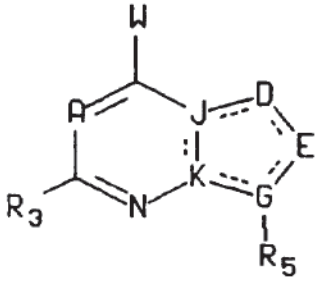
centers, it is understood that the invention includes the racemic mixtures as well as all individual enantiomers and diastereomers of such compounds, and mixtures thereof.

Detailed Description of the Invention

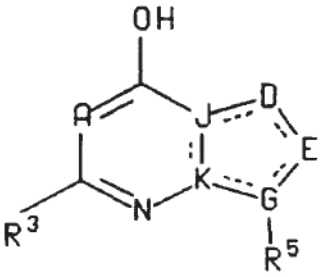
The following compounds having the formulas II, III, IV and V are useful as intermediates in the synthesis of compounds of the formula I.



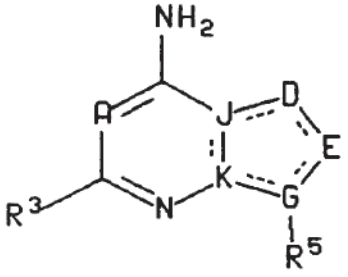
II



III



IV

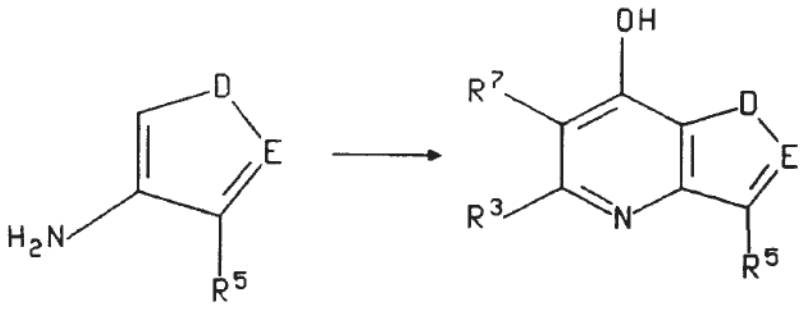


V

wherein T is chloro, bromo, iodo or $-OSO_2CF_3$; W is cyano, formyl, or $-COO(C_0-C_4$ alkyl) and A, J, K, D, E, G, R^3, and R^5 are as defined above with reference to formula I.

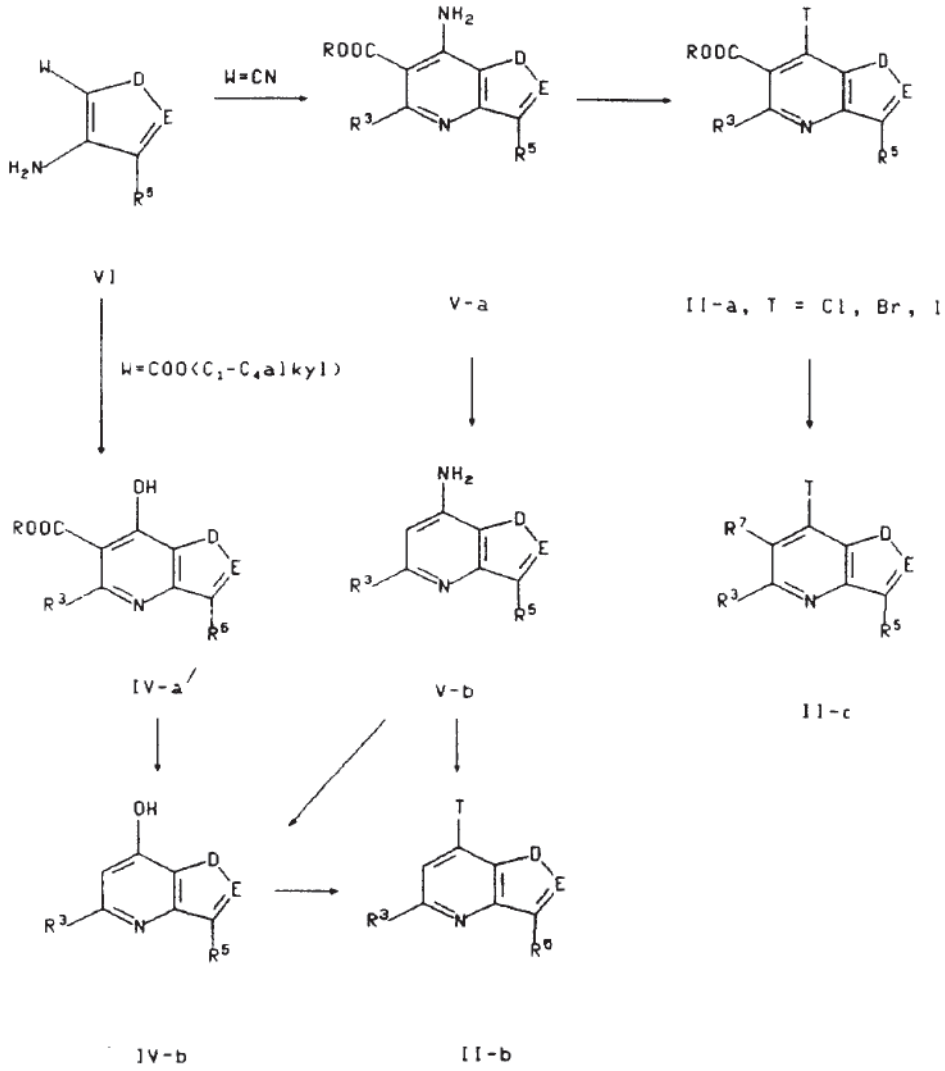
Compounds of the formula I may be prepared as described below. In the reaction schemes and discussion that follow, A, B, D, E, G, J, K, R^3, R^5 and structural formulae I, II, III, IV, and V are defined as above.

SCHEME 1

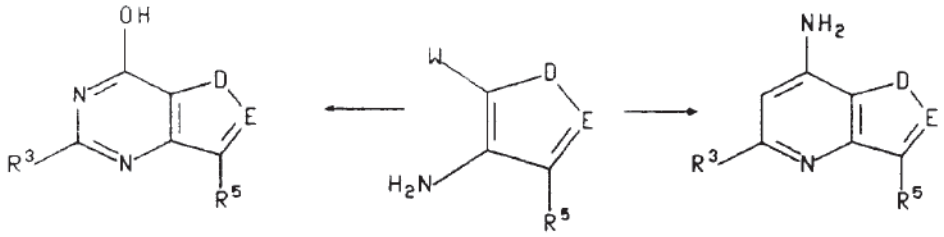


VI-a IV-a

SCHEME 2

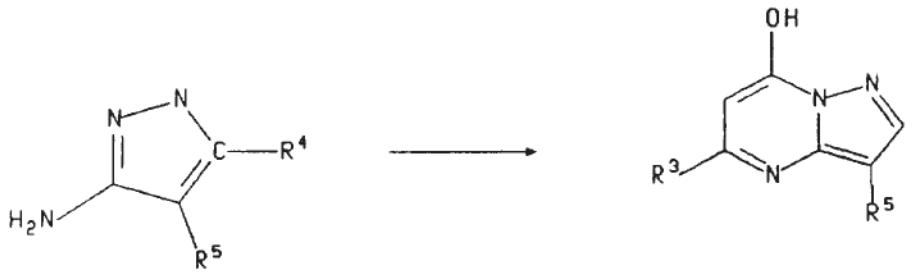


SCHEME 3



IV-c VI (W=CN, -COO(C_1-C_4 alkyl), -$CONH_2$) V-b

SCHEME 4



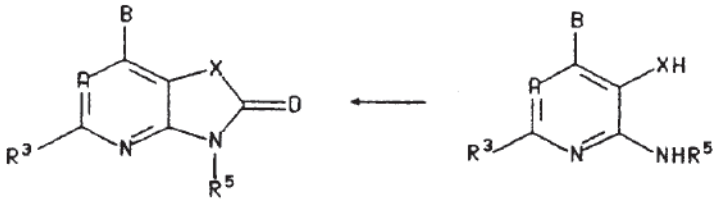
IX IV-d

SCHEME 5



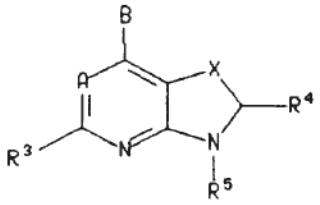
X I-N

SCHEME 6



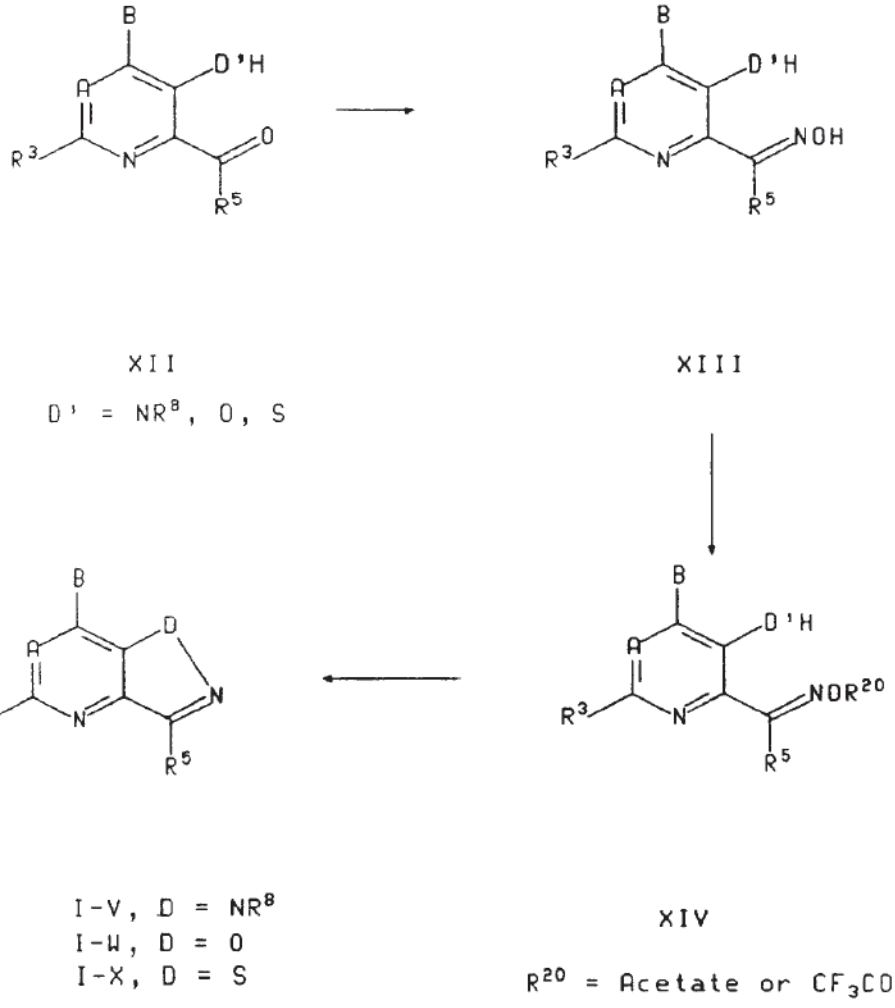
I-K, X=S or O, Y=O
I-U, X=S or O, Y=S

XI

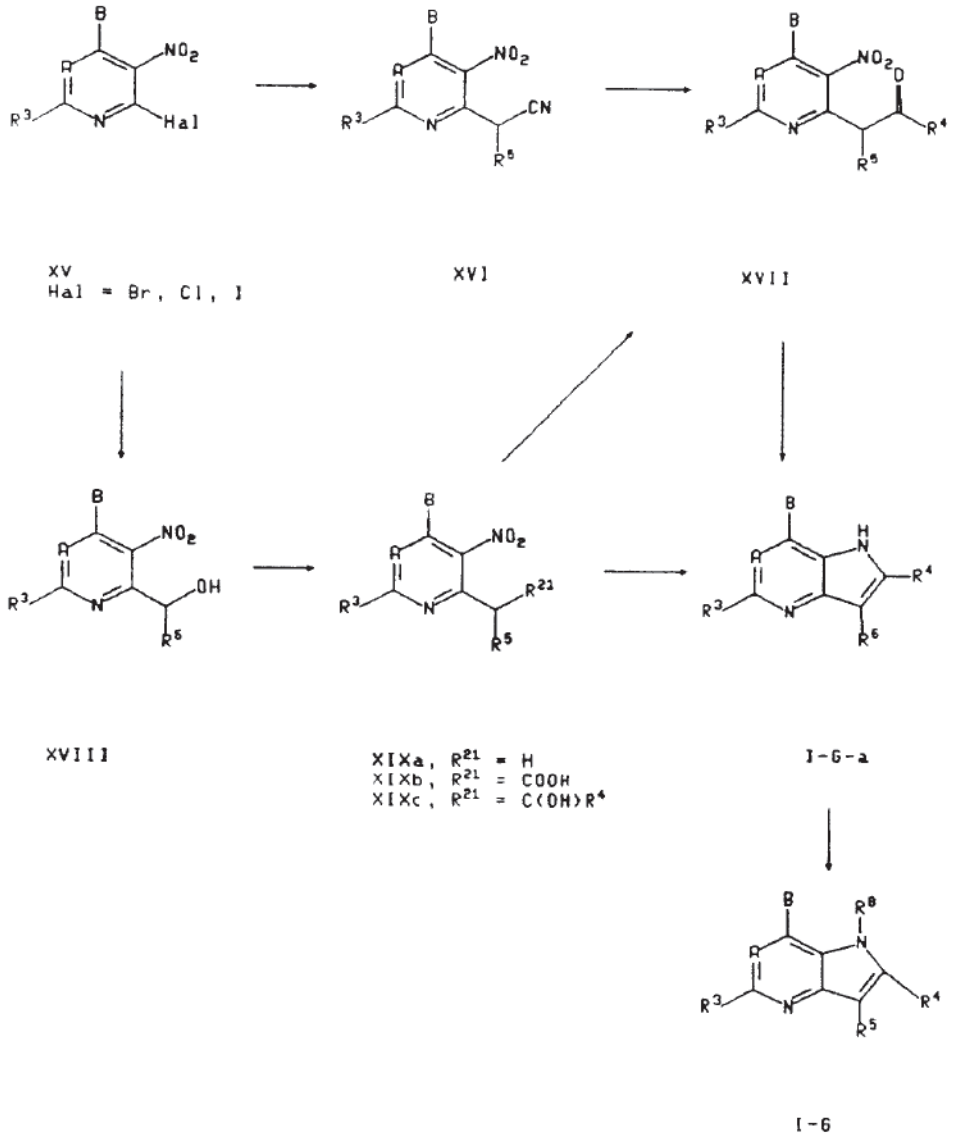


I-L, X=S
I-M, X=O

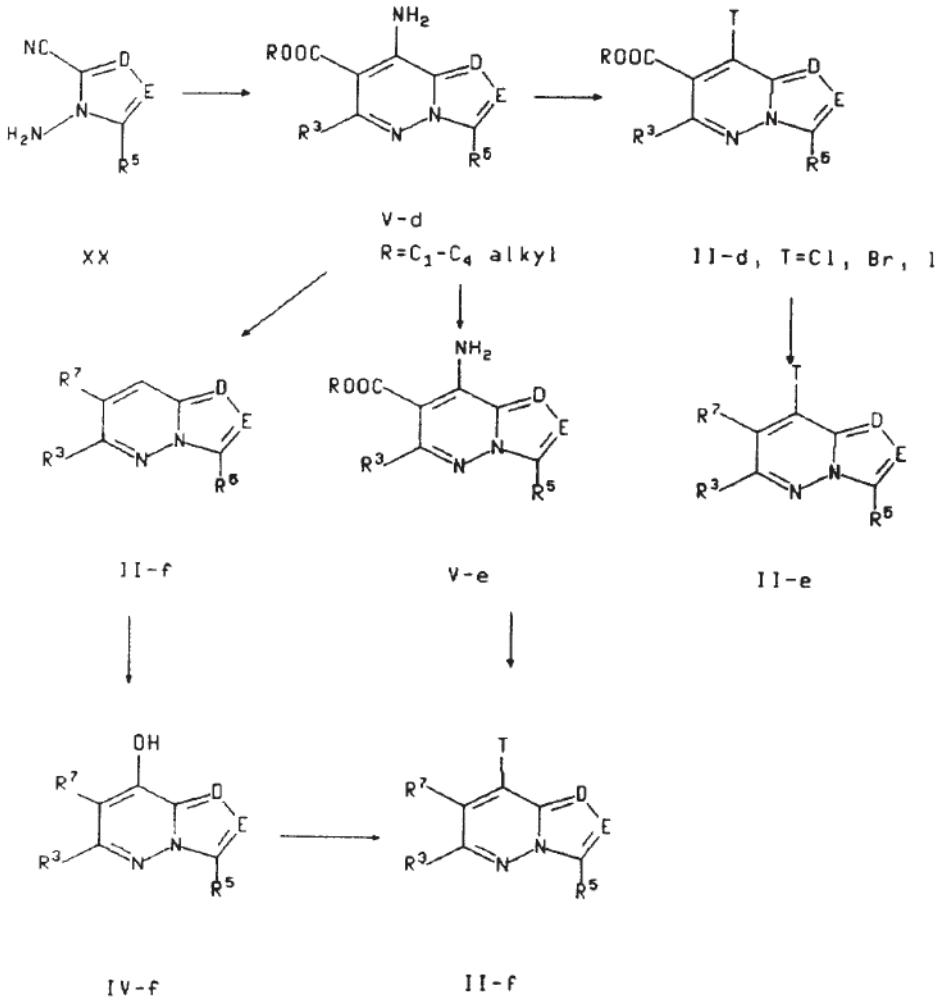
SCHEME 7


B
D'H
A
R3
N
O
R5
NOH
NOR20
D
I-V, D = NR8
I-W, D = O
I-X, D = S
XII
D' = NR8, O, S
XIII
XIV
R20 = Acetate or CF3CO

SCHEME 8


XV
Hal = Br, Cl, I
XVI
XVII
XVIII
XIXa, R21 = H
XIXb, R21 = COOH
XIXc, R21 = C(OH)R4
I-G-a
I-G

SCHEME 9


NC
D
E
N
H2N
R5
XX
NH2
ROOC
R3
V-d
R=C1-C4 alkyl
T
II-d, T=Cl, Br, I
R7
II-f
V-e
II-e
OH
IV-f

Compounds of the formula I wherein B is $-NR^1R^2$ or $-NHCR^1R^2R^{11}$ may be prepared by reacting a compound of the formula II wherein T is chloro, bromo, or iodo with a compound of the formula BH, in the presence of a base, with or without an organometallic compound such as Cu(I)X, wherein X is chloro, bromo or iodo, or an acid (such as p-TsOH (Ts=Tosyl) or another sterically hindered phenol) or an equivalent agent known to those of skill in the art. Suitable solvents for this reaction include DMSO, NMP, dimethylacetamide and THF. An excess of BH may be used as both the reagent and the base. Other bases such as potassium or sodium carbonate, a trialkylamine, a potassium or sodium (C_1-C_4 alkoxide) and sodium hydride may also be used. When R^7 is an electron withdrawing group such as -COO(C_1-C_4alkyl) or CN, the reaction generally is carried out at a temperature between about room temperature and about 100°C. When R^7 is a non-electron withdrawing group, the reaction temperature can generally range from about 50°C to about 270°C and the pressure can generally range from about 4 psi to about 300 psi. A pressure reactor may be used.

Alternatively, the compounds of formula I may be prepared by reacting a compound of the formula II wherein T is bromo or iodo with 1 equivalent or an excess of BH and a base such as sodium or potassium carbonate or a sodium or potassium (C_1-C_4 alkoxide), in the presence of a palladium (II) or a palladium (0) catalyst such as $Pd(OAc)_2$ or $Pd(PPh_3)_4$, together with a racemic or chiral phosphino agent such as 2,2-bis(diphenylphosphino)-1,1-binaphthyl (BINAP). Alternatively, premade Pd(II)(BINAP) may be used in an appropriate inert (i.e., inert with respect to the reaction at hand) solvent such as toluene, xylene, dioxane or sulfolane, at a temperature from about room temperature to about 180°C, preferably at about reflux temperature.

Compounds of the formula I wherein B is $-OCR^1R^2R^{11}$, $-SCR^1R^2R^{11}$, or $-NHCR^1R^2R^{11}$ may be prepared by reacting compounds in the formula II wherein T is chloro, bromo or iodo with a compound of the formula BH in the presence of a base which is capable of deprotonation of BH (e.g., sodium or potassium hydride, or an organometallic base such as sodium diisopropylamide, sodium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, a sodium C_1-C_4 alkoxide or n-butyllithium), in an inert organic solvent such as tetrahydrofuran, acetonitrile, dimethylsulfoxide, acetone, a C_2-C_5 alcohol, chloroform, benzene, xylene, toluene, N,N-dimethylformamide (DMF), methylene chloride, 1-methyl-2-pyrrolidinone or a mixture of

two or more of the above solvents (e.g., DMSO and THF), at a temperature from about 0°C to about 180°C, preferably from about 50°C to about 180°C.

Compounds of the formula I wherein B is $-CR^1R^2R^{11}$, $-C(C=CR^2R^{12})R^1$, $-CR^2R^{11}NHR^1$, $-CR^2R^{11}OR^1$, $-CR^2R^{11}SR^1$, or $-C(O)R^2$ may be prepared from compounds of the formula III wherein W is cyano, formyl or carboxy, as described below.

Reacting compounds of formula III wherein W is cyano with a Grignard reagent containing the group R^2 in an inert solvent such as THF, glyme, ether or dioxane, will yield corresponding compounds of formula I wherein B is $-COR^2$. Further reaction of the compounds of formula I wherein B is COR^2 with a Grignard reagent containing R^1, using a solvent such as those referred to above, will yield the corresponding the compounds of formula I wherein B is $-CR^1R^2OH$. Reacting compounds of formula III wherein W is formyl with a Grignard reagent containing the group R^2, in an ethereal solvent such as those referred to above, will yield the corresponding compounds of formula I wherein B is $-CHR^2OH$.

Compounds of formula I wherein B is $-CR^1R^2R^{11}$ or $-C(C=CR^2R^{11})R^1$ may be prepared by conventional methods. Thus, reaction of a compound of the formula I wherein B is $-CR^{1'}R^{2'}OH$, (wherein $R^{1'}$ and $R^{2'}$ are defined as R^1 and R^2, respectively, except that $R^{1'}$ may not be R^1 and $R^{2'}$ may not be R^2), with an acid such as concentrated sulfuric acid in acetic acid, or a Burgess inner salt such as (carboxysulfamoyl)triethylammonium hydroxide methyl ester, will yield a compound of the formula I wherein B is $-C(=CR^2R^{11})R^1$. Hydrogenation of a compound of formula I wherein B is $-C(=CR^2R^{11})R^1$ using palladium on carbon (Pd/C) or a platinum dioxide catalyst in a (C_1-C_4)alkanol solvent will yield a compound of the formula I wherein B is $-CHR^1R^2$. Reaction of a compound of the formula I wherein B is $-CR^1R^2OH$ with diethylaminosulfur trifluoride or triphenylphosphine/carbon tetrachloride in an inert solvent such as carbon tetrachloride will afford a compound of the formula I wherein B is $-CR^1R^2F$ or $-CR^1R^2Cl$, respectively.

Reduction of a compound of formula I wherein B is $-COR^2$ with sodium borohydride, in an inert solvent such as a (C_1-C_4)alkanol, will yield a compound of the formula I wherein B is $-CHR^2OH$. Alkylation of a compound of the formula I wherein B is $-CHR^2OH$ with an alkyl halide (such as alkyl iodide) in the presence of a base such as sodium hydride (NaH) at room temperature, in an inert solvent such as toluene, THF,

dioxane or ether, will yield the corresponding compound of the formula I wherein B is $-CHR^2OR^1$.

Compounds of the formula I wherein B is $-CR^2R^{10}NHR^1$ may be prepared by conventional methods such as reductive amination of the corresponding compounds of the formula I wherein B is $-C(O)R^2$ with an appropriate amine and reducing agent (such as sodium cyanoborohydride, sodium triacetoxyborohydride, or lithium aluminum tetrahydride) in an appropriate inert solvent such as a C_1-C_4 alkanol or acetic acid.

Conversion of compounds in formula I wherein B is $-C(O)R^2$ into compounds in formula I wherein B is $-C(S)R^2$ can be accomplished using standard methods well known in the art (e.g., using Lawesson's Reagent or diphosphorus pentasulfide (P_2S_5)). Reduction of compounds of the formula I wherein B is $-C(S)R^2$ with a reducing agent such as sodium borohydride or lithium aluminum tetrahydride gives the corresponding compounds of the formula I wherein B is $-CHR^2SH$. Alkylation of compounds of the formula I wherein B is $-CHR^2SH$ with alkyl halide (such as alkyl iodide) in the presence of a base such as sodium hydride in an inert solvent such as THF, DMF or toluene at about room temperature will afford the corresponding compounds of the formula I wherein B is $-CHR^2SR^1$.

Compounds in formula II may be prepared from compounds of the formula IV or V as described below.

Compounds of formula II wherein T is chloro, bromo or iodo can be prepared by reacting compounds of the formula IV with from one equivalent to an excess of POT_3 (wherein T is chloro, bromo or iodo) in the presence or absence of a di(C_1-C_4 alkyl)aniline, preferably diethylaniline, with or without a solvent (such as dichloroethane, DMF, dimethylsulfoxide (DMSO) or acetamide), at a temperature from about room temperature to about 180°C, preferably from about 100°C to about 150°C. Alternatively, compounds of formula II wherein T is chloro, bromo or iodo can be prepared by reacting the corresponding compounds of formula II wherein T is $-O-SO_2CF_3$ with a sodium or potassium halide, in an appropriate inert solvent such as THF, sulfolane, DMSO, DMF or acetonitrile, at a temperature from about 60°C to about 180°C. Compounds of formula II wherein T is $-OSO_2CF_3$ can be prepared by reacting compounds of formula IV with Tf_2O in the presence of a base such as triethylamine or pyridine, in an appropriate inert solvent such as THF, methylene chloride, dioxane,

ether or toluene, at an temperature from about 0°C to about 50°C, preferably from about 0°C to about room temperature.

Alternatively, compounds of formula II wherein T is chloro, bromo or iodo may be prepared by reacting compounds of formula V with a (C_1-C_7 alkyl)-nitrite and Cu(I)T_2 (wherein T is chloro, bromo or iodo) in an appropriate inert solvent such as acetonitrile, acetone, methylene chloride, THF, dioxane, benzene, toluene, dichloroethane, DMF, DMSO or N-methylpyrrolidinone (NMP) at a temperature from about room temperature to about 150°C, preferably from about 40°C to about 100°C.

Compounds of the formula IV may be prepared by reacting the appropriate compounds of formula V with sodium nitrite ($NaNO_2$) in an aqueous acid such as sulfuric acid, acetic acid or phosporic acid, with or without an organic solvent, preferably in acetonitrite (CH_3CN) or acetone.

Compounds of formula III wherein W is cyano can be prepared by reacting the corresponding compounds of formula II wherein T is chloro, bromo or iodo with potassium cyanide, copper cyanide, sodium cyanide or a di(C_1-C_4alkyl)aluminum cyanide in an appropriate inert solvent such as dimethylsulfoxide, DMF, toluene or xylene, at temperature from about room temperature to about 180°C, preferably from about 60°C to about 150°C, with or without Pd(II)OAc or Pd(0)(PPh_3)$_4$.

Compounds of formula III wherein W is -CHO or -COOH may be prepared by reacting compounds in formula II wherein T is bromo or iodo with an organolithium reagent such as t-BuLi, s-BuLi, or n-BuLi in an appropriate inert solvent such as THF, dioxane, ether, benzene or methylene chloride, at temperature from about -120°C to about room temperature, preferably from about -110°C to about -60°C, followed by quenching with an appropriate electrophile such as DMF or CO_2 (gas or dry ice), to give compounds of formula III wherein W is -CHO and -COOH, respectively.

It is understood that the general organic chemistry knowledge can be applied to change the steps of the reaction sequences described herein depending on the feasibility of the reaction. For example, a protecting group may be used at any stage of the various syntheses described above at which it is workable, or an ester group may be reduced to the corresponding C_1-C_4 alkyl group at any convenient stage. Compounds of formulas I - XVIII, wherein R^3 is chloro, bromo, -COO(C_1-C_4 alkyl) or -COOH, can be converted to the corresponding compounds wherein R^3 is (C_1-C_4 alkyl), -O(C_1-C_4 alkyl), fluoro, -S(C_1-C_4 alkyl) at any convenient stage, as appropriate, in the

syntheses referred to above using methods described in the literature. Compounds of formula I - XVIII, wherein R^3 is -O(C_1-C_4 alkyl) or -S(C_1-C_4 alkyl) can be prepared by reacting the corresponding compounds wherein R^3 is chloro, bromo or iodo, with a nucleophile such as a C_1-C_4 alkanol or a C_1-C_4 alkanethiol, in the presence of an organic or inorganic base. Suitable bases for such a reaction include sodium and sodium hydride. Compounds of formulas I - XVIII wherein R^3 is fluoro can be prepared by reacting the corresponding compounds wherein R^3 is chloro with tetrabutylammonium fluoride in a suitable inert solvent such as DMSO, methylene chloride, or tetrahydrofuran. Tetrahydrofuran is preferred.

Reduction of an ester or carboxylic acid using lithium aluminum tetrahydride/aluminum trichloride ($LiAlH_4/AlCl_3$) in an appropriate inert solvent such as THF, ether, or dioxane, at temperature from about 100°C to about room temperature, will afford the corresponding compound wherein R^3 is CH_3. Conversion of compounds wherein B is -COOH to the corresponding compounds wherein B is -CO(C_1-C_3 alkyl) may be accomplished using standard alkylation methods well known in art. Reduction of compounds wherein B is -CO(C_1-C_3 alkyl) using standard methods well known in the art will afford the corresponding compounds wherein R^3 is one of various (C_1-C_4 alkyl) derivatives.

Compounds of the formula IV-a wherein A is CR^7 and G, J, and K are carbon may be prepared by heating compounds of formula VI-a with an appropriate compound of the formula $R^3C(O)CR^7COO(C_1$-C_4 alkyl) under acid or Lewis acid conditions with or without a solvent, as shown in Scheme 1. Examples of such reaction conditions are: a) heating in polyphosphoric acid; b) heating in toluene, benzene or xylene in the presence of acid catalyst (such as p-TsOH, sulfuric acid or HCl(g)) using a Dean-Stark trap; or c) heating in an appropriate solvent such as dichloroethane, diphenylether (Ph_2O) or Dowtherm A in the presence of a Lewis acid such as $SnCl_4$, $ZnCl_2$/HCl or $AlCl_3$.

Compounds of formula VI-a may be prepared using methods described in the scientific literature. (See Gazz. Chim. Ital.; 111, p167-172(1981); Chem. Pharm. Bull.; 24, 3001-3010 (1976); J. Org. Chem., 38, 1777-1780 (1973); Chem. Abstr. 68, 68982f (1968); Aust. J. Chem.; 22, 563-572(1969); J. Chem. Soc. Perkin Trans.2, p1954, p1957 (1972); J. Heterocycl. Chem.; FR, 19, 443-445(1982); J. Heterocycl. Chem., 22,

1496-1502 (1985); Tetrahedron, 47, 4639-4644 (1991); J. Heterocycl. Chem., 28, 2053-2055 (1991); J. Heterocycl. Chem., 29, 251-153 (1992).

Compounds of formula V-a and IV-a', wherein R is C_1-C_4alkyl can be prepared by heating compounds of formula VI wherein W is -CN and -COO(C_1-C_4 alkyl), respectively, with an appropriate $R^3C(O)CH_2COO(C_1$-C_4 alkyl) in the presence of a Lewis acid such as $SnCl_4$, $AlCl_3$, $TiCl_3$ or $ZnCl_2$, in a inert solvent such as dichloroethane, at about the reflux temperature, as shown in Scheme 2. Base hydrolysis of a compound of the formula V-a or IV-a' with sodium hydroxide in H_2O/(C_1-C_4 alcohol) at reflux, or with lithium hydroxide in water/THF or water/dioxane at temperature from about room temperature to about the reflux temperature, followed by decarboxylation by heating in a oil bath at a temperature from about 140-180°C will give a compound of formula V-b or IV-b, respectively. Compounds of the formulas V-a and IV-a' may be converted into compounds of the formula II-a, and compounds of the formulas V-b and IV-b may be converted into compounds of the formula II-b by the procedures described above. The conversion of compounds of the formula II-a into those of the formula II-c can be accomplished using procedures analogous to those described above for converting compounds wherein R^3 is -COO(C_1-C_4 alkyl) into those wherein R^3 is C_1-C_4 alkyl.

Compounds of formula VI may be prepared using methods described in the literature. (See Liebigs Ann Chem., 1534-1546, 1979; Gazz. Chim. Ital., 97, 25-33, 1967; Gazz. Chim. Ital., 120, 725-730, 1990; Eur. J. Med. Chem. Chim. Ther., 26, 143-158, 1991; J. Heterocycl. Che., Fr. 19, 443-445, 1982; J. Heterocycl. Chem., 22, 1496-1502, 1985; J. Heterocycl. Chem., 31, 305-312, 1994; J. Heterocycl. Chem., 24, 243-245, 1987; J. Org. Chem. 57, 3713-3716, 1992; Liebigs Ann Chem., 1702-1710, 1984; Chem. Pharm. Bull., 34, 701-702, 1986; Pharmazie, 48, 849-853, 1993; Bull. Soc. Chim. Belg., 103, 181-184, 1994; and Indian. J. Chem. Sect. B, 33, 436-440, 1994).

Compounds of formula IV-c wherein A is N and G, J, and K are carbon may be prepared, as shown in Scheme 3, by reacting compounds of formula VI with $(R^3CO)_2O$, R^3COOH or $R^3CO(OC_1$-C_2 alkyl)$_3$, in acetic acid or an appropriate inert organic solvent such as toluene, dioxane, acetonitrile, methylene chloride or chloroform, at a temperature from about 25°C to about 150°C, preferably at about the reflux temperature, followed by heating in 85% phosphoric acid or an aqueous acid such as acetic acid, hydrochloric acid or sulfuric acid, preferably in 50-85% phosphoric acid. Compounds of formula V-b may be prepared, as shown in Scheme 3, by heating the

corresponding compounds of formula VI with excess of the appropriate compound of the formula R^3CONH_2.

Compounds of formula IV-d may be prepared, as shown in Scheme 4, by reacting compounds of formula IX with an appropriate reagent having the formula $R^3C(O)CHR^7COO(C_1\text{-}C_4alkyl)$ in an R^3COOH solvent at temperature from about 60°C to about 180°C, preferably at about the reflux temperature.

Compounds of formula I-N may be prepared, as shown in Scheme 5, by reacting the corresponding compounds of formula X with a (C_1-C_7 alkyl)nitrite, with or without $CuBr_2$, $CuCl_2$, or CuI_2, in an appropriate inert solvent such as acetonitrile, acetone, methylene chloride, chloroform, benzene or toluene, preferably acetonitrile at a temperature from about 25°C to about 150°C, preferably from about 60°C to 100°C.

Compounds of formula I-L and I-M may be prepared, as shown in Scheme 6, by reacting compounds of formula XI wherein X is S or O with a compound of the formula R^4CHO or $R^4CH(OC_1\text{-}C_2\ alkyl)_2$ and an acid catalyst such as p-TsOH, HCl, HBr, H_2SO_4, or HCl, in toluene, xylene or benzene, preferably toluene, with from one to ten equivalents of water, at temperature from about 70°C to about 160°C, using a Dean-Stark trap or in the presence of anhydrous sodium sulfate.

Compounds of formula I-K and I-U may be prepared by reacting the corresponding compounds of formula XI with triphosgene and thiophosgene, respectively, and a base such as triethylamine or pyridine in an appropriate inert solvent such as methylene chloride, THF, dioxane, ether, benzene or chloroform, preferably methylene chloride or dry THF, at temperature from about 0°C to about 25°C.

Compounds of formula I-V, I-W, and I-X may be prepared, as illustrated in Scheme 7, starting from compounds of formula XII. Compounds of formula XIII may be prepared by reacting the corresponding compounds of formula XII with hydroxylamine in acidic (e.g., in trifluoroacetic acid) or basic (e.g., in NaOAc or NaOH and hydroxylamine hydrochloride in a C_1-C_4 alcohol/water mixture) conditions at temperatures from about 25°C to about 150°C, preferably at about the reflux temperature. Compounds of formula XIV can be prepared by heating the corresponding compounds of formula XIII in acetic anhydride, trifluoroacetic anhydride or Tf_2O, with or without a solvent such as acetic acid or methylene chloride, in the presence of an appropriate amine base such as triethylamine or pyridine. Compounds of formula I-V, I-W and I-X may be prepared by heating the corresponding compounds

of formula XIV and pyridine in an inert solvent such as DMF, DMSO, NMP, sulfolane or acetamide at a temperature from about 80°C to about 180°C.

Compounds of formula I-G may be prepared, as illustrated in Scheme 8, by reducing the corresponding compounds of formula XVII. This reduction can be performed using standard methods known in literature for reduction of a nitro group to an amino group. Such methods include hydrogenation or reduction by iron in acetic acid. Cyclization may occur upon reduction or heating in an appropriate solvent such as a C_1-C_4 alcohol, acetonitrile, toluene, THF, methylene chloride or acetic acid.

The conversion of compounds of formula XVI into those of formula XVII can be accomplished using methods analogous to those described above for the conversion of compounds of formula V wherein W is cyano into compounds of formula I wherein B is a group having a carbon atom directly attached to the bicyclic ring. The best method for conversion of a cyano group to a -COOH group is acid hydrolysis, for example, heating the cyano compound in 50-85% phosphoric acid or 50-90% acetic acid, preferably phosphoric acid. The best method for converting a cyano group into a -CO(C_1-C_4 alkyl) is reacting the cyano compound with a Grignard reagent at a temperature from about 0°C to about 25°C in ether, THF or dioxane. The best method for converting a cyano group into a -CHO group is a diisobutylaluminum hydride reduction in THF, dioxane, or ether at a temperature from about -78°C to about 25°C, preferably from about -78°C to about -40°C.

Compounds of the formula XVI may be prepared by reacting compounds of formula XV, wherein Hal is chloro, bromo or iodo, with a sodium, potassium, or lithium salt of R^5CH_2CN in an appropriate inert solvent such as toluene, benzene, a C_1-C_5 alcohol, THF, DMSO, dioxane, or pyridine, with or without a Pd(II) or Pd(0) catalyst, at a temperature from about -78°C to about 130°C.

Alternatively, compounds of formula XVII may be prepared by subjecting compounds of the formula XV to halogen-metal exchange (e.g., using an organo lithium agent such as tBuLi, s-BuLi or BuLi at -78°C in ether, THF, or dioxane), followed by quenching with an electorphile such as R^5CHO, to give compounds of formula XVIII. Compounds of formula XIX-a may be prepared by reacting the corresponding compounds of formula XVIII with thionyl chloride, followed by reduction. Reacting compounds of formula XIX-a with a base (such as organolithium agent (e.g., lithium diisopropylamide or BuLi), followed by quenching with an electrophile (such as carbon

dioxide) will yield the corresponding compounds of formula XIX-b wherein R^{21} is -COOH. Compounds of formula XIX-c wherein R^{21} is -C(OH)R^4 may be prepared in a similar fashion by quenching the appropriate compound of formula XIX-a with an electrophile of the formula C_1-C_3 alkyl-CHO. Compounds of formula XVII can be prepared by reacting compounds of formula XIX-c with PCC (pyridinium chlorochromate) using standard PCC oxidation methods that are well known in the art.

Compounds of formula II-d, II-e and II-f, wherein T is chloro, bromo or iodo and D, E, R^3, R^5 and R^7 are as defined to those in formula I may be prepared, as shown in Scheme 9, by methods analogous to those described in Scheme 2. Alternatively, Compounds of formula II-d to II-f may be prepared using procedures analogous to those described in the literature (See: Pharm. Bull, 5, 229-231, 1957; Monatsh Chem, 100, 671-678, 1969; J. Heterocycl. Chem., 3, 218-220, 1966, Chem. Pharm. Bull,. 23, 2891-2895, 1975; J. Heterocycl. Chem., 8, 1-6, 1971; Justus Liebigs Ann. Chem, 735, 35-44, 1970; Tetrahedron Lett, 1479, 1968; and Chem. Abstr., 1939, 4988.)

The acid addition salts of compounds of the formula can be prepared in a conventional manner by treating a solution or suspension of the corresponding free base with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques can be employed to isolate the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

The compounds of formula I and their pharmaceutically acceptable salts (hereinafter referred to, collectively, as "the active compounds of this invention") may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions, oils (e.g., sesame oil, peanut oil) and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of formula I and pharmaceutically acceptable carriers can then be readily administered in a variety of dosage forms such as tablets, oil gel, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients

such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, methylcellulose, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions containing an active compound of this invention or a pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosages for the active compounds of this invention will depend on the intended route of administration and factors such as the age and weight of the patient, as generally known to a physician. The dosages will also depend on the particular illness to be treated. For instance, the daily dosage for stress-induced illnesses, inflammatory disorders, Alzheimer's disease, gastro-intestinal diseases, anorexia nervosa, hemorrhagic stress and drug and alcohol withdrawal symptoms will generally range from about 0.1 to about 50 mg/kg body weight of the patient to be treated.

Methods that may be used to determine the CRF antagonist activity of the active compounds of this invention and their pharmaceutically acceptable salts are described in Endocrinology, 116, 1653-1659 (1985) and Peptides, 10, 179-188 (1985). The binding activities for compounds of the formula I, expressed as IC_{50} values, generally range from about 0.5 nanomolar to about 10 micromolar. Methods that can be used

to determine the CRF binding protein inhibiting activity of compounds of the formula I are described in Brain Research, (1997), 745 (1,2),248-255.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) and C^{13} nuclear magnetic resonance spectra (C^{13} NMR) were measured for solutions in deuterochloroform ($CDCl_3$) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

The following abbreviations are used in the Examples: Ph=phenyl; iPr=isopropyl.

EXAMPLE 1

7-(1-Ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

A solution of 3-pentanol (140 mg, 1.5 mmol) in 1 ml of dry THF was treated with 60% sodium hydride in oil (28 mg, 0.7 mmol) and stirred at room temperature for 10 min. A solution of 7-chloro-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine (75 mg, 0.262 mmol) in 1 ml of dry THF was added and the resulting mixture was heated at reflux for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give the crude material. The residue was purified through silica gel column chromatography using 3:7 chcloroform:hexane as eluent to give 75mg (88%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 7.97(s,1H), 6.97(s,2H), 6.03(s,1H), 4.56(m,1H), 2.53(s,3H), 2.32(s,3H), 2.13(s,6H), 2.10(m,4H), 1.09(t,6H) ppm.

EXAMPLE 2

[2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine

A mixture of 7-Chloro-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a] pyrimidine (60 mg, 0.2 mmol) and 1-ethylpropylamine (4 ml) in 1ml of N-methylpyrrolidinone was heated at 125°C oil bath for 15 hrs. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated and purified through silica gel column chromatography using 20% ethyl acetate in hexane as eluent to give 35 mg of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) δ

6.96(s,2H), 6.00(d,1H), 5.77(s,1H), 3.47 (m,1H), 2.43(s,3H), 2.32(s,3H), 2.22(s,3H), 2.05(s,6H), 1.5-1.9(m,4H), 1.04(t,6H) ppm.

EXAMPLE 3

(1-Ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine

A mixture of 7-chloro-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a] pyrimidine (190 mg, 0.63 mmol) and 1-ethylpropylamine (4 ml) in 1ml of N-methylpyrrolidinone was heated at 125°C oil bath for 15 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated and purified through silica gel column chromatography using chloroform to 2% methanol in chloroform as eluent to give 195 mg (87%) of the title compound as a green solid. ^{1}H NMR ($CDCl_3$) δ 7.87(s,1H), 6.97(s,2H), 6.12(d,1H), 5.85(s,1H), 3.52(m,1H), 2.48(s,3H), 2.09(s,3H), 2.16(s,6H), 1.6-1.9(m,4H), 1.05(t,6H)ppm.

EXAMPLE 4

7-(1-Ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo [1,5-a]pyrimidine

To a suspension of 60% Sodium hydride in oil (160 mg) in 4 ml of DMSO was added 3-pentanol (853 mg), and then 7-chloro-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl) -pyrazolo[1,5-a]pyrimidine (580 mg) at room temperature. The mixture was heated at 88°C overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated and purified through silica gel column chromatography using 10% hexane in chloroform as eluent to give the title compound as an orange oil. ^{1}H NMR ($CDCl_3$) δ 6.96(s,2H), 5.95(s,1H), 4.52(m,1H), 2.48(s,3H), 2.33(s,3H), 2.27(s,3H), 2.03(s,6H), 1.75-2.00(m,4H), 1.08(t,6H)ppm.

EXAMPLE 5

[2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-propyl-amine

A mixture of 7-chloro-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a] pyrimidine (200 mg, 0.66 mmol) and N-propylethylamine (2 ml) in 1ml of N-methylpyrrolidinone was heated at 135°C oil bath for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated and purified through silica gel column chromatography using hexane to 10% ethyl acetate in hexane as eluent to give 150 mg of the title compound as a clear

green oil. ^{1}H NMR ($CDCl_3$) δ 6.95(s,2H), 5.80(s,1H), 3.85(q,2H), 3.67(dd,2H), 2.41(s,3H), 2.32(s,3H), 2.21(s,3H), 2.03(s,6H), 1.76(m,2H), 1.29(t,3H), 0.98(t,3H) ppm.

EXAMPLE 6

[6-Bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b] pyridin-7-yl]-(1-ethyl-propyl)-amine

To a solution of butyl nitrite (119 mg, 1.15 mmol) and CuBr2 (205 mg, 0.919 mmol) in 16 ml of acetonitrile was added N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine (250 mg, 0.766 mmol). The resulting mixture was heated at 65°C for 1.5 hrs. The mixture was cooled to room temperature and 2N HCl (16 ml) was added. The mixture was neutralized with 2N NaOH and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give a brown oil. The oil residue was purified through silica gel column chromatography using 1:1 hexane :ethyl acetate as eluent to give 61mg of [6-bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b] pyridin-7-yl]-(1-ethyl-propyl)-amine as white crystals. Mp 123-125°C. ^{1}H NMR ($CDCl_3$) δ 7.06(s,2H), 5.53(d,1H), 5.22(m,1H), 4.67(s,2H), 2.39(s,3H), 1.96(s,6H), 1.6-1.9(m,4H), 1.06(t,6H)ppm and 103 mg of [6-bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine as white solid. Mp 115-117°C. ^{1}H NMR ($CDCl_3$) δ 7.04(s,2H), 5.36(d,1H), 5.21(m,1H), 2.64(s,3H), 2.38(s,3H), 1.95(s,6H), 1.6-1.9(m,4H), 1.05(t,6H)ppm.

EXAMPLE 7

(1-Ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b] pyridin-7-yl]-amine

A mixture of butyl nitrite (119 mg, 1.15 mmol) and N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine (250 mg, 0.766 mmol) in anhydrous acetonitrile (16 ml) was heated at 65°C for 2 hours. The mixture was cooled to room temperature and 2N HCl (16 ml) was added. The mixture was neutralized with 2N NaOH and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 250 mg of the crude product as a brown oil. The oil residue was purified through silica gel column using chloroform as eluent to give 201 mg of the title compound as golden yellow solid. Mp 131-133°C. ^{1}H NMR ($CDCl_3$) δ 7.022(s,2H), 6.20(s,1H), 5.44(d,1H), 3.65(m,1H), 2.50(s,3H), 2.36(s,3H), 1.96(s,6H), 1.5-1.8(m,4H), 1.03(t,6H)ppm.

EXAMPLE 8

[6-Bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-methyl-amine

To a solution of [6-bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo [4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine (50 mg, 0.12 mmol) in dry THF)1.5 ml) was added 2.5 M n-BuLi in hexane (0.14 ml) at -78°C. After stirring at -78°C for 10 min, 0.5 ml of methyl iodide was added at that temperature then allowed to warmed to room temperature and stirred for 15 min for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 46 mg of brown oil. The residue was purified through silica gel coliumn chromatography using 1:1 chloroform:hexane as eluent to give the title compound as a golden oil. ^{1}H NMR ($CDCl_3$) δ 7.04(s,2H), 4.35(m,1H), 3.32(s,3H), 2.70(s,3H), 2.38(s,3H), 1.94(s,6H), 1.7-2.0(m,4H), 1.01(t,6H)ppm.

EXAMPLE 9

7-(1-Ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3] triazolo[4,5-b]pyridine

A mixture of 4-(1-Ethyl-propoxy)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3-diamine (50 mg, 0.153 mmol) and butyl nitrite (24 mg, 0.229 mmol) in 4 ml acetonitrile was heated at 65°C for 2 hours. An additional 0.13 ml of butyl nitrite was added and the resulting mixture was heated at 65°C for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 58 mg of brown oil. The oil was purified through silica gel column chromatography using 5% ethyl acetate in hexane as eluent to give 46 mg (88%) of the title compound as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.04(s,2H), 6.60(s,1H), 5.26(m,1H), 2.57(s,3H), 2.38(s,3H), 1.94(s,6H), 1.8-2.0(m, 4H), 1.07(t,6H) ppm.

EXAMPLE 10

4-(1-Ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine

To a solution of 3-pentanol (0.09 ml, 0.883 mmol) in dry THF was added 60% NaH in oil (20 mg, 0.500 mmol) and stirred for 5 min. A solution of 4-chloro-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine (50 mg, 0.166 mmol) in dry THF was added to the reaction mixture and the resulting mixture was heated at reflux for 2 hr. The mixture was quenched with water, extracted with ethyl acetate. The

organic layer was washed with brine, separated, dried and concentrated to dryness to give the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 6.92(s,3H), 5.43(m,1H), 4.02(s,3H), 2.56(s,3H), 2.29(s,3H), 2.08(s,6H), 1.80(m,4H), 0.99(t,6H).

The title compounds of Examples 11-14 were prepared by the method analogous to that described in Example 10 starting from of 4-chloro-2-methyl-5-substituted-7-(substituted-phenyl)-5H-pyrrolo[3,2-d]pyrimidine or 7-chloro-5-methyl-1-substituted-3-(substituted-phenyl)-1H-pyrrolo[3,2-b]pyridine and an appropriate alcohol or thiol and a base.

EXAMPLE 11

(+)-2,5-Dimethyl-4-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine.

^{1}H NMR ($CDCl_3$) δ 6.95(s,1H), 6.92(s,2H), 5.88(m,1H), 3.9-4.08(m,4H), 4.01(s,3H), 2.56(s,3H), 2.29(s,3H), 2.2-2.4(m,2H), 2.07(s,6H) ppm.

EXAMPLE 12

2,5-Dimethyl-4-(S)-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine.

^{1}H NMR ($CDCl_3$) δ 6.95(s,1H), 6.92(s,2H), 5.88(m,1H), 3.9-4.08(m,4H), 4.01(s,3H), 2.56(s,3H), 2.29(s,3H), 2.2-2.4(m,2H), 2.07(s,6H) ppm.

EXAMPLE 13

2,5-Dimethyl-4-(1-propyl-butoxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine.

^{1}H NMR ($CDCl_3$) δ 6.93(s,2H), 6.92(s,1H), 5.58(m,1H), 4.02(s,3H), 2.56(s,3H), 2.29(s,3H), 2.09(s,6H), 1.6-1.8(m,4H), 1.4-1.6(m,4H), 0.96(t,6H)ppm.

EXAMPLE 14

4-sec-Butylsulfanyl-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine.

^{1}H NMR ($CDCl_3$) δ 6.97(s,1H), 6.94(s,2H), 4.34(m,1H), 4.13(s,3H), 2.63(s,3H), 2.30(s,3H), 2.07(s,6H), 1.7-1.9(m,2H), 1.48(d,3H), 1.09(t,3H) ppm.

The title compounds of Examples 15-18 were prepared using the following procedure.

PROCEDURE FOR EXAMPLES. 15 - 18

A mixture of 4-chloro-2-methyl-5-substituted-7-(substituted-phenyl)-5H-pyrrolo[3,2-d]pyrimidine or 7-bromo-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-

pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester (1 mmol) and an appropriate amine in DMSO (2 ml) was heated in 130°C oil bath until all the starting material was consumed. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give the corresponding 4-alkylamino-2-methyl-5-substituted-7-(substituted-phenyl)-5H-pyrrolo[3,2-d]pyrimidineor 7-alkylamino-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester derivative. Silica gel column chromatography may be used for purification.

EXAMPLE 15

[2,5-Dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]-(1-ethyl-propyl)-amine

^{1}H NMR ($CDCl_3$) δ 6.91(s,2H), 6.76(s,1H), 4.61(d,1H,NH), 4.33(m,1H), 4.04(s,3H), 2.49(s,3H), 2.28(s,3H), 2.09(s,6H), 1.72(m,2H), 1.60(m,2H), 0.98(t,6H)ppm.

EXAMPLE 16

Butyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]-ethyl-amine

^{1}H NMR ($CDCl_3$) δ 6.96(s,1H), 6.92(s,2H), 3.93(s,3H), 3.44(q,2H), 3.40(m,2H), 2.57(s,3H), 2.29(s,3H), 2.09(s,6H), 1.57(m,2H), 1.30(m,2H), 1.14(t,3H), 0.88(t,3H)ppm.

EXAMPLE 17

2,5-Dimethyl-4-thiazolidin-3-yl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine

^{1}H NMR ($CDCl_3$) δ 7.03(s,1H), 6.92(s,2H), 4.78(s,2H), 4.02(s,3H), 3.96(m,2H), 3.18(m,2H), 2.56(s,3H), 2.29(,3H), 2.06(s,6H) ppm.

EXAMPLE 18

7-(1-Ethyl-propylamino)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester

^{1}H NMR ($CDCl_3$) δ 6.98(s,1H), 6.93(s,2H), 5.40(d,1H), 3.97(s,3H), 3.91(s,3H), 3.35(m,1H), 2.57(s,3H), 2.30(s,3H), 2.09(s,6H), 1.52(m,4H), 0.87(t,6H) ppm.

EXAMPLE 19

7-(1-Ethyl-propylamino)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]-pyridine-6-carboxylic acid

A mixture of 7-(1-ethyl-propylamino)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester and NaOH in a 1:1 mixture of

MeOH/water was heated at reflux over night. The resulting mixture was acidified with 2N HCl to a pH of 4-5, and extracted with chloroform. The organic layer was dried and concentrated to give the title compound.

^{1}H NMR ($CDCl_3$) δ 7.02(s,1H), 6.82(s,2H), 3.98(s,3H), 3.78(m,1H), 2.59(s,3H), 2.07(s,3H), 2.00(s,6H), 1.64(m,4H), 0.90(t,6H) ppm.

EXAMPLE 20

[1,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]-(1-ethyl-propyl)-amine

A mixture of 7-(1-ethyl-propylamino)-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid was heated in 150-160°C oil bath until all the starting material was consumed. ^{1}H NMR ($CDCl_3$) δ 6.94(s,2H), 6.87(s,1H), 6.15(s,1H), 6.10(d,1H), 4.24(s,3H), 3.50(m,1H), 2.64(s,3H), 2.30(s,3H), 2.05(s,6H), 1.77(m,4H), 1.02(t,6H)ppm.

PREPARATION A

4-(2,4,6-Trimethyl-phenyl)-2H-pyrazol-3-ylamine

A mixture of 3-oxo-2-(2,4,6-trimethyl-phenyl)-propionitrile (2.300 g, 12.3 mmol), hydrazine hydrate (0.93 g) and glacial acetic acid (1.55 ml) in 20 ml benzene was heated at reflux for 4.5 hours. Reaction mixture was cooled to room temperature and 50 ml of 18.5% HCl in water was added. The benzene layer was separated and reextracted with 18.5% HCl. The aqueous layer were combined and neutralized with ammonium hydroxide and stirred at rt. overnight. Precipitate formed and was filtered to yield the title compound (0.256 g) as a yellow solid. The benzene layer was concentrated and purified through silica gel column using 5% methanol in chloroform as eluent to give an additional 1.450 g of the title compound; ^{1}H NMR ($CDCl_3$) δ 7.24(s,1H), 6.95(s,2H), 4.75(brs,2H), 2.32(s,3H),2.13(s,6H) ppm.

PREPARATION B

5-Methyl-4-(2,4,6-trimethyl-phenyl)-2H-pyrazol-3-ylamine

The title compound was prepared as white solid by the method analogous to that described in preparation A starting from 3-oxo-2-(2,4,6-trimethyl-phenyl)-butyronitrile. ^{1}H NMR ($CDCl_3$) δ 7.7(brs,1H), 6.96(s,2H), 2.32(s,3H), 2.13(s,3H), 2.06(s,6H) ppm.

PREPARATION C

2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-4H-pyrazolo[1,5-a]pyrimidin-7-one

Methyl acetoacetate (0.38 ml) was added to a solution of 5-methyl-4-(2,4,6-trimethyl-phenyl)-2H-pyrazol-3-ylamine (641 mg, 2.98 mmol) in 4 ml of acetic acid. The reaction mixture was heated at reflux for overnight. The mixture was concentrated to dryness and the residue was purified through silica gel column chromatography using 5% methanol in chloroform as eluent to give 560 mg (65.5%) of the title compound as a white solid; ^{1}H NMR (DMSO-d_6) δ 11.7(s,1H), 6.98(s,2H), 5.52(s,1H), 2.29(s,3H), 2.20(s,3H), 1.97(s,3H), 1.95(s,6H) ppm.

PREPARATION D

5-Methyl-3-(2,4,6-trimethyl-phenyl)-4H-pyrazolo[1,5-a]pyrimidin-7-one

Methyl acetoacetate (0.7 ml) was added to a solution of 4-(2,4,6-Trimethyl-phenyl)-2H-pyrazol-3-ylamine (1.120 g, 5.57 mmol) in 5 ml of acetic acid and the resulting mixture was heated at reflux for two days. Reaction mixture cooled and a white solid formed. Ethanol (6 ml) was added and stirred at room temperature overnight, filtered to give white solid which was recrystallized from ethanol to give 673 mg(45.2%) of the title compound as white crystals. ^{1}H NMR (DMSO-d_6) δ 11.9(s,1H), 7.7(s,1H), 6.95(s,2H), 5.55(s,1H), 2.25(s,3H), 2.20(s,3H), 2.0(s,6H)ppm.

PREPARATION E

7-Chloro-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

A suspension of 5-methyl-3-(2,4,6-trimethyl-phenyl)-4H-pyrazolo[1,5-a]pyrimidin -7-one (590 mg, 2.2 mmol) in 9 ml of $POCl_3$ was treated with diethylaniline (0.7 ml) and the resulting mixture was stirred at reflux for 15 hours. The reaction mixture was concentrated to dryness. The residue was treated with ice water and stirred for 20 min, then extracted with chloroform. The organic layer was dried and concentrated to yield an orange oil which crystallized upon standing. The material was purified through silica gel column chromatography using chloroform as eluent to give 590 mg (94%) of the title compound as a yellow solid; ^{1}H NMR ($CDCl_3$) δ 8.08(s,1H), 6.98(s,2H), 6.86(s,1H), 2.56(s,3H), 2.33(s,3H), 2.09(s,6H) ppm.

PREPARATION F

7-Chloro-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

The title compound was prepared as an oil by the method analogous to that described in preparation E starting from 2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-4H-pyrazolo[1,5-a]pyrimidin-7-one. ^{1}H NMR ($CDCl_3$) δ 6.98(s,2H), 6.77(s,1H), 2.51(s,3H), 2.33(s,3H), 2.31(s,3H), 1.99(s,6H) ppm.

PREPARATION G

2,5-Dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol

A mixture of 3-amino-1-methyl-4-(2,4,6-trimethylphenyl)-1H-pyrrole-2-carbonitrile (0.4 mmol) and acetic anhydride (0.043 ml) in acetic acid (0.01 ml) was heated at reflux untill all the starting material was consumed. The reaction mixture was concentrated to dryness. The residue was quenched with water and extracted with ethyl acetate. The organic extracts was washed with brine and concentrated to dryness. The residue was suspended in 0.5 ml of 85% phosphoric acid and heated at 130°C for 1 hour. The mixture was cooled and poured into ice-water, stirred until solid formed. The solid was filtered to give 2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol. The alternative way for the work up is via extraction technique. The ice water was extracted with chloroform. The organic layer was dried and concentrated to dryness to give the desired product.

^{1}H NMR δ ($CDCl_3$) 6.92(s,2H), 6.88(s,1H), 4.14(s,3H), 2.43(s,3H), 2.29(s,3H), 2.09(s,6H).

The following compounds can be prepared in a similar manner:

2,5-Dimethyl-7-(2,6-dimethyl-4-chloro-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

2,5-Dimethyl-7-(2,6-dimethyl-4-bromo-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

2-Methyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

2-Methyl-7-(2,6-dimethyl-4-chloro-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

2-Methyl-7-(2, 6-drimethyl-4-bromo-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol; and

2-Methyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol;

PREPARATION H

4-Chloro-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine

A mixture of 2, 5-dimethyl-7-(2,4,6-trimethylphenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-ol (1 mmol) in $POCl_3$ (1.3 ml) was heated at reflux until all the starting material were

consumed (about 1-3 hours). The mixture was concentrated to dryness. The residue was porued into ice-water and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give the title compound.

^{1}H NMR ($CDCl_3$) δ 7.18(s,1H), 6.95(s,2H), 4.16(s,3H), 2.69(s,3H), 2.31(s,3H), 2.05(s,6H) ppm.

PREPARATION I

7-Amino-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester

A mixture of 3-amino-1-methyl-4-(2,4,6-trimethylphenyl)-1H-pyrrole-2-carbonitrile (2 mmol), methyl acetoacetate (4 mmol) and $SnCl_4$ (4 mmol) in 1, 2-dichloroethane was heated at reflux for about six hours until all the starting material were consumed. The mixture was quenched with acetone, basified with saturated $NaHCO_3$, then filtered through Celite®. The filtrate was concentrated to dryness. The residue was quenched with water and extracted with chloroform. The chloroform layer was washed with brine, dried and concentrated to dryness to give 7-amino-1,5-dimethyl -3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester. The product may be purified by trituration.

^{1}H NMR ($CDCl_3$) δ 6.91(s,2H), 6.85(s,1H), 6.28(brs,2H), 4.10(s,3H), 3.89(s,3H), 2.62(s,3H), 2.28(s,3H), 2.09(s,6H) ppm.

PREPARATION J

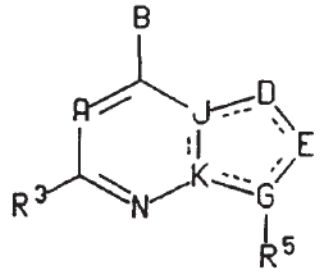
7-Bromo-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester

A mixture 7-amino-1, 5-dimethyl-3-(2, 4, 6-trimethylphenyl)-1H-pyrrolo[3, 2-b]pyridine-6-carboxylic acid methyl ester (1 mmol), n-butylnitrite (BuONO) (1.5 mmol) and $CuBr_2$ in acetonitrile was heated at 60-70°C until all starting material was consumed. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give the title compound.

^{1}H NMR ($CDCl_3$) δ 7.09(s,1H), 6.94(s,2H), 4.16(s,3H), 3.98(s,3H), 2.52(s,3H), 2.30(s,3H), 2.04(s,6H) ppm. 2,7-dibromo-1,5-dimethyl-3-(2,4,6-trimethyl-phenyl) -1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid methyl ester was also produced as a minor component. ^{1}H NMR ($CDCl_3$) δ 7.00(s,2H), 4.45(s,3H), 4.03(s,3H), 2.51(s,3H), 2.34(s,3H), 2.12(s,6H) ppm.

CLAIMS

1. A compound of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$ $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

J and K are each independently nitrogen or carbon and both J and K are not nitrogens ;

D and E are each selected, independently, from nitrogen, CR^4, C=O, C=S, sulfur, oxygen, CR^4R^6 and NR^8 ;

G is nitrogen or carbon;

the ring containing D, E, G, K, and J in formula I may be a saturated or unsaturated 5-membered ring and may optionally contain one or two double bonds and may optionally contain from one to three heteroatoms in the ring and may optionally have one or two C=O or C=S groups;

R^1 is C_1-C_6 alkyl optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, -O-(C_1-C_4 alkyl), CF_3, -C(=O)O-(C_1-C_4alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, $-NO_2$, -SO(C_1-C_4 alkyl), $-SO_2$(C_1-C_4 alkyl), $-SO_2$NH(C_1-C_4 alkyl) and $-SO_2$N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4

alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or $CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, (C_1-C_2 alkylene)-O-(C_1-C_2 alkyl), (C_1-C_2 alkylene)-OH, or -S(C_1-C_4 alkyl);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C_1-C_2 alkylene)-OH, CF_3, CH_2SCH_3, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl);

R^6 is hydrogen, methyl or ethyl;

R^8 is hydrogen or C_1-C_4 alkyl;

R^5 is phenyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{13} wherein one to three of said substituents may be selected, independently, from fluoro, chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, OH, (C_1-C_4 alkylene)-OH, (C_1-C_4alkylene)-O-(C_1-C_2 alkyl), -CN, -CF_3, -NO_2,

$-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_2$ alkyl)$(C_1-C_6$ alkyl), $-OCO(C_1-C_4$ alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), -S(C_1-C_6 alkyl), (C_1-C_4 alkylene)-S-(C_1-C_4 alkyl), $-C(=O)O(C_1-C_4$ alkyl), $-C(=O)(C_1-C_4$ alkyl), -COOH, $-SO_2NH(C_1-C_4$ alkyl), $-SO_2N(C_1-C_2$ alkyl)$(C_1-C_4$ alkyl), $-SO_2NH_2$, $-NHSO_2(C_1-C_4$ alkyl), -S(C_1-C_6 alkyl) and $-SO_2(C_1-C_6$ alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally have one or two double bonds;

R^7 is hydrogen, C_1-C_4 alkyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, $-O(C_1-C_4$ alkyl), $-C(=O)(C_1-C_4$ alkyl), $-C(=O)O(C_1-C_4$ alkyl), $-OCF_3$, $-CF_3$, $-CH_2OH$ or $-CH_2O(C_1-C_2$ alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: a) when both J and K are carbons and D is CR^4 and E is nitrogen, then G can not be nitrogen; (b) when both J and K are carbons and D and G are nitrogens, then E can not be CR^4 or C=O or C=S; (c) when both J and K are carbons and D and E are carbons, then G can not be nitrogen; (d) when G is carbon, it must be double banded to E; and (e) in the ring containing J, K, D, E and G, there can not be two double bonds adjacent to each other;

and the pharmaceutically acceptable salts of such compounds.

2. Compounds according to claim 1 wherein B is $-NR^1R^2$, $-NHCHR^1R^2$, $-OCHR^1R^2$ and R^1 is C_1-C_6 alkyl, which may optionally be substituted with one fluoro, or C_1-C_4 alkoxy group and which may optionally contain one double or triple bond; and R^2 is C_1-C_4 alkyl or (C_1-C_2 alkyl)-CO-(C_1-C_2 alkyl) which may optionally contain one double or triple bond.

3. Compounds according to claim 1, wherein B is $-CHR^1R^2$, $-NR^1R^2$, $-NHCHR^1R^2$, $-OCHR^1R^2$, $-SCHR^1R^2$; and R^1 is C_1-C_6 alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3, cyclopropyl or C_1-C_4 alkoxy group and which may optionally contain one double or triple bond; and R^2 is benzyl or C_1-C_6 alkyl, which may optionally contain one double or triple bond, wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl may optionally be substituted with one fluoro, hydroxy, CF_3, cyclopropyl, C_1-C_2 alkyl, C_1-C_2 alkoxy or chloro group.

4. Compounds according to claim 1 wherein R^3 is methyl.

5. Compounds according to claim 1 wherein R^4, R^6, R^8, R^9, and R^{12} are hydrogen or methyl.

6. Compounds according to claim 1 wherein R^5 is di- or tri-substituted phenyl in which the two or three substitutents are independently selected from C_1-C_4 alkyl, O-(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4alkyl), CF_3, OCF_3, CHO, (C_1-C_4alkylene)-OH, cyano, chloro, fluoro, bromo and iodo, wherein each of the forgoing (C_1-C_4) alkyl groups may optionally contain one double or triple bond.

7. Compounds 1 wherein R^3 is methyl, ethyl, chloro or methoxy; and each of R^4, R^6, R^8, R^9, and R^{12} is, independently, hydrogen, methyl or ethyl.

8. Compounds wherein R^5 is di- or tri-substituted pyridyl, or pyrimidyl in which the two or three substitutents are independently selected from C_1-C_4 alkyl, O-(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), CF_3, OCF_3, CHO, (C_1-C_4 alkylene)-OH, cyano, chloro, fluoro, bromo and iodo, wherein each of the forgoing (C_1-C_4) alkyl groups may optionally contain one double or triple bond.

9. Compounds according to claim 1 wherein A is N, CH or CCH_3.

10. Compounds according to claim 1 wherein A is CH, J and K are carbon and D, E, and G are nitrogen.

11. Compounds according to claim 1 wherein J and D are nitrogen, and K and G are carbon, and E is CH, CCH_3 or CC_2H_5.

12. Compounds according to claim 1 wherein J and K are carbon, and D--EG is O-C(CH_3)=C, O-CH=C, S-C(CH_3)=C, S-CH=C, N(CH_3)-C(CH_3)=C, NHC(CH_3)=C, NHC(CH_3CH_2)=C, N(CH_3)-CH=C, O-N=C, S-N=C, N(CH_3)-N=C, O-CH_2N or S-CH_2N.

13. A compound according to claim 1 wherein B is -CHR^1R^2, -$NCHR^1R^2$ or -$OCHR^1R^2$, and the CHR^1R^2 group of B is a cyclopentane ring, a tetrahydrofuran ring or a tetrahydrothienyl ring.

14. A compound according to claim 1 wherein the NR^1R^2 group of B is a five membered saturated or unsaturated heterocyclic ring.

15. A compound according to claim 14 wherein the NR^1R^2 is a pyrrolo ring, a pyrrolidino ring, a thiazolidino ring or a morpholino ring.

16. A pharmaceutical composition for the treatment, prevention or inhibition of (a) 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, or (b) 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, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer;diarrhea; stress-induced fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; 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; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., 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; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; and hypoglycemia in a mammal, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder, and a pharmaceutically acceptable carrier.

17. A method for the treatment, prevention or inhibition of (a) 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, or (b) 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 premenstrual syndrome, and

postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; 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; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., 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; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; and hypoglycemia in a mammal, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder.

18. A method of treating or preventing a disorder or condition, the treatment or prevention of which can be effected or facilitated by inhibiting CRH binding protein in a mammal, comprising administering to said mammal a CRH binding protein inhibiting amount of a compound according to claim 1.

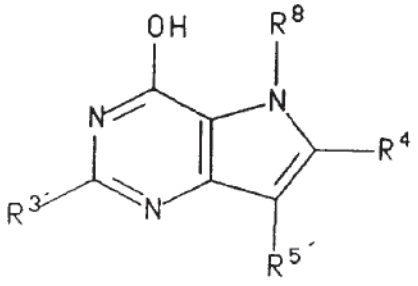
19. A pharmaceutical composition for treating or preventing a disorder or condition, the treatment or prevention of which can be effected or facilitated by inhibiting CRH binding protein in a mammal, comprising a CRH binding protein inhibiting amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

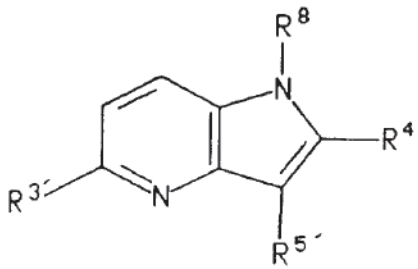
20. A compound according to claim 11 or 12 wherein A is N or CH, R^3 is methyl and each R^4, R^6, R^8, R^9 and R^{12} is, independently, hydrogen or methyl.

21. A compound according to claim 20, wherein R^5 is di- or tri-substituted phenyl, wherein the two or three substitutents are independently selected from C_1-C_4

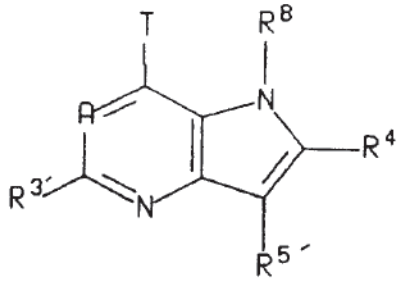
alkyl, O-(C_1-C_4 alkyl), (C_1-C_4 alkylene)-O-(C_1-C_4alkyl), CF_3, OCF_3, CHO, (C_1-C_4alkylene)-OH, cyano, chloro, fluoro, bromo and iodo, wherein each of the forgoing (C_1-C_4) alkyl groups may optionally contain one double or triple bond.

22. A compound of the formula





or



wherein $R^{3'}$ is C_1-C_4 alkyl, $R^{7'}$ is hydrogen, methyl, chloro, bromo, -COOH or -COO(C_1-C_4 alkyl), T is chloro, bromo, iodo or triflate, R^8 is hydrogen or C_1-C_4 alkyl and R^4 is hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C_1-C_2 alkylene)-OH, CF_3, CH_2SCH_3, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl);

23. A compound according to claim 1 wherein said compound is:

7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

(1-Ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

7-(1-Ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-propyl-amine;

[6-Bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

(1-Ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-amine;

[6-Bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-methyl-amine;

7-(1-Ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridine;

4-(1-Ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;

(±)-2,5-Dimethyl-4-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;

2,5-Dimethyl-4-(S)-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;

2,5-Dimethyl-4-(1-propyl-butoxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine; or

4-sec-Butylsulfanyl-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;

or a pharmaceutically acceptable salt of such compound.

INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/IB 97/00922

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 C07D471/04 A61K31/505 A61K31/435
//(C07D487/04,239:00,231:00),(C07D471/04,249:00,221:00),
(C07D487/04,239:00,209:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 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	WO 95 33750 A (PFIZER) 14 December 1995 see claims 1,13 ---	1,16
P,X	WO 96 35689 A (NEUROGEN) 14 November 1996 see page 3, line 18 - line 25; claim 1; examples IE,II,ID -----	1,16,22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1997	04. 11. 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	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/IB 97/00922

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:

Remark: Although claim(s) 17 and 18 is(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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ial Application No
PCT/IB 97/00922

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9533750 A	14-12-95	AU 2453095 A	04-01-96
		BR 9502708 A	30-04-96
		EP 0764166 A	26-03-97
		FI 964894 A	05-12-96
		HU 75774 A	28-05-97
		NO 965237 A	06-02-97
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

Form PCT/ISA/210 (patent family annex) (July 1992)

Patents KR-20090052366-A

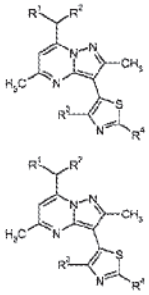
Thiazole pyrazolopyrimidines as crf1 receptor antagonists

Abstract

translated from Korean

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, neurological diseases and metabolic syndromes.

<Formula I>



Thiazole pyrazolopyrimidine, pharmaceutical composition, CRF1 receptor antagonist

Classifications

- C07D487/04 Ortho-condensed systems

View 22 more classifications

KR20090052366A

South Korea

Download PDF Find Prior Art Similar

Other languages: Korean

Inventor: 차오젠 첸, 차피크 함도우치, 예릭 제임스 햄드렉, 윌림 마씨 헐스캄드, 제이슨 제네쓰 마이어스, 타카코 타카쿠와, 제임스 리 로쓰

Worldwide applications

2007 AT SI ES BR MY DK AU UA CA EA CN RS PL MX WO NZ KR DE JP EP PT US AR PE TW CL 2009 IL TN GR MA NO 2010 HK HR CY

Application KR1020097005602A events

Priority claimed from US82628406P

First worldwide family litigation filed

2007-09-17 Application filed by 얼리어 랄리 엘트 캄파니

2009-05-25 Publication of KR20090052366A

2011-11-30 Application granted

2011-11-30 Publication of KR101108228981

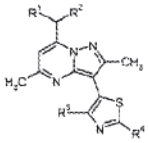
Info: Patent citations (10), Cited by (15), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

Claims (17)

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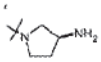
A compound of formula (I) or a pharmaceutically acceptable salt thereof. <Formula I>



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, acetamido, pyridin-4-yl, morpholin-4-yl,



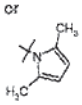
,



,



or



ego; 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 $CH_3CH_2CH_2NHCH_2CH_2-$to be. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl, Br, methyl or trifluoromethyl. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl or Br. The compound according to claim 1, wherein R^4 is $R^a R^b N$—, pyridin-4-yl, morpholin-4-yl or



Phosphorus compounds or pharmaceutically acceptable salts thereof. The compound of claim 1, wherein R^4 is morpholin- ^{4}-yl or



Phosphorus compounds or pharmaceutically acceptable salts thereof. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^4 is $R^a R^b$ N- and R^a and R^b are independently C_1-C_3 alkyl. The compound of claim 1, wherein 3- [4-bromo-2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl] -2,5- Dimethyl-7- (1-propyl-butyl) - pyrazolo [1,5-a] pyrimidine or a pharmaceutically acceptable salt thereof. The compound of claim 1, wherein 3- (4-bromo-2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl) -7- (1 -Ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine or a pharmaceutically acceptable salt thereof. The compound of claim 1, wherein 3- (4-chloro-2-morpholin-4-yl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1 , 5-a] pyrimidine, or a pharmaceutically acceptable salt thereof. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. A therapeutically effective amount of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, is used for depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke , Sleep disorders, allergies, migraines, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, preterm labor, stress-induced gastric ulcer, inflammatory disorders, pituitary or ectopic pituitary-induced tumors, chronic fatigue syndrome, Depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergies, including administration to patients in need of treatment of myofascial pain, long-term pain or multiple sclerosis Migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, preterm labor, stress-induced gastric ulcer, A method of treating an inflammatory disorder, pituitary or ectopic pituitary-induced tumor, chronic fatigue syndrome, myofiber pain, organ pain or multiple sclerosis. A method of treating anxiety or depression in a patient, comprising administering to the 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. Way. A method of treating alcohol or substance abuse in a patient 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. How to treat. A compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof for use in therapy. The method of claim 1, wherein depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergies, migraine, premenstrual syndrome, infertility Used in the treatment of sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, preterm labor, stress-induced gastric ulcer, inflammatory disorder, pituitary or ectopic pituitary-induced tumor, chronic fatigue syndrome, myofiber pain, organ pain or multiple sclerosis Compounds or pharmaceutically acceptable salts thereof for The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, for use in the treatment of anxiety or depression. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of alcohol or substance abuse.

Description

translated from Korean

THIAZOLE PYRAZOLOPYRIMIDINES AS CRF1 RECEPTOR ANTAGONISTS) as a CJF1 Receptor Antagonist

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

Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological modulator of proopiomelanocortin (POMC) induced peptide secretion from the anterior pituitary gland. In addition to its endocrine role in the pituitary gland, immunohistochemical localization of CRF has a wide range of autonomic and electrophysiological behavioral effects in which hormones have a broad hypothalamic distribution in the central nervous system and are equivalent to the role of neurotransmitters or neuromodulators in the brain. Prove that. There is also evidence that CRF plays an important role in integrating responses in the immune system to physiological, psychological and immunological stressors.

CRF is associated with Alzheimer's disease, Huntington's disease, progressive nuclear palsy, Amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and related withdrawal symptoms, obesity, metabolism, as well as psychiatric disorders and neurological disorders, including depression and anxiety Syndrome, congenital adrenal hyperplasia, Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulcer, premenstrual syndrome, sexual dysfunction, preterm labor, inflammatory disorders, allergies, multiple sclerosis, long term pain, sleep disorders, pituitary gland It is associated with tumors or ectopic pituitary-induced tumors, chronic fatigue syndrome and myofascial pain.

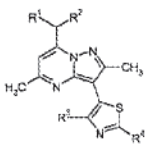
CRF receptor subtypes CRF1 and CRF2 have been identified and are heterogeneously distributed in the brain, suggesting potential functional diversity. For example, widely distributed brain CRF1 receptors are strongly associated with the emotions involved in exposure to environmental stressors. Importantly, CRF1 receptors other than CRF2 appear to mediate the selection of anxiety-like behavior. The more discrete septal / hypothalamic distribution, and the availability of other endogenous ligands, suggests a different functional role of the CRF2 receptor. For example, new CRF-like neuropeptides with selective affinity for CRF2 over CRF1 receptors have been reported to inhibit appetite without generating behavioral activation profiles observed with selective CRF1 agonism. In other cases, CRF2 competition provides a similar effect as reported for CRF1 antagonists or CRF1 gene deletions. For example, while CRF2 agonists are proposed as appetite suppressants, CRF1 antagonists may also be important therapeutics for obesity.

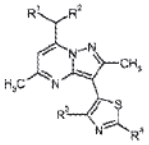
Specific pyrrolo [2,3-d] pyrimidines, pyrrolo [3,2-d] pyrimidines, pyrazolo [1,5-a] pyrimidines, 1,2,3-triazolo [useful as CRF antagonists 4,5-b] pyridine and pyrazolo [1,5-a] -1,3,5-triazine are disclosed in WO 94/13676, WO 97/29109, WO 98/08847 and WO 98/03510. It is described.

The present invention provides novel thiazole pyrazolopyrimidines useful as CRF1 receptor antagonists. In light of the above, it is desirable to find new CRF1 antagonists that are effective and selective as potentially useful therapeutics for the treatment of psychiatric and neuroendocrine disorders, neurological diseases and metabolic syndrome. In addition, since most commercial CNS and cardiovascular drugs exhibit undesirable bioavailability and pharmacokinetic profiles, they find novel compounds with desirable bioavailability and pharmacokinetic profiles over known CRF antagonists such as CP154526 and NBI30775. It is also preferred.

<Overview of Invention>

In one embodiment, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof.





Where

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

R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl or methoxy;



,



,



또는



이고;R 4 is hydrogen, 또, R a R b N-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



,



,



or



ego;

R^a and R^b are independently hydrogen, C_1 -C_3 alkyl, H_2 NCH_2 CH_{2-}, $(CH_3)_3$ COC (O) $NHCH_2$ CH_2 -or CH_3 CH_2 CH_2 $NHCH_2$ CH_2 -to be.

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 provides a therapeutically effective amount of a compound of formula (i) or a pharmaceutically acceptable salt thereof in a patient with depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, Stroke, sleep disorders, allergies, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulcer, inflammatory disorder, pituitary or ectopic pituitary-induced tumor, chronic fatigue syndrome Depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, including administration to patients in need of treatment of myofascial pain, long-term pain or multiple sclerosis, Allergies, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, preterm labor, stress-induced A method of treating gastric ulcers, inflammatory disorders, pituitary or ectopic pituitary-induced tumors, chronic fatigue syndrome, myofibromyalgia, organ pain or multiple sclerosis.

In another embodiment, the present invention is directed to depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergies, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal gland Formula (i) for the manufacture of a medicament for the treatment of hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulcer, inflammatory disorder, pituitary or ectopic pituitary-induced tumor, chronic fatigue syndrome, myofascial pain, long-term pain or multiple sclerosis The use of a compound or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention is directed to depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergies, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal gland A compound of formula (i) for use in the treatment of hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulcer, inflammatory disorder, pituitary or ectopic pituitary-induced tumor, chronic fatigue syndrome, myofascial pain, organ pain or multiple sclerosis or To pharmaceutically acceptable salts thereof.

In another embodiment, the present invention relates to a compound of formula (i) or a pharmaceutically acceptable salt thereof for use in therapy.

Throughout the above and the description of the invention, the following terms should be understood to have the following meanings unless stated otherwise.

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

"Pharmaceutically acceptable excipient" refers to a pharmaceutically acceptable formulation carrier, solution, or additive for improving formulation properties. Such excipients must be compatible with the other ingredients of the formulation, not harmful to the recipient thereof, and are well known to those skilled in the art (see, eg, *Remingtons Pharmaceutical Sciences* , 19 th Edition, Mack Publishing Company, 1995). .

"Pharmaceutically acceptable salts" refer to inorganic and organic acid addition salts and base addition salts of the compounds of the present invention which are relatively nontoxic. These salts can be prepared in situ during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by individually reacting the purified compound in free base form with a suitable organic or inorganic acid and isolating the salt so formed (eg, *Remingtons Pharmaceutical Sciences* , 19 th Edition). , Mack Publishing Company, 1995).

A "therapeutically effective amount" or "effective amount" refers to the invention, which will induce a desired therapeutic effect, or a biological or medicinal response to a tissue, strain, animal or human, as sought by a researcher, veterinarian, physician or other clinician. The amount of a compound of formula (I) or a pharmaceutical composition containing a compound of formula (I) of the present invention.

The terms "treatment", "treat", "treating", etc., are meant to include both slowing and reversing the progression of the disorder. These terms also include alleviating, ameliorating, attenuating, eliminating or reducing one or more symptoms of a disorder or condition, even if the disorder or condition does not substantially disappear, and the progression of the disorder or condition itself does not slow down or reverse. In addition, the terms "treatment" and like terms include prophylactic (eg, prophylactic) and conventional treatment. Prevention of the disease indicates prolongation or delay in the onset of disease symptoms.

"는 특정 치환기의 부착 위치를 나타낸다. Symbols In Molecular Structure "

"Represents the attachment position of a specific substituent.

When any variable exists more than one place within any component or formula (I), the definition of each existence is independent of the definition of all other entities. In addition, combinations of substituents and / or variables are only acceptable if such combinations result in stable compounds. In the selection of the compounds of the present invention, those skilled in the art will recognize that various substituents, ie, R ^{1} , R ^{2} etc., will be selected according to well known chemical structure connectivity principles.

Under standard nomenclature used throughout this application, the terminal portion of the designated side chain is first described, followed by adjacent functional groups toward the point of attachment. For example, the arylcarbonylaminoalkyl substituent is aryl-C (O) -NH-alkyl-.

The invention includes the following embodiments, which may alternatively be further combined:

(a) a compound of Formula I wherein R ^{1} and R ^{2} are ethyl;

(b) a compound of Formula I wherein R ^{1} and R ^{2} are n-propyl;

(c) a compound of Formula I wherein R ^{3} is Cl, Br, methyl or trifluoromethyl;

(d) a compound of Formula I wherein R ^{3} is Cl;

(e) a compound of Formula I wherein R ^{3} is Br;



인 화학식 I의 화합물;(f) R ^{4} is R ^{a} R ^{b} N-, pyridin-4-yl, morpholin-4-yl or



A compound of formula (i);

(g) a compound of Formula I wherein R ^{4} is morpholin- ^{4} -yl;



인 화학식 I의 화합물;(h) R ^{4} is



A compound of formula (i);

(i) compounds of formula I, wherein R ^{a} and R ^{b} are independently C $_{1}$ -C $_{3}$ alkyl;

(j) a compound of Formula I wherein R ^{1} and R ^{2} are ethyl, R ^{3} is Cl and R ^{4} is morpholin- ^{4} -yl;

(k) a compound of Formula I wherein R ^{1} and R ^{2} are n-propyl, R ^{3} is Cl and R ^{4} is morpholin- ^{4} -yl;

(l) a compound of Formula I wherein R ^{1} and R ^{2} are ethyl, R ^{3} is Br and R ^{4} is morpholin- ^{4} -yl;

(m) a compound of Formula I wherein R ^{1} and R ^{2} are n-propyl, R ^{3} is Br and R ^{4} is morpholin- ^{4} -yl;



인 화학식 I의 화합물;(n) R^1 and R^2 are ethyl, R^3 is Cl and R^4 is



A compound of formula (I);



인 화학식 I의 화합물;(o) R^1 and R^2 are n-propyl, R^3 is Cl and R^4 is



A compound of formula (I);



인 화학식 I의 화합물;(p) R^1 and R^2 are ethyl, R^3 is Br and R^4 is



A compound of formula (I);



인 화학식 I의 화합물;(q) R^1 and R^2 are n-propyl, R^3 is Br and R^4 is



A compound of formula (I);

(r) the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment of depression or anxiety;

(s) the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment of alcohol or substance abuse;

(t) the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment of alcohol or substance abuse and related withdrawal symptoms;

(u) a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the Ki value for CRF1 binding is less than or equal to 500 nM;

(v) a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the Ki value for CRF1 binding is 50 nM or less;

(w) a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the Ki value for CRF1 binding is 5 nM or less;

(x) a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein the Ki value for CRF1 binding is no greater than 500 nM and selectively binds to CRF1 (ie, has a lower Ki) than CRF2;

(y) a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the Ki value for CRF1 binding is 50 nM or less and selectively binds to CRF1 (ie, has a lower Ki) than CRF2;

(z) a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein the Ki value for CRF1 binding is 5 nM or less and selectively binds to CRF1 (ie, has a lower Ki) than CRF2;

(aa) Certain exemplary compounds having better bioavailability and pharmacokinetic profiles compared to some known CRF antagonists (eg, CP154526 and NBI30775), such as Example 15.

The compounds of the present invention are preferably formulated as pharmaceutical compositions administered by various routes. Preferably such composition is for oral administration. Such pharmaceutical compositions and methods for their preparation are well known in the art (see, eg, *Remington: The Science and Practice of Pharmacy* , A. Gennaro, et al., Eds., 19th ed., Mack Publishing Co. , 1995).

In general, the compounds of formula (I) are effective over a wide range of dosages. For example, the dosage per day is usually in the range of about 0.0001 to about 30 mg per kg of body weight. In some cases, dosage levels below the lower limit of the aforementioned ranges may be more appropriate, while in some cases even larger doses may be used without causing any adverse side effects, and thus the dosage ranges may it is not intended to limit the scope. The amount of compound actually administered will be determined by the physician in light of the relevant circumstances, including the condition to be treated, the route of administration chosen, the actual compound or compounds administered, the individual patient's response, age and weight, and the severity of the patient's symptoms. I will understand.

The compound of formula (I) is a CRF-1 antagonist and is useful for the treatment of a treatable condition, as described above, by reducing CRF1 receptor tension or stimulation. 41 amino acid peptide (J. Rivier et al., *Proc. Natl. Acad)* , which is the primary physiological regulator of proplomemelanocortin (POMC) induced peptide secretion from the anterior pituitary gland, a corticotropin releasing factor (CRF) . *Sci* (USA) 80: 4851 (1983); W. Vale et al., *Science* 213: 1394 (1981)) are linked to a number of medical conditions. For example, in addition to the endocrine role in the pituitary gland, immunohistochemical localization of CRF is characterized by a wide range of autonomic, electrical, hormones with a broad hypothalamic distribution in the central nervous system and the same role as neurotransmitters or neuromodulators in the brain. To provide a physiological behavioral effect (W. Vale et al., *Rec. Prog. Horm. Res.* 39: 245 (1983); GF Koob, *Persp. Behav . Med.* 2:39 (1985) EB De Souza et al., *J. Neurosci* . 5: 3189 (1985)). There is also evidence that CRF plays an important role in integrating responses in the immune system to physiological, psychological and immunological stressors (eg, JE Blalock, *Physiological Reviews* 69: 1 (1989); and See JE Morley, *Life Sci* . 41: 527 (1987).

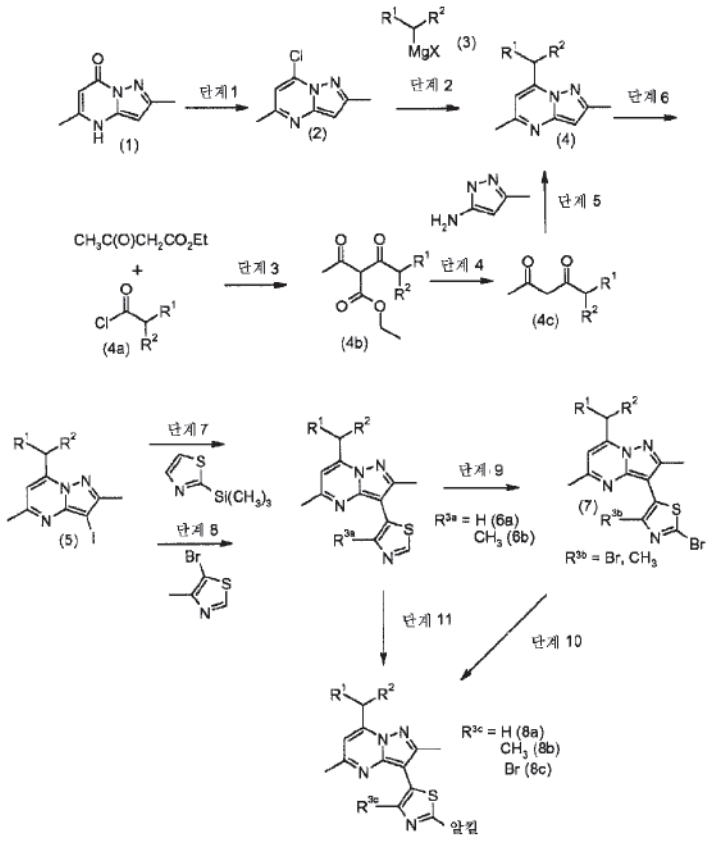
CRF is associated with psychiatric disorders and neurological disorders, including depression and anxiety (DM Nielsen, *Life Sci* . 78: 909-919; HE Kunzel et al., *J. Psychiatr. Res.* 37: 525-533 DR Gehlert et al., *Eur. J. Pharmacol* . 509: 145-153). In addition, the role of CRF in the etiology and pathophysiology of Alzheimer's disease,

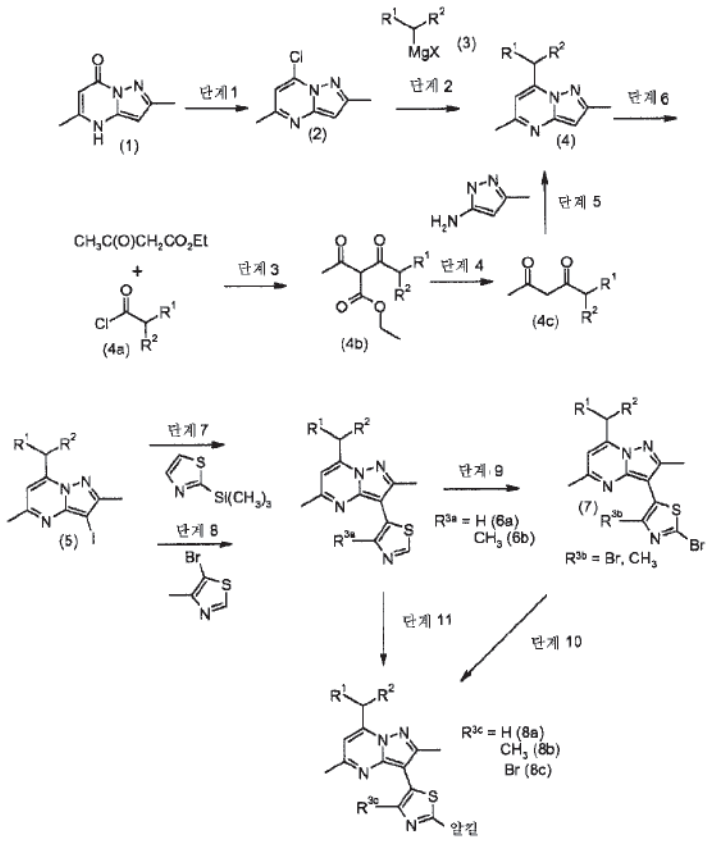
Huntington's disease, progressive nuclear palsy and amyotrophic lateral sclerosis has been claimed to be linked to dysfunction of CRF neurons in the central nervous system (overview , EB De Souza, *Hosp. Practice* 23:59 (1988). Chronic administration of CRF has been shown to cause damage to the dopamine lineage, suggesting a role in Parkinson's disease [E. Izzo et al., *Pharmacol. Biochem. Behav* . 81: 701-708 (2005). Other neurological disorders associated with CRF include epilepsy [TZ Baram et al., *Brain Res* . 770: 89-95 (1997) and migraine headaches [TC Theoharides et al., *Endocrinology* 136: 5745-5750 (1995)]. CRF is associated with alcohol and substance abuse and related withdrawal symptoms [DH Overstreet et al., *Pharmacol. Biochem. Behav* . 77: 405-413; Y. Shaham et al., *Psychopharmacology* (*Berl*) 137: 184 -190]]. In addition, CRF can be used in various endocrine disorders and cardiovascular diseases such as obesity [E. Timofeeva and D. Richard, *Neuroendocrinology* 66: 327-340 (1997)], metabolic syndrome [AM Ward et al., *Metabolism* 53: 720-726 (2004)], congenital adrenal hyperplasia [DP Merke and GB Cutler Jr., *Endocrinol . Metab. Clin. North Am* . 30: 121-135 (2001)], Cushing's disease [M. Labeur et al., *Curr. Drug Targets Immune Endocr. Metabol. Disord* . 4: 335-342 (2004)], hypertension [RJ Briscoe, et al., *Brain Res.* 881: 204-207 (2000) and stroke [SL Stevens et al., *J. Cereb. Blood Flow Metab.* 23: 1151-1159 (2003). Gastrointestinal disorders such as irritable bowel syndrome [Y. Yache 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). In addition, CRF can be used in various areas of 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 [JE Jones et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 283: R591-597 (2002)] and early analgesia [PD Wadhwa et al., *Am. J. Obstet. Gynecol.* 191: 1063-1069 (2004)]. There is also evidence that CRF plays an important role in the immune system, which is an inflammatory disorder [A. Gravanis and AN Margioris, *Curr. Med. Chem* . 12: 1503-1512 (2005)], allergies [LK Singh et. al., *Brain Behav. Immun* . 13: 225-239 (1999)], multiple sclerosis and other autoimmune disorders [C. Benou et al., *J. Immunol.* 174: 5407-5413 (2005)]. In addition to the above, CRF is associated with long term pain [M. Nijsen et al., *Neurogastroenterol. Motil* . 17: 423-432 (2005)], sleep disorders [TM Buckley and AF Schatzberg, *J. Clin. Endocrinol. Metab* . 90: 3106-3114 (2005)], pituitary tumor or ectopic pituitary-induced tumor [KD Dieterich et al., *J. Clin. Endocrinol. Metab* . 83: 3327-3331 (1998)], chronic fatigue syndrome and myofascial pain [G. Neeck and LJ Crofford, *Rheum. Dis. Clin. North Am* . 26: 989-1002 (2000).

CRF receptor subtypes, CRF1 and CRF2, have been identified and are heterogeneously distributed in the brain [DT Chalmers et al., *TIPS* 17: 166-72 (1996)], indicating potential functional diversity [SC Heinrichs et al., *Regul. Peptides* 71:15 (1997). For example, widely distributed brain CRF1 receptors are strongly related to the emotions associated with exposure to environmental stressors [G. Liebsch et al., Regul. *Peptide* s 59: 229-39 (1995); DW Schulz, PNAS 93: 10477-82 (1996)]. Importantly, CRF1 receptors, but not CRF2, appear to mediate the selection of anxiety-like behavior (Heinrichs et al., 1997). More discrete septal / hypothalamic distribution [DT Chalmers et al., *J. Neurosci* . 15 (10): 6340-50 (1995)], and the availability of other endogenous ligands [J. Vaughan et al., *Nature* 378: 287-92 (1995) suggest a different functional role for the CRF2 receptor [Heinrichs et al., 1997]. For example, new CRF-like neuropeptides with selective affinity for CRF2 over CRF1 receptors have been reported to inhibit appetite without generating behavioral activation profiles observed with selective CRF1 competition (H. Tezval et al., *PNAS* 101 (25): 9468-9473 (2004).] In some cases. CRF2 competition is determined by the CRF1 antagonist or CRF1 gene deletion [SC Heinrichs, Trends in Pharmacological Sciences 20 (8): 311-5 (1999), for example, while CRF2 agonists are proposed as appetite suppressants, CRF1 antagonists may also be important therapeutics for obesity [C. Contoreggi et al., *Neuroendocrinology* 80 (2): 111-23 (2004).

Preparation of Compound of the Invention

All compounds of the present invention can be prepared chemically, for example according to the synthetic routes described below. However, the following discussion is not intended to limit the scope of the invention in any way. For example, additional synthetic compounds of formula (I) may be prepared by combining the specific synthetic steps for each of the routes described in various ways, or in combination with the steps of different schemes. The product of each step can be recovered by conventional methods including extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization and the like. In the following schemes, all substituents are as previously defined unless otherwise noted, and suitable reagents are well known and recognized in the art.





The formation of compounds of formula (6a, b), (7) or 8 (ac) can be carried out according to the reaction as shown in Scheme 1. Suitable compounds of formula (6a, b), (7) or (8a-c) are those in which R^1 and R^2 are as defined in formula I and R^{3a} is H or CH_3 and R^{3b} is Br or CH_3 and R^{3c} is a compound that is H, CH_3 or Br.

In step 1 of Scheme 1, pyrazolo [1,5-a] pyrimidin-7-one of formula (1) is reacted with phosphorus oxychloride and dimethylaniline in an inert solvent such as toluene at the reflux temperature of the solvent. -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) in an inert solvent such as toluene at reflux temperature to react the 7-alkyl pyrazolopyri of formula (4) Provides midines.

Alternatively, 7-alkyl pyrazolopyrimidines of formula (4) can be obtained as shown in steps 3, 4 and 5. In step 3, ethyl acetoacetate is acylated with an acid halide of formula (4a) in the presence of magnesium chloride to 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, decarboxylation is carried out by heating (4b) in dimethyl sulfoxide at a temperature of about 130 to 170 ° C. In step 5, the diketone of formula (4c) is cyclized using 3-amino-5-methylpyrazole to form a 7-alkyl pyrazolopyri of formula (4) in a protic solvent such as methanol, ethanol or acetic acid Produces midines. Preferred conditions are the use of acetic acid at a temperature of about 0 to 60 ° C.

The pyrazolopyrimidines of formula (4) are functionalized with iodopyrazolopyrimidines of formula (5) using excess N-iodosuccinimide in acetonitrile in step 6.

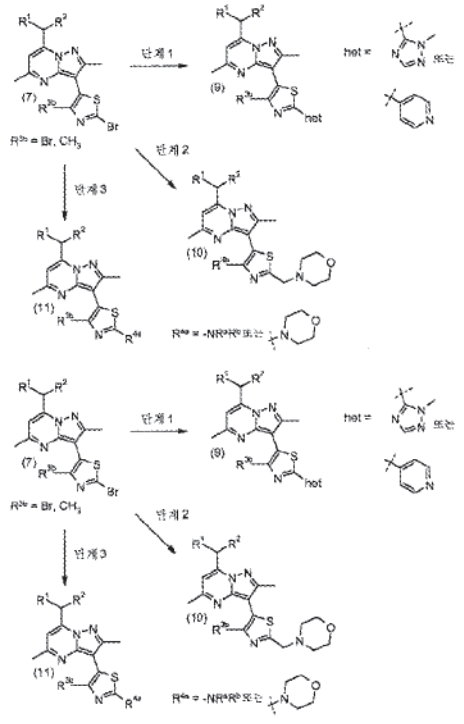
In step 7 or 8 of Scheme 1, iodopyrazolopyrimidine of formula (5) is reacted with thiazole zinc chloride in a Negishi cross coupling reaction to thiazolyl pyrazolo of formula (6a) or (6b). Pyrimidine is provided (Jensen, J .; Skjaerbaek, N .; Vedso, P. *Synthesis* 2001, 128). Thiazole zinc chloride is produced using methods well known to those skilled in the art. For example, in step 7, 2-trimethylsilanylthiazole is treated with n-, sec- or tert-butyl lithium and then lithium-zinc exchanged with $ZnCl_2$. The organozinc reagent is reacted in an inert solvent such as THF for about 12 to 36 hours at reflux in the presence of a palladium catalyst, for example dichloro [1,1'-bis (diphenyl-phosphino) ferrocene] palladium (ii) dichloromethane. Coupling with iodopyrazolopyrimidine of formula (5) provides thiazole pyrazolopyrimidine of formula (6a).

Alternatively, in step 8, 5-bromo-4-methylthiazole and zinc metal are used to generate thiazole zinc bromide, and essentially used for Negishi cross coupling as described for step 7 The thiazole pyrazolopyrimidine of (6b) is provided.

In step 9 of Scheme 1, the thiazole of formula (6a, b) is brominated to produce bromo or dibromo thiazole of formula (7), wherein R^{3b} is Br or CH_3. Thiazoles are brominated with 1 or 2 equivalents of N-bromosuccinimide, respectively, depending on whether R^{3a} is CH_3 or H.

Alkyl thiazoles of formula (8a-c) are obtained from thiazoles of formula (6a, b) in step 11 or bromothiazoles of formula (7) in step 10. In step 10, halogen-lithium exchange with n-, sec- or t-butyl lithium provides a thiazole lithium reagent, which is subsequently electrophilic such as iodomethyl methylether or iodobutane, such as an alkyl halide React with in step 11, the thiazole lithium reagent is formed via deprotonation with n-, sec- or tert-butyl lithium, followed by reaction with an electrophile such as iodomethyl methylether or iodobutane.

Those skilled in the art will readily functionalize the thiazole ring line and thiazole intermediates such as 2-trimethylsilanyl-thiazole (Dondoni, A .; et. Al. *J. Org. Chem*. 1988, 53, 1748) It will be appreciated that it can be readily manufactured. 5-Bromo-4-methylthiazole is obtained by bromination of 4-methylthiazole with bromine in acetic acid (Collins, IJ, et. Al. WO2003093252, 13 Nov 2003). 2,5-dimethyl-4H-pyrazolo [1,5-a] pyrimidin-7-one (1) is used for condensation of ethyl acetoacetate and 5-methyl-2H-pyrazol-3-ylamine in reflux acetic acid. It is easily manufactured by.

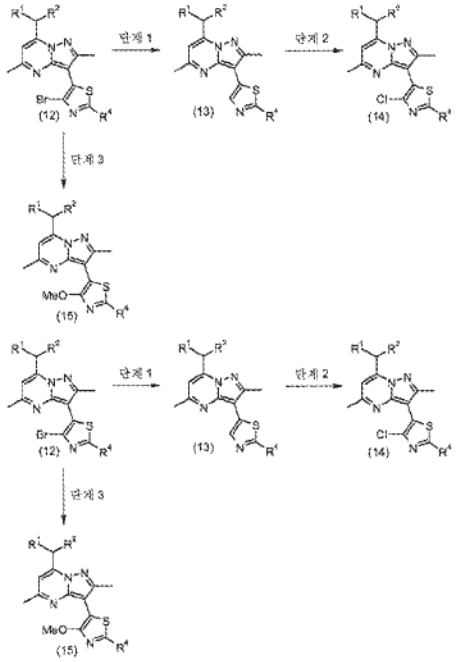


The formation of compounds of formula (9), (10) or (11) can be carried out according to the reaction as shown in Scheme 2. Suitable compounds of formula (9), (10) or (11) are those in which R^1, R^2, R^a and R^b are as defined in formula I, R^{3b} is Br or CH_3 and R^{4a} is $-NR^aR^b$ or -N-morpholinyl and "het" is a compound as defined.

In step 1, bromothiazole of formula (7) is coupled with heterocyclic zinc reagent in a Negishi cross coupling reaction to provide a thiazole heterocycle of formula (9). For example, 1-methyl-1,2,4-triazole is treated with n-, sec- or tert-butyl lithium followed by zinc chloride at about -80 to -65 ° C. and bromoti of formula (7) React in situ with azoles. The reaction is carried out in the presence of a palladium catalyst such as dichloro [1,1'-bis (diphenyl-phosphino) ferrocene] palladium (II) dichloromethane or tetrakis (triphenylphosphine) palladium (0) in an inert solvent such as THF is performed preferentially. The reaction is warmed to reflux. Alternatively, heterocyclic zinc reagents are formed from halcheterocycles such as 4-iodopyridine and zinc metal.

In step 2 of Scheme 2, intermediate 2-formyl thiazole is formed via reaction with N-formyl morpholine after halogen-lithium exchange with n-, sec- or t-butyl lithium. Formyl thiazole is reductively aminated in the presence of an organic amine such as morpholine to give morpholinyl methyl thiazole of formula (10). Reductive aminations typically using inorganic borohydride reagents such as sodium borohydride or sodium cyanoborohydride are well known in the art. Preferred conditions are the use of sodium triacetoxyborohydride in an inert solvent such as dichloromethane or THF.

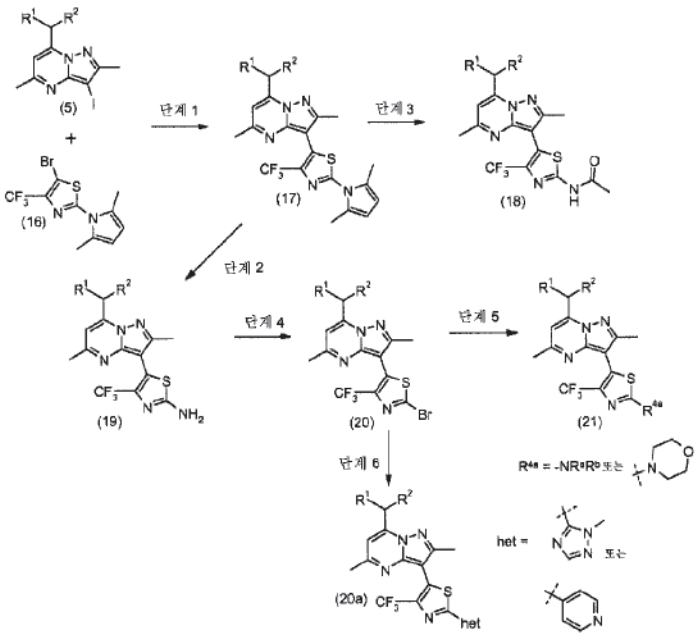
In step 3, bromothiazole of formula (7) is substituted with an amine or morpholine of formula $-NR^aR^b$ to provide an aminothiazole of formula (11). The reaction is carried out at 70 to 110 ° C. using an inorganic base such as cesium carbonate in an inert solvent such as THF or dioxane.

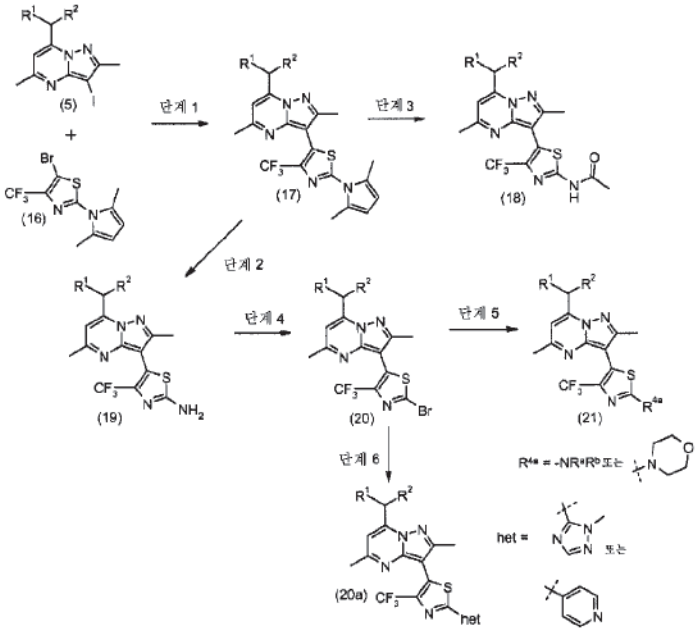


The formation of compounds of formula (13), (14) or (15) can be carried out according to the reaction as shown in Scheme 3. Suitable compounds of formula (13), (14) or (15) are those wherein R^1, R^2 and R^4 are as defined for formula (I).

Those skilled in the art will appreciate that 4-bromothiazoles, such as 4-bromothiazole of formula (12), are readily manipulated with other functional groups. For example, in step 1, the bromide is dehalogenated with cuprous chloride to obtain thiazole of formula (13), which is subsequently chlorinated with N-chlorosuccinimide to give 4-chloro of formula (14) Thiazole may be provided.

In step 3 of Scheme 3, 4-bromothiazole of formula (12) is substituted with sodium methoxide at about 100 to 120 ° C. in an inert solvent such as dimethylformamide in the presence of copper (I) iodide in methanol 4-methoxy thiazole.





The formation of compounds of formulas (17), (18), (19), (20), (20a) or (21) can be carried out according to the reaction as shown in Scheme 4. Suitable compounds of formula (17), (18), (19), (20), (20a) or (21) are those in which R^1, R^2, R^a and R^b are as defined in formula I and R^{4a} is $-NR^aR^b$ or -N-morpholinyl and "het" is a compound as defined.

In step 1 of Scheme 4, iodopyrazolopyrimidine of formula (5) and 5-bromothiazole of formula (16) are negisy cross coupled to form dimethylpyrrolylthiazole of formula (17). For example, 5-bromothiazole of formula (16) is treated with n-, sec- or tert-butyl lithium followed by zinc chloride at about -80 to -65 ° C. The organozinc reagent is reacted in situ with iodopyrazolopyrimidine of formula (5). The coupling reaction is preferentially carried out in an inert solvent such as THF at reflux in the presence of a palladium catalyst such as bis (tri-t-butylphosphine) palladium (0).

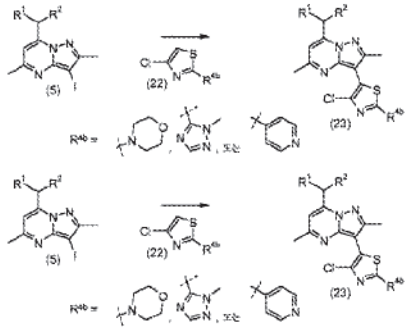
In step 2, dimethylpyrrolylthiazole of formula (17) is deprotected to provide an aminothiazole of formula (19). Dimethylpyrrole is treated with hydroxyamine in acetic acid at a temperature of about 60-100 ° C. for about 4-8 hours, preferably about 6 hours. In step 3, the same conditions as in step 2 are used, except that the reaction is continued for about 72 hours to form thiazole acetamide of formula (18).

In step 4 of Scheme 4, the 2-aminothiazole of formula (19) is converted to 2-bromothiazole of formula (20) using a modified Sandmeyer reaction. Preferred conditions are the use of alkylnitriles such as t-butylnitrile and copper bromide (II) in acetonitrile at temperatures of about 60 to 80 ° C.

In step 5, 2-bromothiazole of formula (20) is substituted with an amine or morpholine of formula -NR ^{a} R ^{b} to provide an aminothiazole of formula (21). The reaction is carried out in an inert solvent such as methanol, THF or dioxane, or the reaction is bulked with excess amine at a temperature of about 70-110 ° C. Alternatively, the reaction is carried out with reactant amine and excess triethylamine, or an inorganic base such as cesium carbonate. In addition, various deprotection steps may be necessary since -NR ^{a} R ^{b} may be necessary or desirable to carry out the reaction in the synthesis of the aminothiazole of formula (21) with additional amine functionality as defined in formula (I). For example, removal of tert-butyl ester carbamic acid (BOC) is also contemplated. The selection and use of suitable protecting groups is well known and recognized in the art (see, eg, *Protecting Groups in Organic Synthesis* , Theodora Greene (Wiley-Interscience)).

In step 6 of Scheme 4, 2-bromothiazole of formula (20) is coupled with a heterocyclic zinc reagent in a Negishi cross coupling reaction to give a formula of formula (20a) in a similar manner as described in step 1 of Scheme 2 Provides a thiazole heterocycle.

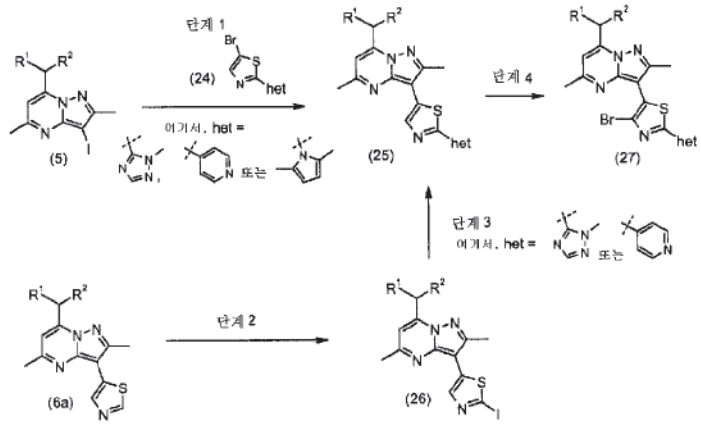
Those skilled in the art will appreciate that the functionalized thiazoles of formula (16) may be prepared by methods known in the art. For example, the cyclization of thioures with bromoketones, such as 3-bromo-1,1,1-trifluoropropan-2-one, is 4-trifluoromethyl-thiazol-2-ylamine To provide. Subsequent bromination and protection of the amine with hexane-2,5-dione provides (16).

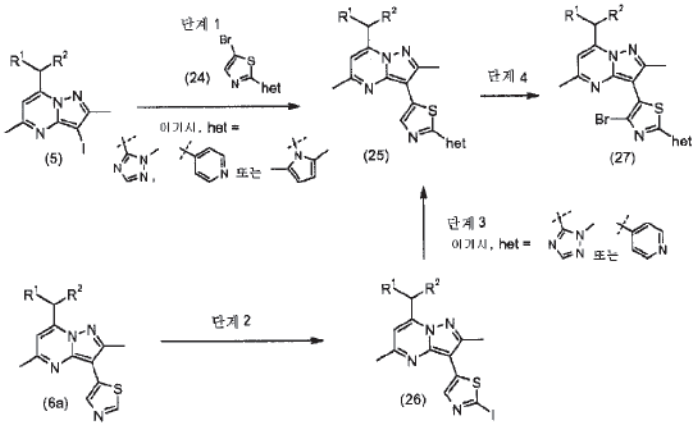


Formation of the compound of formula (23) can be carried out according to the reaction as shown in Scheme 5. Suitable compounds of formula (23) are those in which R ^{1} and R ^{2} are as defined in formula (I) and R ^{4b} is defined as indicated.

Iodidopyrazolopyrimidine of formula (5) and 4-chloro-2-morpholino-thiazole of formula (22) are cross-linked to form pyrazolopyrimidine thiazole of formula (23) Form. For example, the reactions are coupled using a base (eg cesium carbonate) in the presence of copper iodide, palladium acetate and triphenylphosphine. The coupling reaction is preferentially carried out for 4 to 24 hours at about 100 to 150 ° C. in an inert solvent such as DMF.

Those skilled in the art will appreciate that the functionalized thiazoles of formula (22) may be prepared in a manner known in the art. For example, 2,4-dichlorothiazole can be reacted with morpholine to afford 2-morpholino-thiazole of formula (22). In addition, 2,4-dichlorothiazole can be completely brominated to provide 2,5-dibromo-4-chlorothiazole. Subsequent bromine-lithium exchange with n-butyl lithium at -90 ° C. in THF and quenching with water gives 2-bromo-4-chlorothiazole [*J. Chem. Soc. Perkin Trans I : Org Bioorg. Chem.* (1972-1999), (2): 215-219 (1992). The 2-bromo-4-chlorothiazole can be crosslinked with a heterocyclic zinc reagent to yield a thiazol-2-yl triazole or pyridine.





Formation of the compound of formula (27) can be carried out according to the reaction as shown in Scheme 6. Suitable compounds of formula (27) are those wherein R ^{1} and R ^{2} are as defined in formula (I) and "het" is defined as indicated for step 1 or step 3, respectively.

In step 1 of Scheme 6, for example, heterocyclic thiazole of formula (25) is obtained by reaction of iodopyrazolopyrimidine of formula (5) with bromothiazole of formula (24). The reaction is carried out with an inert solvent such as N-methylpyrrolidone in the presence of N-butylammonium bromide and a base such as potassium acetate and a palladium catalyst such as palladium acetate and tris (2,4-di-tert-butyl-phenyl) -phosphane in a temperature of about 100 to 150 ° C.

Alternatively, in step 2, thiazolyl pyrazolopyrimidine of formula (6a) is iodoized to give 2-iodothiazole of formula (26). Thiazole is treated with lithium diisopropylamide for about 1 hour at a temperature of -70 to -80 ° C, followed by N-iodosuccinimide in an inert solvent such as THF at about the same temperature. This is followed by step 3 of forming triazolyl or 4-pyridyl thiazole of formula (25) using Negishi cross coupling conditions similar to that described for step 1 of Scheme 2.

In step 4 of Scheme 6, thiazolyl pyrazolopyrimidine of formula (25) is brominated to produce bromothiazole of formula (27). Bromination is carried out using N-bromosuccinimide in an inert solvent such as acetonitrile in the presence of a small amount of acetic acid.

As described in steps 2, 3, 4 and 5 of Scheme 4, compounds of formula (27) may be further used in which het is 2,5-dimethyl-pyrrole-1-yl.

Those skilled in the art will appreciate that the heterocycle thiazoles of formula (24) may be readily prepared by methods known in the art. For example, thiazole-2-carboxylic acid amide can be cyclized to triazole using 1,1-dimethoxy-N, N-dimethyl-methanamine followed by N-methyl-hydrazine to give triazolyl thiazole. Which can subsequently be brominated using N-bromosuccinimide. The literature procedure can yield 4-thiazol-2-yl-pyridine, which is brominated to give 4- (5-bromo-thiazol-2-yl) -pyridine. 5-Bromo-2- (2,5-dimethyl-pyrrole-1-yl) -thiazole can be easily obtained by the reaction of 2-amino-5-bromothiazole with hexane-2,5-dione. .

As used herein, "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "LC / MS" refers to liquid chromatography / mass spectroscopy; "GC / MS" refers to gas chromatography / mass spectroscopy "" HR-ToF "refers to high-resolution time-of-flight;" APCI "refers to atmospheric pressure chemical ionization;" δ "Ran refers to one million parts down-field from tetramethylsilane;" THF "refers to tetrahydrofuran;" EtOAc "refers to ethyl acetate;" MeOH "refers to methanol "EtOH" refers to ethanol and "DMF" refers to dimethylformamide.

It is believed that one skilled in the art can, using the above description, practice the invention to its fullest extent without further effort. 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 this way in any way. Reagents and starting materials are readily available to one of ordinary skill in the art or can be readily synthesized by one of ordinary skill in the art. Examples 1-35 provide representative compounds and illustrate their preparation. Examples A through D illustrate various biological assays that can be used to determine the biological properties of the compounds of the present invention. Those skilled in the art will immediately recognize appropriate modifications from the procedures described in the examples. The name of the compound of the present invention is provided by ChemDraw Ultra® version 7.0.1. Salts are named as free bases and conjugate acids.

Preparation Example 1

2,5-dimethyl-4H-pyrazolo [1,5-a] pyrimidin-7-one

Ethyl acetoacetate (128 g, 0.98 mol) was added dropwise to an acetic acid solution (500 mL) of 5-methyl-2H-pyrazol-3-ylamine (100 g, 0.95 mol) while maintaining the temperature at 25-28 ° C. It was. The mixture was heated to reflux for 10 hours and then cooled to room temperature. The reaction was added to tert-butyl methyl ether (5 L) cooled to 5 ° C while maintaining the temperature below 10 ° C. Stir at 5 ° C. for 1 h and filter. The resulting material was dried under vacuum overnight to yield a white solid (158 g, 96%).

Preparation Example 2

7-chloro-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine

ES/MS m/z (^{35}Cl) 182.3 (M+1)$^{+}$.

N, N-dimethylaniline (9.7 mL, 76.7) in a suspension of 2,5-dimethyl-4H-pyrazolo [1,5-a] pyrimidin-7-one (10.0 g, 61.3 mmol) in toluene (150 mL) mmol) was added. To the white suspension was added dropwise phosphorus oxychloride (11.2 mL, 122.6 mmol). Reflux under inert atmosphere for 3 hours, cool to room temperature and concentrate the reaction to brown oil using reduced pressure. The oil was dissolved in ethyl acetate (250 mL) and basified with 1.0 N NaOH. The organic phase was separated and the basic aqueous phase was extracted with ethyl acetate (2 x 100 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a brown solid. The material was purified using flash chromatography eluting from 80% hexanes / 20% (30% THF / hexanes) to 0% hexanes / 100% (30% THF / hexanes) in a 20% incremental gradient step to give a light green solid. (6.65 g, 59%) was obtained.
ES/MS m/z (^{35}Cl) 182.3 (M+1)$^{+}$.

Alternative procedure:

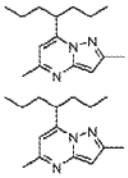
ES/MS m/z (^{35}Cl) 182.3 (M+1)$^{+}$.

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, then N, N-diethylaniline

(20.8 mL, 128 mmol) was added. After further stirring for 5 minutes, phosphorus oxychloride (11.7 mL, 126 mmol) was added over 15 minutes. The mixture was stirred at 22 ° C. for 15 minutes, then heated to 80-85 ° C. over 35 minutes and the reaction was left at this temperature for 1.5 hours. The cooled reaction mixture was slowly added to a solution of potassium dibasic phosphate (106.7 g, 612.82 mmol) in water (325 mL) cooled to 0-5 ° C., while maintaining the temperature below 5 ° C. during the addition. The mixture was stirred at 22 ° C. and then 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 x 100 mL). The organic portions were combined, dried over sodium sulphate, filtered and the solvent was evaporated. Purification by silica gel chromatography eluting with hexanes / ethyl acetate (2/1) gave the title compound as a yellow solid (20.7 g, 88%).
ES/MS m/z (^{35}Cl) 182.3 $(M+1)^+$.

Preparation Example 3

7- (1-propyl-butyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine



ES/MS m/z 246.3 $(M+1)^+$.

The oven dried flask, equipped with a reflux condenser, was charged with anhydrous THF (40 mL), iodine (catalyst amount), magnesium ribbon (1.92 g, 78.9 mmol) and 4-bromoheptane (9.4 mL, 52 mmol). The reaction was heated to reflux in an oil bath. The temperature of the reaction spike was initiated as the Grignard reaction. The reaction was further stirred at 90 ° C. for 4 hours and cooled to room temperature. The magnesium metal is precipitated (may be centrifuged) and the Grignard reagent is brought under 7 * chloro-2,5-dimethylpyrazolo [1,5-e] pyrimidine in anhydrous toluene (20 mL) under positive argon pressure. The flask filled with (4.80 g, 26.3 mmol) was placed using cannula. The reaction was refluxed under inert atmosphere overnight. The reaction was cooled to rt and quenched with water. Diluted with ethyl acetate (150 mL), then water (100 mL) and saturated ammonium chloride (50 mL) were added. The aqueous phase was separated and extracted with dichloromethane (75 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified using flash chromatography eluting from 80% hexanes / 20% (20% ethyl acetate / hexanes) to 0% hexane / 100% (20% ethyl acetate / hexanes) in a 20% incremental gradient step. Yellow crystals (3.08 g, 48%).
ES/MS m/z 246.3 $(M+1)^+$.

Alternative procedure:

ES/MS m/z 246 $(M+1)^+$.

A mixture of magnesium turning (3.5 g, 144 mmol) with a catalytic amount of iodine (100 mg) in THF (100 mL) was heated to 65 ° C. under a nitrogen atmosphere. A few drops of bulk 4-bromoheptane were added and the mixture was heated until the reaction started. Then a solution of 4-bromoheptane (17.6 mL, 94.9 mmol) in THF (42 mL) was added and the temperature was maintained at 65-70 ° C. over 2 hours. The mixture was further refluxed for 1 hour, then the reaction was cooled to 22 ° C. A solution of 7-chloro-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (10.2 g; 53.3 mmol) in THF (60 mL) in which the prepared Grignard reagent was cooled to 0 ° C. under nitrogen atmosphere. Was added. Magnesium reagent solution was added via cannula over 45 minutes while maintaining the temperature below 10 ° C. Then, the mixture was further stirred at 5 ° C. for 30 minutes. To the mixture was added 10% (wt / wt) aqueous ammonium chloride solution (125 mL) and stirred at 22 ° C for 30 minutes. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 25 mL). The organic layers were combined and dried over sodium sulfate. The mixture is filtered and the solvent is evaporated. The crude material was purified by silica gel flash chromatography using hexanes / ethyl acetate (5/1) eluent to afford 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), then ethyl acetoacetate (19.55 mL, 20.00 g, 153.79 mmol) was added in one portion and stirred at room temperature for 1 hour. The mixture was cooled in a cold water bath and pyridine (24.86 mL, 24.32 g, 307.39 mmol) was added dropwise. To the white slurry, di-n-propylacetyl chloride (25.00 g, 153.70 mmole) was added dropwise 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 1 N 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%). The 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 mmole) was dissolved in dimethyl sulfoxide (100 mL) and water (5 mL). The solution was heated at 150 ° C. for 6-8 hours or the reaction was tracked by GC / MS. The reaction was cooled down 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 heptanes. 23.29 g of oil were obtained and used directly in the next step.

Step 3 : 7- (1-propyl-butyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine

^{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).

5-propyl-octane-2,4-dione (15 g, 81.40 mmole) was mixed in 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. Compared with the authentic sample from the GC, it was found that it is the correct isomeric region. Excess acetic acid was distilled off. Water (50 mL) was added and extracted with heptane (50 mL). Heptanes were

washed with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to give 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 Preparation Example 3. Grignard reagent was prepared using 3-bromopentane.

제조예	화학적 명칭	물리적 데이타
4	7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	ES/MS m/z 218.1 $(M+1)^+$

제조예	화학적 명칭	물리적 데이타
4	7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	ES/MS m/z 218.1 $(M+1)^+$

Preparation Example 5

7- (1-propyl-butyl) -3-iodo-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine

^{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).

7- (1-propyl-butyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (3.08 g, 12.5 mmol) is dissolved in anhydrous acetonitrile (25 mL) and N-Iodo Succinimide (4.2 g, 18.7 mmol) was added in 6 portions (0.70 g each) at 10 minute intervals. Stir at room temperature over the weekend. Acetonitrile was stripped and the oil diluted with dichloromethane (100 mL). Wash with saturated ammonium chloride solution (2 × 50 mL). The organic phase was collected, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give a dark red oil. The oil was purified using flash chromatography eluting from 100% hexanes / 0% (20% ethyl acetate / hexanes) to 0% hexanes / 100% (20% ethyl acetate / hexanes) in 50% incremental gradient steps to give an orange color. Oil (10.97 g, 87%) was obtained.

^{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.

제조예	화학적 명칭	물리적 데이타
6	7-(1-에틸-프로필)-3- 요오도 -2,5-디메틸-피라졸로[1,5-a]피리미딘	1H NMR (400 MHz, $CDCl_3$): 6.44 (s, 1H), 3.59 (m, 1H), 2.61 (s, 3H), 2.49 (s, 3H), 1.86-1.76 (m, 4H), 0.85 (t, J = 7.5 Hz, 6H).

제조예	화학적 명칭	물리적 데이타
6	7-(1-에틸-프로필)-3- 요오도 -2,5-디메틸-피라졸로[1,5-a]피리미딘	1H NMR (400 MHz, $CDCl_3$): 6.44 (s, 1H), 3.59 (m, 1H), 2.61 (s, 3H), 2.49 (s, 3H), 1.86-1.76 (m, 4H), 0.85 (t, J = 7.5 Hz, 6H).

Alternative Procedure of Preparation Example 6 :

ES/MS m/z 344 $(M+1)^+$.

Acetic acid (1 mL) and a solution of 7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (6 g, 27.5 mmol) in acetonitrile (60 mL) and N-Iodosuccinimide (6.7 g, 29.9 mmol) was added in one portion. The mixture was stirred at 22 ° C for 2 h. 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 sulphate, 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

^{1}H NMR (400 MHz, $CDCl_3$) 8.13 (d, 1H, J=2.6 Hz), 7.54 (d, 1H, J = 2.6 Hz), 0.43 (s, 9H).

In a three-necked flask equipped with a dropping funnel and thermometer, n-butyl lithium (20.4 mL, 51.0 mmol, 2.5 M in hexane) and diethyl ether (50 mL) were mixed. Cool to -78 ° C and add a solution of thiazole (4.25 g, 50.0 mmol) in diethyl ether (50 mL) dropwise. 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. Stirred at -78 ° C. for 1 hour and then allowed to warm to room temperature. Saturated sodium bicarbonate was added to quench the reaction. 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 mm Hg) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) 8.13 (d, 1H, J=2.6 Hz), 7.54 (d, 1H, J = 2.6 Hz), 0.43 (s, 9H).

Preparation Example 8

5-bromo-4-methylthiazole

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 2.43 (s, 3H).

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. Dilute with dichloromethane and wash with 1 N NaOH and brine. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography eluting with hexanes / ethyl acetate (5/1) to afford 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

ES/MS m/z 158 $(M+1)^+$.

To a mixture of 2-trimethylsilylthiazole (135 g, 858.1 mmol) in toluene (1350 mL), a solution of ethyl chloroformate (98.4 mL, 1.03 mol) in toluene (1350 mL) was added over 15 minutes. The reaction was stirred at 22 ° C for 2 h. The solution was added onto 25% (wt / wt) aqueous sodium carbonate (5 L) and stirred for 30 minutes. The organic layer was separated and the aqueous layer was reextracted 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

ES/MS m/z 129 $(M+1)^+$.

To a mixture of methanol (75 mL) and 30% aqueous ammonium hydroxide (750 mL) was added thiazole-2-carboxylic acid ethyl ester (150 g, 0.9 mol) and the mixture was heated to reflux for 1 hour. Then cooled to 22 ° C. and methanol was evaporated in vacuo. The mixture was stirred at rt for 30 min and the solid was filtered off. The isolated solid was dried under vacuum to afford 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 amide (60 g, 421 mmol) was added in three portions. The mixture was stirred at 10 ° C for 30 minutes. The mixture was then gradually heated to reflux within 45 minutes. The methanol formed was distilled off and then the reaction was heated to 100 ° C. for 1.5 h. 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. The mixture was triturated for 15 minutes, filtered and the solids were dried to constant weight before use in the next step.

ES/MS m/z 167 $(M+1)^+$.

The isolated solid (68 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 such that the temperature was maintained below 15 ° C. The mixture was warmed to 20 ° C within 30 minutes and then gradually heated to 90 ° C. Stir at 90 ° C. for 30 minutes and then cool to 22 ° C. Acetic acid was removed by vacuum distillation. The residue was added to water and the pH was adjusted to 8 by addition of 25% aqueous sodium hydroxide solution. The aqueous layer was extracted with methyl-t-butyl ether (3 x 600 mL). The organic layers are combined and the solvent is evaporated. The resulting residue was purified by silica gel chromatography using hexane / isopropanol (9/1) eluent to afford 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

ES/MS m/z (^{79}Br/^{81}Br) 245/247 $(M+1)^+$.

N-bromosuccinimide (14) in a mixture of methyl-5-thiazol-2-yl-1H- [1,2,4] triazole (6.55 g, 39.4 mmol) and dimethylformamide (32 mL) g, 78.8 mmol) was added in 3 portions over 1 hour. The mixture was stirred at 22 ° C for 18 h 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 x 200 mL). The organic layers were combined, washed with 7% aqueous sodium bicarbonate (100 mL) and then dried over sodium sulfate. Filtration and evaporation of the solvent gave the title compound (9.5 g, 93%).
ES/MS m/z (^{79}Br/^{81}Br) 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

ES/MS m/z 410 $(M+1)^+$.

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) was combined in N-methylpyrrolidone (58 mL) and stirred in complete solution under nitrogen. 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 with three cycles of vacuum / nitrogen purge. Then palladium acetate (216 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 h 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 combined and evaporated. The residue was purified by filtration through a pad of silica gel eluting hexane / ethyl acetate (4/1). The products containing fractions 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

ES/MS m/z 329.0 $(M+1)^+$.

The oven dried flask was charged with 2-trimethylsilanylthiazole (1.765 g, 11.24 mmol) dissolved in anhydrous THF (30 mL) and cooled to -78 ° C under inert atmosphere. n-butyl lithium (2.5 M hexane solution, 4.5 mL, 11.24 mmol) was added slowly and stirred at -78 ° C. for 30 minutes. One aliquot of anhydrous zinc chloride (2.26 g, 16.58 mmol) was added 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 rt, quenched with saturated sodium bicarbonate and diluted with ethyl acetate (150 mL). The aqueous was separated and extracted with ethyl acetate (75 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified using flash chromatography eluting from 100% hexanes / 0% (30% THF / hexanes) to 0% hexanes / 100% (30% THF / hexanes) in a 10% incremental gradient step to give white Solid (0.720 g, 42%) was obtained.
ES/MS m/z 329.0 $(M+1)^+$.

The following compounds were prepared essentially as described in Preparation 14.

제조예	화학적 명칭	물리적 데이터
15	7-(1-에틸-프로필)-2,5-디메틸-3-티아졸-5-일-피라졸로[1,5-a]피리미딘	1H NMR (400 MHz, $CDCl_3$): d 8.75 (s, 1H), 8.75 (s, 1H), 8.28 (s, 1H), 6.47 (s, 1H), 3.62-3.55 (m, 1H), 2.65 (s, 3H), 2.61 (s, 3H), 1.89-1.75 (m, 4H), 0.85 (t, 6H, J = 7.5 Hz), 0.85 (t, 6H, J = 7.5 Hz).

제조예	화학적 명칭	물리적 데이터
15	7-(1-에틸-프로필)-2,5-디메틸-3-티아졸-5-일-피라졸로[1,5-a]피리미딘	1H NMR (400 MHz, $CDCl_3$): d 8.75 (s, 1H), 8.75 (s, 1H), 8.28 (s, 1H), 6.47 (s, 1H), 3.62-3.55 (m, 1H), 2.65 (s, 3H), 2.61 (s, 3H), 1.89-1.75 (m, 4H), 0.85 (t, 6H, J = 7.5 Hz), 0.85 (t, 6H, J = 7.5 Hz).

Alternative procedure for preparation 15 :

n-butyl lithium (76.5 mL, 191 mmol, 2.5 M in hexane) is added to a solution of 2-trimethylsilylthiazole (30 g, 191 mmol) in THF (450 mL) at -78 ° C. under nitrogen and added The temperature was kept below -74 ° C. The mixture was stirred at -78 ° C for 30 min, 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 h. 7- (1-ethyl-propyl) -3-iodo-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (30 g, 87 mmol) and 1,1'-bis (diphenylforce Pino) ferrocene palladium (II) chloride (6.5 g, 8 mmol) was added and the mixture was heated to 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 x 100 mL). The organic portions were combined, dried over sodium sulphate, filtered and the solvent was evaporated to give the title compound (20.4 g, 78%). ES / MS m / z 301 $(M + I)^+$.

Preparation Example 16

7- (1-ethyl-propyl) -3- (2-iodo-thiazol-5-yl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine

ES/MS m/z 427 $(M+1)^+$.

Of 7- (1-ethyl-propyl) -2,5-dimethyl-3-thiazol-5-yl-pyrazolo [1,5-a] pyrimidine (17.8 g, 62.4 mmol) in THF (100 mL) To the mixture, a freshly prepared solution of lithium di-i-propylamide (150 ml, 62.4 mmol, 0.6 M in THF) was added at −78 ° C. under a nitrogen atmosphere, and the temperature was kept below −74 ° C. during the addition. The mixture was stirred at -78 ° C for 1 h, then a solution of N-iodosuccinimide (15 g, 63 mmol) in THF (100 mL) was added while maintaining 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 x 200 mL). The organic layers were combined, dried over sodium sulphate, filtered and the solvent was evaporated. The resulting residue was purified by silica gel chromatography eluting with hexane / acetone (5/1) to afford the title compound (15 g, 60%).
ES/MS m/z 427 $(M+1)^+$.

Example 1

7- (1-ethyl-propyl) -2,5-dimethyl-3- (4-methyl-thiazol-5-yl) -pyrazolo [1,5-a] pyrimidine

^{1}H NMR (400 MHz, $CDCl_3$): δ

8.80 (s, 1H), 6.48 (s, 1H), 3.63 (m, 1H), 2.57 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J = 7.3Hz). ES/MS m/z 315 $(M+1)^+$.

Rieke® zinc (10 g in 100 mL THF, 13.2 mL, 18.48 mmol) was added to 5-bromo-4-methylthiazole (2.13 g, 18.48 mmol) and heated to reflux for 2 hours. The mixture was cooled to room temperature and zinc was precipitated by centrifugation. Through 7- (1-ethyl-propyl) -3-iodo-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (900 mg, 2.62 mmol) in dry tetrahydrofuran (10 mL) Nitrogen gas was bubbled, organo zinc bromide solution was added followed by [1,1'-bis (diphenylphosphino) ferrocene] -dichloropalladium (II) (106 mg, 0.13 mmol). The reaction mixture was heated to reflux overnight and cooled to room temperature. To the reaction mixture was added ammonium chloride solution and extracted with dichloromethane. The organic portion was dried over sodium sulphate, 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 = 7.3Hz). 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

ES/MS m/z (^{79}Br^{81}Br) 486.7 $(M+1)^+$.

2,5-dimethyl-7- (1-propyl-butyl) -3-thiazol-5-yl-pyrazolo [1,5-a] pyrimidine (3.15 g, 9.59 mmol) was diluted to acetonitrile (100 mL). Dissolve in and add 1 aliquot of N-

bromosuccinimide (4.27 g, 24.0 mmol). Stir overnight under inert atmosphere and confirm that the reaction was complete using TLC. Concentrated under reduced pressure, 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. The resulting oil was converted to 100% hexanes / 0% (30% THF / hexanes) in a gradient (30% THF / hexane 0-10-15-20-25-30-35-40-45-50-100%). Purification was carried out using flash chromatography eluting with 0% hexane / 100% (30% THF / hexane) at to give yellow crystals (3.70 g, 79%). ES/MS m/z ($^{79}Br^{81}Br$) 486.7 $(M+1)^+$.

Except for using dichloromethane as solvent, the following compounds were prepared essentially as described in Preparation Example 17.

실시예	화학적 명칭	물리적 데이타
2	3-(2,4-디브로모-티아졸-5-일)-7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	MS (APCI) m/z ($^{79}Br^{81}Br$) 459.1 $(M+1)^+$
3*	3-(2-브로모-4-메틸-티아졸-5-일)-7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	ES/MS m/z (^{79}Br) 393 $(M+1)^+$

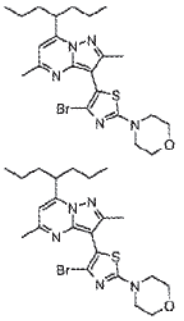
*NBS 1.1 당량 사용 및 3일 동안 교반

실시예	화학적 명칭	물리적 데이타
2	3-(2,4-디브로모-티아졸-5-일)-7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	MS (APCI) m/z ($^{79}Br^{81}Br$) 459.1 $(M+1)^+$
3*	3-(2-브로모-4-메틸-티아졸-5-일)-7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	ES/MS m/z (^{79}Br) 393 $(M+1)^+$

*NBS 1.1 당량 사용 및 3일 동안 교반

Example 4

3- (4-Bromo-2-morpholin-4-yl-thiazol-5-yl) -2,5-dimethyl-7- (1-propyl-butyl) -pyrazolo [1,5-a] Pyrimidine



ES/MS m/z (^{79}Br) 491.7 $(M+1)^+$.

The 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). It was refluxed in oil bath (105 ° C.) overnight under inert atmosphere. LC / MS was used to confirm the reaction was complete. Dilute with ethyl acetate (100 mL), wash with water (50 mL), and extract the aqueous back with ethyl acetate (50 mL). The organic phases were combined, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The resulting residue was taken from 0% hexane / 100% (40% in 100% hexanes / 0% (7 N ammonia / 36% hexane in 40% dichloromethane / 20% ethyl acetate / 2% methanol) in a 10% incremental gradient step. Purification using flash chromatography eluting with dichloromethane / 20% ethyl acetate / 2% methanol in 7N ammonia / 36% hexane) gave 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 2.0 dimethylamine / THF or morpholine as the amine and THF or dioxane as the solvent. The reaction was run in a sealed vessel or Schlenk tube.

실시예	화학적 명칭	물리적 데이타
5*	{4-브로모-5-[2,5-디메틸-7-(1-프로필-부틸)-피라졸로[1,5-a] 피리미딘-3-일]-티아졸-2-일}-디메틸아민	ES/MS (^{79}Br) 449.8 $(M+1)^+$.
6	3-(4-브로모-2-모르폴린-4-일-티아졸-5-일)-7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	MS (APCI) m/z (^{81}Br) 466.5 $(M+1)^+$
7	{4-브로모-5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-티아졸-2-일}-디메틸-아민	MS (APCI) m/z (^{81}Br) 424.4 $(M+1)^+$
8	{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-메틸-티아졸-2-일}-디메틸-아민	ES/MS m/z 358 $(M+1)^+$
9	7-(1-에틸-프로필)-2,5-디메틸-3-(4-메틸-2-모르폴린-4-일-티아졸-5-일)-피라졸로[1,5-a]피리미딘	ES/MS m/z 400 $(M+1)^+$

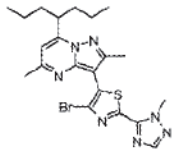
*탄산세슘 6 당량 사용.

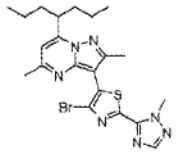
실시예	화학적 명칭	물리적 데이타
5*	{4-브로모-5-[2,5-디메틸-7-(1-프로필-부틸)-피라졸로[1,5-a] 피리미딘-3-일]-티아졸-2-일}-디메틸아민	ES/MS (^{79}Br) 449.8 $(M+1)^+$.
6	3-(4-브로모-2-모르폴린-4-일-티아졸-5-일)-7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	MS (APCI) m/z (^{81}Br) 466.5 $(M+1)^+$
7	{4-브로모-5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-티아졸-2-일}-디메틸-아민	MS (APCI) m/z (^{81}Br) 424.4 $(M+1)^+$
8	{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-메틸-티아졸-2-일}-디메틸-아민	ES/MS m/z 358 $(M+1)^+$
9	7-(1-에틸-프로필)-2,5-디메틸-3-(4-메틸-2-모르폴린-4-일-티아졸-5-일)-피라졸로[1,5-a]피리미딘	ES/MS m/z 400 $(M+1)^+$

*탄산세슘 6 당량 사용.

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





ES/MS m/z (^{79}Br) 487.7 $(M+1)^+$.

The 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 inert atmosphere. n-butyl lithium (2.5 M hexane solution, 2.4 mL, 6.0 mmol) was added slowly and stirred for 30 min. One aliquot of anhydrous zinc chloride (1.36 g, 10.0 mmol) was added and stirred at -78 ° C for 30 minutes. The reaction is allowed to warm 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 inert atmosphere. The reaction was cooled to rt, quenched with water and diluted with ethyl acetate (100 mL). The aqueous portion was separated and extracted with dichloromethane (50 mL). The organic phases were combined, dried over anhydrous

magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was taken in 100% hexanes / 0% (10% acetonitrile / 40% THF / 50% hexanes) in 10% incremental gradient steps from 0% hexane / 100% (10% acetonitrile / 40% THF / 50% Purification using flash chromatography eluting with hexane) afforded a white solid (0.090 g, 9%).
ES/MS m/z (^{79}Br) 487.7 $(M+1)^+$.

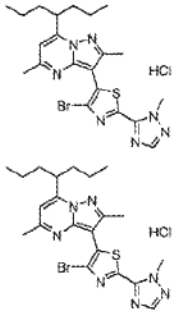
Alternative Manufacturing Example:

ES/MS m/z (^{79}Br/^{81}Br) 488/490 $(M+1)^+$.

2,5-dimethyl-3- [2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl] -7- in acetonitrile (60 mL) To a solution of (1-propyl-butyl) -pyrazolo [1,5-a] pyrimidine (6 g, 14.65 mmol), N-bromosuccinimide (2.74 g, 15.4 mmol) is added in one portion, 22 Stir at 10 ° 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 x 50 mL). The organic portions were combined and the solvent was evaporated. The resulting material was purified by filtration through a pad of silica gel eluting with hexanes / ethyl acetate (3/1). The products containing fractions were combined and the solvent was evaporated. Heptane (25 mL) was added and the solid was triturated. The solid was filtered off and dried under vacuum to afford the title compound (5.5 g, 77%).
ES/MS m/z (^{79}Br/^{81}Br) 488/490 $(M+1)^+$.

Example 10a

3- [4-bromo-2- (2-methyl-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) is dissolved in acetone (5 mL) and added to 1 M HCl (1.84 mL, 1.84 mmol) in diethyl ether. It was. The mixture was stirred at rt for 3 h and concentrated in vacuo. The residue was dissolved in diethyl ether / hexane = 1/1 (5 mL) and crystallized with 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.

실시예	화학적 명칭	물리적 데이타
11*	7-(1-에틸-프로필)-2,5-디메틸-3-[4-메틸-2-(2-메틸-2H-[1,2,4]트리아졸-3-일)-티아졸-5-일]-피라졸로[1,5-a]피리미딘	ES/MS m/z 396 $(M+1)^+$

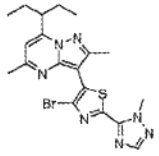
*무수 염화아연 대신에 THF 중의 0.5 M 염화아연을 사용. 80 °C에서 3일 동안 가열

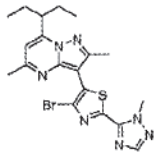
실시예	화학적 명칭	물리적 데이타
11*	7-(1-에틸-프로필)-2,5-디메틸-3-[4-메틸-2-(2-메틸-2H-[1,2,4]트리아졸-3-일)-티아졸-5-일]-피라졸로[1,5-a]피리미딘	ES/MS m/z 396 $(M+1)^+$

*무수 염화아연 대신에 THF 중의 0.5 M 염화아연을 사용. 80 °C에서 3일 동안 가열

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





MS (APCI) m/z (^{79}Br) 460.4 $(M+1)^+$.

To a solution of 1-methyl-1,2,4-triazole (124.5 mg, 1.5 mmol) in THF (3 mL) under nitrogen atmosphere add n-butyl lithium (2.5 M in hexane, 0.6 mL, 1.5 mmol). Add at 78 ° C. and stir for 30 minutes. Anhydrous zinc chloride (409 mg, 3.0 mmol) was added and stirring continued for 30 minutes, warmed to room temperature and stirred for 2 hours. 3- (2,4-dibromo-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (229 mg, 0.5 mmol) followed by tetrakis (triphenylphosphine) palladium (58 mg, 0.05 mmol) and refluxed overnight. Cool to room temperature, dilute with ethyl acetate and wash with saturated ammonia chloride. The organic portion was dried over sodium sulphate, filtered and concentrated to residue. The crude material was purified by flash chromatography eluting with hexanes: ethyl acetate (10: 2.5) to afford the title compound as a yellow foam (77 mg).
MS (APCI) m/z (^{79}Br) 460.4 $(M+1)^+$.

Alternative Preparation of Example 21:

ES/MS (m/z): (^{79}Br/^{81}Br) 460/462 $(M+1)^+$.

7- (1-ethyl-propyl) -2,5-dimethyl-3- [2- (2-methyl-2H- [1,2,4] triazol-3-yl)-in acetonitrile (80 mL). To a solution of thiazol-5-yl] -pyrazolo [1,5-a] pyrimidine (8 g, 21 mmol) was added acetic acid (1 mL) and N-bromosuccinimide (4.1 g, 22 mmol). Added. The mixture was stirred at 22 ° C for 2 h. The solvent was then 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 sulphate, 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-toluene sulfonic acid

3- (4-Bromo-2- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiazol-5-yl) -7- (1-ethyl-propyl)- 2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (50 mg, 0.109 mmol) was dissolved in acetone (3 mL). A 0.25 M aqueous solution of p-toluene sulfonic acid (434.4 µl, 0.109 mmol) was added and the resulting mixture was evaporated to dryness. Ethyl acetate (12 mL) was added to give a partial lysate of a solid. Methanol (1 mL) was added to achieve a clear solution. The solution was concentrated by slow evaporation until crystals were observed. The crystals were isolated by filtration and dried at 25 ° C. under vacuum to afford about 50 mg of the title compound.

The stoichiometry of the salts was determined by ion chromatography using the following HPLC conditions: Column: Phenomenex Phenosphere SAX, 4.6 × 150 mm at 30 ° C .; Mobile phase: at pH = 4.5, 50% acetonitrile / 50% 0.025 M sodium phosphate buffer; Flow rate = 1.5 mL / min; Detection: UV at 205 nm; Injection volume = 5 µl; Uptime = 3 minutes. Theoretical calculations: 27.2% tosylate; Found: 28.4% tosylate (average of 3 HPLC runs).

Example 13

(4-Chloro-5- [2,5-dimethyl-7- (1-propyl-butyl) -pyrazolo [1,5-a] pyrimidin-3-yl] -thiazol-2-yl) -dimethyl Amine

ES/MS m/z (^{35}Cl) 406.0 $(M+1)^+$.

The oven-dried flask was poured into (4-bromo-5- [2,5-dimethyl-7- (1-propyl-butyl) -pyrazolo [1,5-a] pyrimidin-3-yl] -thiazole- Charged with 2-yl-dimethylamine (0.20, 0.44 mmol) and anhydrous THF (3.0 mL) and cooled to -78 ° C under inert atmosphere. n-butyl lithium (1.6 M hexane solution, 0.42 mL, 0.67 mmol) was added slowly and stirred for 30 min. One aliquot of N-chlorosuccinimide (0.120 g, 0.889 mmol) was added and stirred at -78 ° C for 30 minutes. The reaction was allowed to warm to rt, stirred for 5 h and checked for progress using LC / MS. Diluted with ethyl acetate (100 mL), washed with saturated ammonium chloride (50 mL) and the aqueous was back extracted with dichloromethane (50 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified using flash chromatography, eluting from 100% hexanes / 0% (25% THF / hexanes) to 0% hexanes / 100% (25% THF / hexanes) in a 10% incremental gradient step to give a white Solid (0.087 g, 48%) was obtained.
ES/MS m/z (^{35}Cl) 406.0 $(M+1)^+$.

Using the appropriate bromothiazole prepared above, the following examples were prepared essentially as described in Example 13.

실시예	화학적 명칭	물리적 데이타
14	3-(4-클로로-2-모르폴린-4-일-티아졸-5-일)-2,5-디메틸-7-(1-프로필-부틸)-피라졸로[1,5-a] 피리미딘	ES/MS m/z (^{35}Cl) 448.0 $(M+1)^+$
15	{4-클로로-5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-티아졸-2-일}-디메틸-아민	MS (APCI) m/z (^{35}Cl) 378.0 $(M+1)^+$

실시예	화학적 명칭	물리적 데이타
14	3-(4-클로로-2-모르폴린-4-일-티아졸-5-일)-2,5-디메틸-7-(1-프로필-부틸)-피라졸로[1,5-a] 피리미딘	ES/MS m/z (^{35}Cl) 448.0 $(M+1)^+$
15	{4-클로로-5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-티아졸-2-일}-디메틸-아민	MS (APCI) m/z (^{35}Cl) 378.0 $(M+1)^+$

Preparation Example 18

2,4-dichlorothiazole

EI/MS m/z : ($^{35}Cl^{35}Cl/^{35}Cl^{37}Cl/^{37}Cl^{37}Cl$) 153/155/157 (M+1)$^+$.

A mixture of thiazolidine-2,4-dione (50 g, 0.43 mol) in phosphorus oxychloride (240 mL) was cooled to 5 ° C and pyridine (34 mL, 0.43 mol) was added over 15 minutes. The mixture was heated to 125 ° C for 4 h and then cooled to 22 ° C. Excess phosphorus oxychloride was removed by vacuum distillation and the residue was added to water (1 L) cooled to a temperature of 5 ° C. The mixture was extracted with methylene chloride (3 x 400 mL). The organic portions were combined and the solvent was evaporated to give the title compound (50 g, 76%).
EI/MS m/z : ($^{35}Cl^{35}Cl/^{35}Cl^{37}Cl/^{37}Cl^{37}Cl$) 153/155/157 (M+1)$^+$.

Preparation Example 19

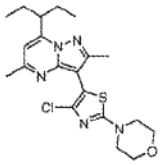
4-chloro-2-morpholino-thiazole

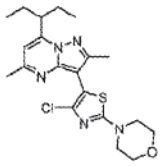
ES/MS m/z (^{35}Cl) 205 (M+1)$^+$.

To a mixture of 2,4-dichlorothiazole (34 g, 0.22 mol) in acetonitrile (425 mL) is added potassium carbonate (60.9 g, 0.44 mol), followed by 30 minutes of morpholine (21.2 mL, 0.226 mol). Dropwise over. The mixture was refluxed at 40 ° C and then cooled to 22 ° C. The mixture is filtered and the filtrate is evaporated. The residue was triturated with i-propyl alcohol (60 mL) at 22 ° C. for 1 hour. The solid was filtered and dried to constant weight under vacuum to afford the title compound (34.5 g, 76%).
ES/MS m/z (^{35}Cl) 205 (M+1)$^+$.

Example 18

3- (4-Chloro-2-morpholin-4-yl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyridine Midine





MS (APCI) m/z (^{35}Cl) 420.6 (M+1)$^+$; ^{1}H NMR (400 MHz, $CDCl_3$): 6.44 (s, 1H), 3.79 (t, 4H, *J*=4.8 Hz), 3.63-3.56 (m, 1H), 3.47 (t, 4H, *J*=4.8 Hz), 2.55 (s, 3H), 2.45 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, 6H, *J*=7.5 Hz).

Under 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-butyl lithium (0.1 mL, 2.5 M in hexanes, 0.25 mmol) was added and stirred at -78 ° C. for 30 minutes. N-chlorosuccinimide (33.4 mg, 0.25 mmol) was added, further stirred for 30 minutes, and slowly warmed to room temperature. After stirring overnight, the reaction was quenched by addition of saturated ammonia chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to residue. The crude material was purified by flash chromatography eluting with hexanes: dichloromethane: ethyl acetate (5: 5: 2) to give the title compound (54 mg).
MS (APCI) m/z (^{35}Cl) 420.6 (M+1)$^+$; ^{1}H NMR (400 MHz, $CDCl_3$): 6.44 (s, 1H), 3.79 (t, 4H, *J*=4.8 Hz), 3.63-3.56 (m, 1H), 3.47 (t, 4H, *J*=4.8 Hz), 2.55 (s, 3H), 2.45 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, 6H, *J*=7.5 Hz).

Alternatives to Preparation Example 6

ES/MS m/z (^{35}Cl) 420 (M+1)$^+$.

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 combined in dimethylformamide (90 mL) previously 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 h and then cooled to 22 ° C. Water (900 mL) was added and extracted with methyl-t-butyl ether (3 x 200 mL). The organic portions were combined and the solvent was evaporated. Purification by silica gel chromatography eluting with hexanes / ethyl acetate (4/1) afforded the title compound (5.4 g, 62%).
ES/MS m/z (^{35}Cl) 420 (M+1)$^+$.

Example 18a

3- (4-Chloro-2-morpholin-4-yl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyridine Midine, hydrochloride

ES/MS m/z (^{35}Cl) 420 (M+1)$^+$; ^{1}H NMR(CDCl3): 9.18 (br, 1H), 6.86 (s, 1H), 3.72 (m, 4H), 3.49(m, 1H), 3.39 (m, 4H), 2.48 (s, 3H), 2.38(s, 3H), 1.79 (m, 4H), 0.79 (m, 6H).

3- (4-Chloro-2-morpholin-4-yl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyridine Midine (1.40 g, 3.33 mmol) was dissolved in acetone (10 mL) at 50 ° C. and cooled to room temperature. Hydrogen chloride (2 M in diethyl ether, 2.0 mL, 4.0 mmol) was added and stirred well in the sonicator. The solution was concentrated slightly and crystallized with HCl salt by addition of the minimum amount of diethyl ether. The mixture was cooled in the refrigerator overnight. Additional hydrogen chloride (2 M in diethyl ether, 2.0 mL, 4.0 mmol) was added and cooled in the refrigerator. The crystalline material was filtered off and dried to give the title compound

(1.15 g, 75%).

ES/MS m/z (^{35}Cl) 420 $(M+1)^+$; ^{1}H NMR(CDCl3): 9.18 (br, 1H), 6.86 (s, 1H), 3.72 (m, 4H), 3.49(m, 1H), 3.39 (m, 4H), 2.48 (s, 3H), 2.38(s, 3H), 1.79 (m, 4H), 0.79 (m, 6H).

Example 17

3- (4-Bromo-2-butyl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine

ES/MS m/z (^{81}Br) 437.4 $(M+1)^+$.

Under nitrogen atmosphere, 3- (2,4-dibromo-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1, in THF (3 mL) To a solution of 5-a] pyrimidine (230 mg, 0.5 mmol) n-butyl lithium (2.5 M in hexane, 0.2 mL, 0.5 mmol) was added at -78 ° C. After 30 minutes, 1-iodobutane (138 mg, 0.75 mmol) was added and stirring continued for 1 hour. Warm to room temperature and stir for 1 hour. The reaction was quenched by addition of saturated ammonia chloride solution and extracted with ethyl acetate. The organic portion was dried over sodium sulphate, filtered and concentrated to residue. The crude material was purified by flash chromatography eluting with hexanes / ethyl acetate (10 / 1.5) to afford 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.

실시예	화학적 명칭	물리적 데이타
18	3-(4-브로모-2-메톡시메틸-티아졸-5-일)-7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	MS (APCI) m/z (^{81}Br) 424.6 $(M+1)^+$

실시예	화학적 명칭	물리적 데이타
18	3-(4-브로모-2-메톡시메틸-티아졸-5-일)-7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘	MS (APCI) m/z (^{81}Br) 424.6 $(M+1)^+$

Example 19

7- (1-ethyl-propyl) -3- (2-methoxymethyl-thiazol-5-yl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine

MS (APCI) m/z 345.3 $(M+1)^+$.

Under nitrogen atmosphere, 7- (1-ethyl-propyl) -2,5-dimethyl-3-thiazol-5-yl-pyrazolo [1,5-a] pyrimidine (300 mg, 1.0 mmol) was added n-butyl lithium (2.5 M in hexane, 0.4 mL, 1.0 mmol) at -78 ° C. Stir for 30 minutes and add 1-iodomethyl methyl ether (205 mg, 1.2 mmol). Stirring continued for 1 hour, then slowly warmed to room temperature and stirred overnight. The reaction was quenched by addition of saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to the residue in vacuo. The crude material was purified by flash chromatography eluting with hexanes / ethyl acetate (10/2) to afford 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

MS (APCI) m/z (^{35}Cl) 379.3 $(M+1)^+$.

7- (1-ethyl-propyl) -3- (2-methoxymethyl-thiazol-5-yl) -2,5-dimethyl-pyrazolo [1,5-a] pyridine in THF (3 mL) To a stirred solution of midine (150 mg, 0.43 mmol) n-butyl lithium (2.5 M in hexanes, 174 mL, 0.43 mmol) was added at -78 ° C. Stir for 30 minutes and add N-chlorosuccinimide (87 mg, 0.653 mmol). After stirring for 30 minutes, the reaction was allowed to slowly warm to room temperature and continued to react overnight. The reaction was quenched by addition of saturated ammonium chloride solution, extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated to residue. Purification by flash chromatography eluting with hexanes / 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

ES/MS m/z 382.0 $(M+1)^+$.

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 chloride (I) (132 mg, 1.33 mmol) were mixed in DMF (5 mL) and brought to 120 ° C. Heated for 24 hours. Cool to room temperature, dilute with ethyl acetate and wash with brine. The organic layer was dried over sodium sulphate, filtered and concentrated to residue under vacuum. Purification by flash chromatography eluting with hexanes then with hexanes / EtOAc (10 / 1.8) gave a yellow-orange solid (45 mg).
ES/MS m/z 382.0 $(M+1)^+$.

Alternative manufacturing example :

ES/MS m/z 382 $(M+1)^+$.

To a solution of N-methyltriazole (11.95 g, 144 mmol) in THF (600 mL) was added n-butyl lithium (2.5 M in hexane, 57.6 mL, 144 mmol) at -78 ° C. under a nitrogen atmosphere and added The temperature was kept below -74 ° C during the process. Zinc chloride dry powder (26 g, 192 mmol) was then added in one portion and the mixture was warmed to 22 ° C. within 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 (triphenyl) phosphine palladium catalyst (1.15 g, 0.01 mol) were added in one portion, and the mixture was heated to 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 x 200 mL). The organic portions

were combined, dried over sodium sulphate, filtered and the solvent was evaporated. Purification by passing over a pad of silica gel eluting with hexanes / ethyl acetate (4/1) gave 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

ES/MS m/z (^{35}Cl) 416.0 $(M+1)^+$.

7- (1-ethyl-propyl) -2,5-dimethyl-3- [2- (2-methyl-2H- [1,2,4] tria le dichloromethane (0.5 mL) and acetonitrile (0.5 mL) Zol-3-yl) -thiazol-5-yl) -pyrazolo [1,5-a] pyrimidine (20 mg, 0.052 mmol) and N-chlorosuccinimide (7.6 mg, 0.0569 mmol) Stir overnight at room temperature in the vial. Concentrated to the residue. Purification by hexane followed by flash chromatography eluting with hexane / ethyl acetate (10 / 1.5) gave the title compound (15 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

ES/MS m/z 416.0 $(M+1)^+$.

3- (4-Bromo-2-morpholin-4-yl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [in methanol (3 mL) Mixture of 1,5-a] pyrimidine (152 mg, 0.35 mmol) with sodium methoxide (57 mg, 1.05 mmol) and copper iodide (I) (67 mg, 0.35 mmol) in a sealed 4-mL vial Stir at 120 ° C. for 15 h. Cool to room temperature, remove solids by filtration and concentrate the filtrate under vacuum. The residue was purified by flash chromatography eluting with hexanes / THF (10/2). The material was recrystallized from methanol to give the title compound (20 mg).
ES/MS m/z 416.0 $(M+1)^+$.

Preparation Example 20

4-Bromo-5- [7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidin-3-yl] -thiazole-2-carbaldehyde

MS (APCI) m/z (^{81}Br) 409.0 $(M+1)^+$.

Under nitrogen atmosphere, 3- (2,4-dibromo-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine To (230 mg, 0.50 mmol) of THF solution (2.5 mL) n-butyl lithium (1.6 M in hexane, 0.312 mL, 0.50 mmol) was added at -78 ° C and stirred for 30 minutes. A solution of THF (0.5 mL) of N-formyl morpholine (58 mg, 0.50 mmol) was added. After stirring for 1 hour, the reaction was stored at -20 ° C overnight. The reaction was warmed to rt, diluted with ether and quenched by addition of 4 N HCl (4 mL). The organic phase was separated and extracted with 4N HCl (2 × 4 mL). The aqueous portions 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 residue. The crude material was purified by flash chromatography eluting with hexanes / dichloromethane / ethyl acetate (5/5/1) to give the title compound (154 mg).
MS (APCI) m/z (^{81}Br) 409.0 $(M+1)^+$.

Example 24

3- (4-Bromo-2-morpholin-4-yl-methyl-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5- a] pyrimidine

ES/MS m/z (^{81}Br) 480.0 $(M+1)^+$.

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 combined in dichloromethane (3 mL) and methanol (0.5 mL). Stir overnight, additional morpholine (35 mg, 0.405 mmol) and sodium triacetoxyborohydride (97 mg, 0.46 mmol) were added and stirred for at least 4 hours. The solvent was removed in vacuo, diluted with dichloromethane and washed with brine. The organic phase was dried over sodium sulphate, filtered and concentrated in vacuo. The resulting material was purified using flash chromatography eluting with 2 M ammonia (10: 1) in dichloromethane: methanol to give a mixture. The mixture was eluted with water / acetonitrile (80/20) with water / acetonitrile (10/90) and purified using a reverse phase column 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] pyri Midine

ES/MS m/z (^{79}Br) 456.0 $(M+1)^+$.

Under nitrogen atmosphere, 3- (2,4-dibromo-thiazol-5-yl) -7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1, in THF (4 mL) To a solution of 5-a] pyrimidine (229 mg, 0.5 mmol) n-butyl lithium (1.6 M in hexane, 0.312 mL, 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 continued for 30 minutes. The reaction was warmed to rt and stirred for 1 h. 4-Iodopyridine (103 mg, 0.5 mmol) was added followed by 1,1'-bis (diphenylphosphino) ferrocene palladium (II) chloride (dichloromethane adduct) (0.40.8 mg, 0.05 mmol). . The reaction was heated to reflux overnight. Cool to room temperature, dilute with ethyl acetate and wash with water and brine. The organic layer was dried over sodium sulphate, filtered and concentrated to residue. The crude material was purified by flash chromatography eluting with 2N ammonia (10: 0.75) in dichloromethane: methanol to give a mixture. The mixture was eluted with water: acetonitrile = 80:20 in water: acetonitrile = 10:90 and purified using a reversed phase column to give the title compound (19 mg).
ES/MS m/z (^{79}Br) 456.0 $(M+1)^+$.

Preparation Example 21

4-trifluoromethyl-thiazol-2-ylamine

ES/MS m/z 169 $(M+1)^+$.

Thiourea (4.0 g, 52.3 mmol) and 3-bromo-1,1,1-trifluoropropan-2-one (5.5 mL, 10 g, 52.3 mmol) are added to ethanol (100 mL), 50 Heat at C for 2 h. Cooled to room temperature and concentrated to dryness. The residue was dissolved in water and the pH was adjusted to greater than 12 with 2 M NaOH. Extracted with diethyl ether (4 x). The combined organic extracts were dried over sodium sulfate, filtered and concentrated in vacuo. 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 dropwise to a solution of 4-trifluoromethyl-thiazol-2-ylamine (6.0 g, 35.7 mmol) in ice-cold diethyl ether (60 mL). . After the addition was complete, the mixture was stirred for 1 hour and then warmed 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 $(M + l)^+$.

Preparation Example 23

5-Bromo-2- (2,5-dimethyl-pyrrol-1-yl) -4-trifluoromethyl-thiazole

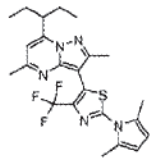
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 2H), 2.27 (s, 6H).

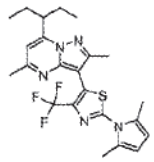
Hexane-2,5-dione (3.5 mL, 3.4 g) in a solution of 5-bromo-4-trifluoromethyl-thiazol-2-ylamine hydrobromide (9.0 g, 27.4 mmol) in methanol (60 mL) , 30.2 mmol) was added. Stir overnight at room temperature. Phosphate buffer (50 mL, pH = 7) was added. The resulting precipitate was collected by filtration 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-pyrrole-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-pyrrole-1-yl) -4-trifluoromethyl-thiazole (2.2 g, 6.6 mmol) in THF (25 mL) was dried in a dry ice bath. Cooled. t-butyl lithium (1.7 M in pentane, 8.5 mL, 14.5 mmol) was added dropwise. After stirring for 45 min, zinc chloride (0.5 M in THF, 14.6 mL, 7.3 mmol) was added dropwise. The mixture was stirred for 5 minutes and the cooling bath was removed. 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. Reflux for 24 hours. The reaction was cooled and the mixture was poured into diethyl ether and washed with water (2 ×). The combined water layers were extracted with diethyl ether. The combined organic portions were dried over sodium sulphate, filtered and concentrated to dryness in vacuo. The resulting residue was purified by silica gel chromatography (75-100% CH_2Cl_2 in hexane) to give the title compound (1.47 g, 72%). HR-ToF-MS m/z calcd for $C_{23}H_{26}F_3N_5S^+H^+$: 462.1939, found: 462.1915.

Example 27

5- [7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidin-3-yl] -4-trifluoromethyl-thiazol-2-ylamine

ES/MS m/z 384 $(M+1)^+$.

3- [2- (2,5-Dimethyl-pyrrole-1-yl) -4-trifluoromethyl-thiazol-5-yl] -7- (1-ethyl-propyl) in acetic acid (10 mL) To a solution of 2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (1.1 g, 2.3 mmol) was added hydroxyamine (2 mL, 50% in water). The reaction was heated to 80 ° C for 6 h. Cool to room temperature. Pour into diethyl ether and wash once with 2M NaOH (2 ×) followed by water. The organic portion was dried over sodium sulphate, filtered and concentrated to dryness in vacuo. 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

ES/MS m/z ($^{79}Br/^{81}Br$) 447, 449 $(M+1)^+$.

A mixture of copper (II) bromide (540 mg, 2.4 mmol) and t-butylnitrile (0.36 mL, 310 mg, 3.0 mmol) in acetonitrile (20 mL) was 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 (3 ×). The organic layer was dried over sodium sulphate, filtered and concentrated to dryness in vacuo. The resulting residue was purified by silica gel chromatography in CH_2Cl_2 to afford 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] pyrimidine (313 mg, 0.7 mmol), and a sealed tube containing dimethyl amine (2 M in THF, 4 mL, 8 mmol) in methanol (4 mL) was heated to 80 ° C for 2 h. The reaction was cooled and concentrated in vacuo. The resulting residue was purified by silica gel chromatography eluting with 0-30% ethyl acetate in CH_2Cl_2 to afford the title compound (0.28 g, 97%). HR-ToF-MS m/z calcd for $C_{19}H_{24}F_3N_5S^+H^+$ 412.1770, found 412.1783.

The following example was prepared essentially as described in Example 28 except that the reaction was refluxed for 8 hours.

실시예	화학적 명칭	물리적 데이타
29	7-(1-에틸-프로필)-2,5-디메틸-3-(2-모르폴린-4-일-4-트리플루오로메틸-티아졸-5-일)-피라졸로[1,5-a]피리미딘	HR-ToF-MS m/z $C_{21}H_{26}F_3N_5OS+H^+$에 대한 계산치: 454.1873, 실측치: 454.1888

실시예	화학적 명칭	물리적 데이타
29	7-(1-에틸-프로필)-2,5-디메틸-3-(2-모르폴린-4-일-4-트리플루오로메틸-티아졸-5-일)-피라졸로[1,5-a]피리미딘	HR-ToF-MS m/z $C_{21}H_{26}F_3N_5OS+H^+$에 대한 계산치: 454.1873, 실측치: 454.1888

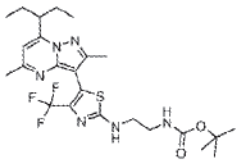
Example 30

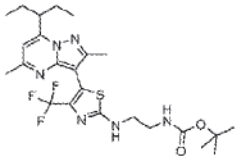
N- {5- [7- (1-ethyl-propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidin-3-yl] -4-trifluoromethyl-thiazole-2 -Yl} -acetamide

3- [2- (2,5-Dimethyl-pyrroie-1-yl) -4-trifluoromethyl-thiazol-5-yl] -7- (1-ethyl-propyl)-in acetic acid (25 mL) To a solution of 2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (2.4 g, 5.2 mmol) was added hydroxyamine (50% in water, 5 mL). The reaction was heated to 80 ° C for 72 h. The reaction was cooled to rt, poured into diethyl ether and washed once with 2 M NaOH (2 ×) followed by water. The organic portion was dried over sodium sulphate, 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 calcd for $C_{19}H_{22}F_3N_5OS^+H^+$ 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-thiazole- 2-ylamino) -ethyl) -carbamic acid tert-butyl ester





ES/MS m/z 527.2 $(M+1)^+$.

Triethylamine (0.3 mL, 222 mg, 2.2 mmol) and 3- (2-bromo-4-trifluoromethyl-thiazol-5-yl) -7- (1-ethyl- in methanol (1 mL) in a solution of propyl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (100 mg, 0.22 mmol) (2-amino-ethyl) -carbamic acid tert-butyl ester (0.5 mL, 506 mg, 3.2 mmol) was added. Methanol was evaporated and heated to 80 ° C overnight. The reaction was cooled to rt and concentrated in vacuo. The resulting residue was purified by column chromatography eluting with 10-50% ethyl acetate in CH_2Cl_2 to afford the title compound (0.11 g, 97%).

ES/MS m/z 527.2 $(M+1)^+$.

Using the appropriate amine, the following compounds were prepared essentially as described in Example 31.

제조예 또는 실시예	화학적 명칭	물리적 데이타
제조예 **25***	[2-({5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-프로필-아미노)-에틸]-카르밤산 tert-부틸 에스테르	ES/MS m/z 569.3 $(M+1)^+$
제조예 **26****	(S)-(1-{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-피롤리딘-3-일)-카르밤산 tert-부틸 에스테르	ES/MS m/z 553.3 $(M+1)^+$
실시예 **32*****	N-{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-N,N'-디프로필-에탄-1,2-디아민, 히드로클로라이드	ES/MS m/z 511.2 $(M+1)^+$

* EtOH 중에서 밤새 환류. EtOH 증발 및 110 °C에서 24시간 동안 가열.
** EtOH 중에서 80 °C 에서 밤새 가열.
*** HCl 염 제조 및 EtOAc/헥산으로부터 재결정.

제조예 또는 실시예	화학적 명칭	물리적 데이타
제조예 **25***	[2-({5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-프로필-아미노)-에틸]-카르밤산 tert-부틸 에스테르	ES/MS m/z 569.3 $(M+1)^+$
제조예 **26****	(S)-(1-{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-피롤리딘-3-일)-카르밤산 tert-부틸 에스테르	ES/MS m/z 553.3 $(M+1)^+$
실시예 **32*****	N-{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-N,N'-디프로필-에탄-1,2-디아민, 히드로클로라이드	ES/MS m/z 511.2 $(M+1)^+$

* EtOH 중에서 밤새 환류. EtOH 증발 및 110 °C에서 24시간 동안 가열.
** EtOH 중에서 80 °C 에서 밤새 가열.
*** HCl 염 제조 및 EtOAc/헥산으로부터 재결정.

~~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~~

~~To 1 M HCl (1 mL) in methanol (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. The reaction was heated at 70 ° C overnight. The reaction was cooled and concentrated from methanol / ethyl acetate in vacuo. 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 in Example 33.~~

실시예	화학적 명칭	물리적 데이타
34	N^1-{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-N^1-프로필-에탄-1,2-디아민, 히드로클로라이드	ES/MS m/z 469.2 $(M+1)^+$
35	(S)-1-{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-피롤리딘-3-일아민, 히드로클로라이드	ES/MS m/z 453.0 $(M+1)^+$

실시예	화학적 명칭	물리적 데이타
34	N^1-{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-N^1-프로필-에탄-1,2-디아민, 히드로클로라이드	ES/MS m/z 469.2 $(M+1)^+$
35	(S)-1-{5-[7-(1-에틸-프로필)-2,5-디메틸-피라졸로[1,5-a]피리미딘-3-일]-4-트리플루오로메틸-티아졸-2-일}-피롤리딘-3-일아민, 히드로클로라이드	ES/MS m/z 453.0 $(M+1)^+$

Example A

In vivo efficacy assessment using ex vivo binding

To assess efficacy in vivo, ex vivo binding was used to evaluate compounds of the present invention. Compounds were administered to rats via the oral route using the procedure provided in DR Gehlert *et al.*, *EJP* 509: 145-153 (2005). The binding of ^{125}I-savazin to the cerebellum was then analyzed in vitro as described in Gehrlert et al., Supra. For example, Example 15 provided a 65% inhibition rate at 10 mg / kg.

Example B

CRF1 filter binding analysis

Restriction of plasmid-based human CRF1 expression on generating recombinant cell lines with sufficient receptor concentration to proceed with binding assays was overcome using a Phoenix retrovirus expression system certified by Stanford. Membranes were prepared using a stable HEK-hCRF1 cell line and binding reactions (200 μl) were set up as follows: 50 μl of ^{125}I-savazin (final 0.2 nM), 50 μl of compound and 100 μl of CRF1 membrane (25 μg / response). The reaction was incubated for 2 hours at room temperature and then terminated by filtration through pretreated FB Millipore glass fiber filter plates (96 wells). Plates were washed twice with ice cold assay buffer (50 mM Tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried overnight and in a MicroBeta counter. Calculated with 100 μl Microscint 40. Non-specific binding (NSB) was determined in the presence of 0.5 μM of unlabeled savazin. Three measurements were typically made and intermediate data points were plotted by Graph Pad Prism.

Using this assay, exemplary compounds of the present invention inhibit the binding of ^{125}I-savazin (4 nM) in roller / adherent cells with KI (inhibition constant) less than 1 μM. For example, KI of Example 15 represented 6.2 nM.

Example C

CRF2 filter binding analysis

Restriction of plasmid-based human CRF2 expression on generating recombinant cell lines with sufficient receptor concentration to proceed with binding assays was overcome using a Phoenix retrovirus expression system approved by Stanford. Membranes were prepared using a stable HEK-hCRF2 cell line and binding reactions (200 μl) were set up as follows: 50 μl of ^{125}I-savazin (final concentration 0.2 nM), 50 μl of compound and 100 μl of CRF2 membrane (25 μg / response). The reaction was incubated for 2 hours at room temperature and then terminated by filtration through pretreated FB Millipore glass fiber filter plates (96 wells). Wash plates twice with ice cold assay buffer (50 mM Tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dry overnight, and 100 μl micro in a microbeta counter. Calculated as Slnt 40. Non-specific binding (NSB) was determined in the presence of 0.5 μM of unlabeled savazin. Alternatively, compounds were evaluated using a scintillation proximity assay. This assay was set up as follows: 50 μl of ^{125}I-savazin (final concentration 0.2 nM), 50 μl compound or unlabeled savazin (NSB), 250 μg wheat germ aggregate (WGA) SPA beads and CRF2 100 μl containing membrane (1.5 μg / reaction). The plates were incubated at room temperature for 4-5 hours and then centrifuged (200 X g) for 10 minutes. Bound radioactivity was measured using a Wallac Trilux scintillation counter. Binding was typically analyzed by three measurements and the intermediate data points were plotted by graph pad prisms. Compounds were first screened at fixed concentrations, and when sufficient activity appeared, subsequent concentration-response curves were generated.

Certain exemplary compounds of the invention were tested in the CRF2 binding assay and showed weak affinity for the CRF2 receptor. For example, Example 15 exhibited 11% inhibition at a concentration of 50 μM. These results suggest that compounds of the invention are selective for the CRF1 receptor (relative to CRF2).

Example D

Bioavailability and Pharmacokinetic Properties

Distribution volume (Vdist) is related to the amount of drug in the body versus the concentration of the drug in blood or plasma. Distribution volume refers to the fluid volume that needs to contain the total amount of drug in the body at the same concentration as in blood or plasma: Vdist = amount of drug in the body / blood or concentration of drug in plasma (Goodman and Gilman's). For a dose of 10 mg and a plasma concentration of 10 mg / L, the distribution volume will be 1 liter. Distribution volume refers to the extent to which the drug is present in extravascular tissue. Large distribution volumes indicate a tendency for the compound to bind tissue components as compared to plasma protein binding. In the clinical setting, Vdist can be used to determine the loading dose to reach steady state concentrations.

To test for distribution volume, male Sprague Dawley rats (N = 3) received a single intravenous dose of 1 mg / kg of compound. Several plasma samples were collected at 0.08 to 24 hours after dosing. Plasma samples were analyzed by LC / MS / MS to determine plasma concentrations. Plasma pharmacokinetic calculations were performed to determine pharmacokinetic parameters including Vdist and plasma clearance (Clp).

The compounds of the present invention preferably had a desirable bioavailability profile. For example, most commercial CNS and cardiovascular drugs have a human Vdist of less than 10 L / Kg. Compared with CRF antagonists, CP154526 (Schulz et al., *Proc. Natl. Acad. Sci.* (USA), 93: 10477 (1996)) and NBI30775 (Chen et al., *Drug Development Research* , 65: 216 (2005)), When analyzed separately, the rat Vdist shows 114 L / Kg and 76 L / Kg, respectively. Example 15 of the present invention shows rat Vdist only 7.2 L / Kg after 1 mg / kg single dose intravenously when analyzed separately.

In addition, the plasma clearance (CLp) is a measure of the rate at which drugs are removed from the body. Depending on the intravenous dose and the primary kinetics, the plasma clearance can be determined using the following equation: CLp = dose / AUC (where AUC is a curve describing the concentration of drug in the plasma as a function of time from zero to infinity). Total area). Reference CRF antagonists CP154526 and NBI37582 show rat clearance rates (CLp) of 83 and 306 mL / min / kg, respectively, when analyzed separately after a single intravenous dose, whereas Example 15 of the present invention, when analyzed separately, CLp showed only 23.6 mL / min / kg

Patent Citations (10)

Publication number	Priority date	Publication date	Assignee	Title
Family To Family Citations				
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AT336498T *	1996-02-07	2006-09-15	Neurocrine Biosciences Inc	PYRAZOLOPYRIMIDINES AS CRF RECEPTOR ANTAGONISTS
HU229024B1	1996-07-24	2013-07-29	Bristol Myers Squibb Pharma Co	Azolo-pyridimidines, pharmaceutical compositions containing the same and use thereof
EA004403B1 *	1996-07-24	2004-04-29	Дюпон Фармасьютикалз Компани	Pirazolotriazine derivatives, pharmaceutical compositions containing them, methods of treating
DE69736711T2	1996-08-28	2007-09-20	Pfizer Inc.	SUBSTITUTED 6,5-HETEROBICYCLIC DERIVATIVES
EP1040831A3 *	1999-04-02	2003-05-02	Pfizer Products Inc.	Use of corticotropin releasing factor (CRF) antagonists to prevent sudden death
WO2000059908A2 *	1999-04-06	2000-10-12	Du Pont Pharmaceuticals Company	Pyrazolopyrimidines as crf antagonists
AT347553T	1999-09-30	2006-12-15	Neurogen Corp	AMINO-SUBSTITUTED PYRAZOLO 1,5-AÖ-1,5-PYRIMIDINE AND PYRAZOLO 1,5-AÖ-1,3,5-TRIAZINE
CZ20032481A3 *	2001-03-13	2007-12-27	Bristol-Myers Squibb Pharma Company	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
JP4926720B2 *	2003-12-22	2012-05-09	スミスクライン ビーチャム（コーク） リミテッド	CRF receptor antagonists and methods related thereto

* Cited by examiner, † Cited by third party

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CN102171212A *	2008-10-02	2011-08-31	伊莱利利公司	Thiazolyl-pyrazolopyrimidine compounds as synthetic intermediates and related synthetic processes
EP2567958B1	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
CN111228274A *	2014-01-21	2020-06-05	纽罗克里生物科学有限公司	CRF for treating congenital adrenal hyperplasia1Receptor antagonists
PL23635B1 *	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
EA202090321A1 *	2017-08-14	2020-09-24	Спрос Биосайенсес, Инк.	RECEPTOR ANTAGONISTS OF THE CORTICOTROPIN-RELEASING FACTOR
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
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
CN109134481B *	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
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GR1010096B *	2020-07-02	2021-10-08	Uni-Pharma Κλεων Τσετης Φαρμακευτικα Εργαστηρια Αβεε,	Pyrazolo[1,5-a]pyrimidines as autotaxin inhibitors

KR20230043222A *	2020-08-12	2023-03-30	스프룻스 바이오사이언시스 엔코포레이티드	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

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Publication	Publication Date	Title
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KR101088196B1	2011-11-30	Thiophene pyrazolopyrimidine compounds
JP5079818B2	2012-11-21	4,5-cyclic indole derivatives for the treatment or prevention of HCV and related viral diseases
AU2009218609A1	2009-09-03	Pyrrolopyrazine kinase inhibitors
EP1567527A1	2005-08-31	Condensed pyrazolo derivatives
NZ524842A	2003-10-31	Azolo triazines and pyrimidines
MX2012010610A	2012-10-03	Pyrrolopyrazine derivatives and their use as jak and syk inhibitors.
US6734185B2	2004-05-11	Pyrrolo[3,4-d]pyrimidines as corticotropin releasing factor (CRF) antagonists

Priority And Related Applications

Applications Claiming Priority (3)

Application	Filing date	Title
US82626406P	2006-09-20	
US60/826,264	2006-09-20	
PCT/US2007/078608	2007-09-17	Thiazole pyrazolopyrimidines as crf1 receptor antagonists

Legal Events

Date	Code	Title	Description
2009-03-19	A201	Request for examination	
2011-02-17	E902	Notification of reason for refusal	
2011-09-27	E701	Decision to grant or registration of patent right	
2011-11-23	GRNT	Written decision to grant	
2014-11-24	LAPS	Lapse due to unpaid annual fee	

Concepts

machine-extracted

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/307,718	**08/01/2023 05:36:11 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 #	62543260	FILING DATE	-
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Stephen Olshemski

Documents

TOTAL DOCUMENTS: 11

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
IDS_50535-709_307_08-01-2023.pdf		8	-	228 KB
IDS_50535-709_307_08-01-2023-TRAN.LET.pdf	(1-4)	4	Transmittal Letter	146 KB
IDS_50535-709_307_08-01-2023-IDS.pdf	(5-8)	4	Information Disclosure Statement (IDS) Form (SB08)	165 KB
FOR_KR20090052366A_Machine_Translation.pdf		28	Foreign Reference	2500 KB
NPL_SARAFOGLOU-SUN-LB064-Supplement.pdf		3	Non Patent Literature	215 KB

NPL_OA-05-25-2023-US16639540.pdf	6	Non Patent Literature	4848 KB
FOR_EP3784233A1_Corr_WO2019210266.pdf	139	Foreign Reference	8455 KB
FOR_EP3984523A1_EFS.pdf	192	Foreign Reference	10832 KB
NPL_SPRUCE-Study-of-SPR001.pdf	7	Non Patent Literature	7580 KB
NPL_SPRUCE-Study-to-evaluate-the-safety.pdf	7	Non Patent Literature	7379 KB
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FOR_WO2023091684A1_Original_document_20230613001557.pdf	108	Foreign Reference	23189 KB

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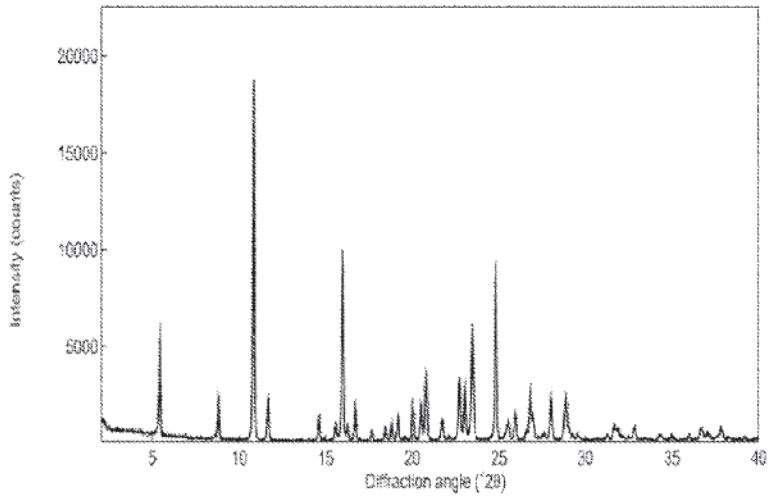
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(54) Title: CRYSTALLINE COMPOSITION OF TILDACERFONT AND METHODS OF USE AND PREPARATION THEREOF

FIG. 1



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

[Continued on next page]

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CRYSTALLINE COMPOSITION OF TILDACERFONT AND METHODS OF USE AND PREPARATION THEREOF

CROSS-REFERENCE

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

INCORPORATION BY REFERENCE

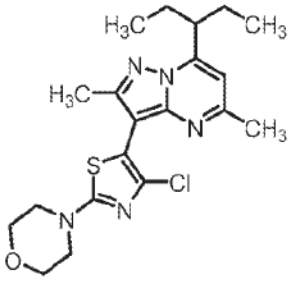
[0002] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BACKGROUND

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

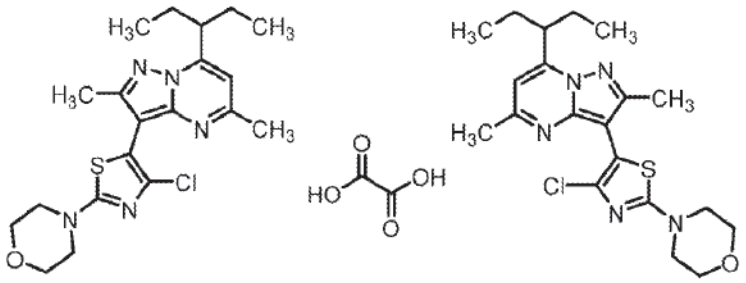
SUMMARY

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



Compound I.

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



Formula I.

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

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

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

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

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

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

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

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

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

(h) combinations thereof.

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

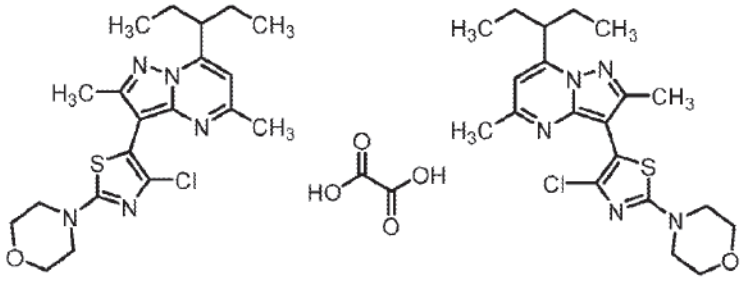
[0009] In some embodiments, the composition comprising a CRF1 antagonist (e.g., a crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by an X-ray powder diffraction pattern comprising one or more peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and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

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

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

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

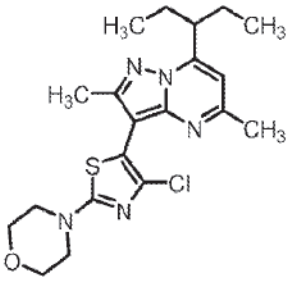
[0012] In some aspects, the present disclosure provides a pharmaceutical composition comprising crystalline composition comprising Formula I:



Formula I,

and at least one pharmaceutically acceptable carrier or excipient.

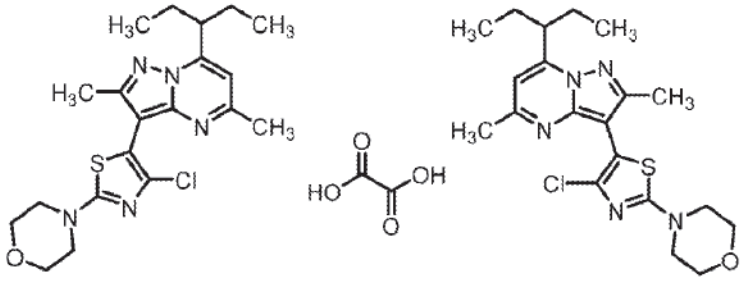
[0013] In some aspects, the present disclosure provides a pharmaceutical composition comprising Compound 1:



Compound 1

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

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



Formula I,

wherein the method comprises:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

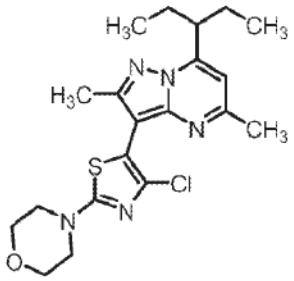
[0025] In various embodiments of the methods as described herein, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent. In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

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

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

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

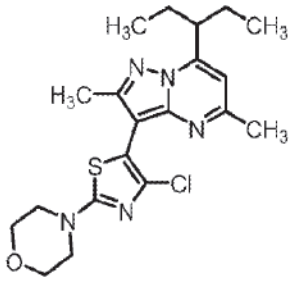
pattern comprising a peak selected from any one or more of 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the composition is characterized by X-ray powder diffraction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



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

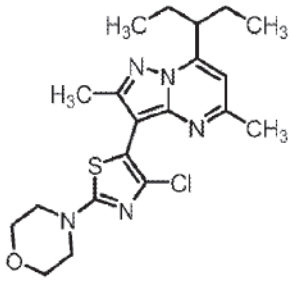
[0029] In additional aspects, provided herein is a pharmaceutical composition comprising a CRF1 antagonist, wherein the pharmaceutical com-position is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments,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

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



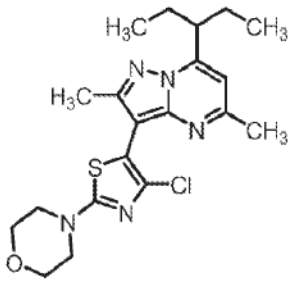
[0030] Compound 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition. In some embodiments, the crystalline pharmaceutical composition further comprises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

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



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

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



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

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

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

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

DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

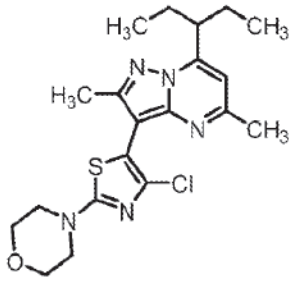
DETAILED DESCRIPTION

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

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

Compound 1

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



Compound 1.

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

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

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

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

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

Definitions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

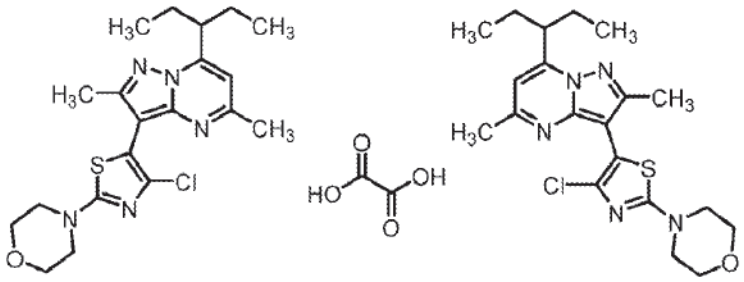
[0081] FIG. 4 shows the dynamic vapor sorption (DVS) trace for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

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

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

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

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



Formula I.

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

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

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

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

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

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

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

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

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

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

(h) combinations thereof.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

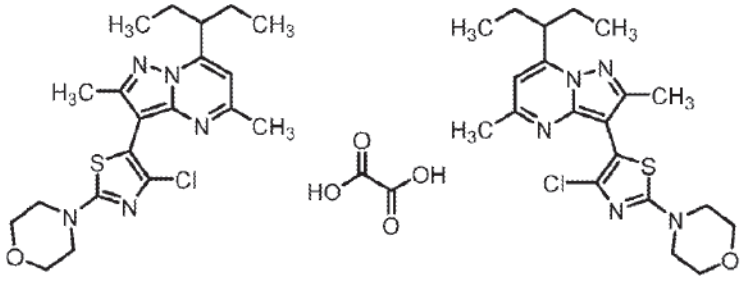
[00102] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by an infrared (IR) spectrum substantially the same as shown in FIG. 5.

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

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

Compositions and Formulations

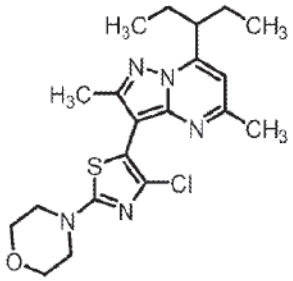
[00105] In some aspects, the present disclosure provides a pharmaceutical composition comprising a crystalline composition comprising Formula I:



Formula I,

and at least one pharmaceutically acceptable carrier or excipient.

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



Compound 1,

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

Dosage Form

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

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

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

Capsule

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

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

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

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

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

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

Tablet

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

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

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

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

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

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

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

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

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

Oral dosage forms

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

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

Pharmaceutically Acceptable Excipients

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Amounts

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Particle size

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

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

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

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

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

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

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

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

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

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

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

Preparation of Crystalline Form I

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Methods of Treatment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADDITIONAL EMBODIMENTS

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

1. A pharmaceutical formulation, comprising:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLES

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

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

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

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

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

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

X-Ray Powder Diffraction

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

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

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

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

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

Differential Scanning Calorimetry (DSC)

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

Thermogravimetric Analysis (TGA)

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

Dynamic Vapor Sorption (DVS)

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

Infrared (IR)

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

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

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

Raman

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

Example 2 – Formulation Comprising Compound 1

General Manufacturing Procedure

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

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

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

Table 2 – Formulation Comprising Tildacerfont				
Material Description	**Function**	**%w/w**	**mg/Tablet**	**Granules**
			50 mg strength	**50 mg strength**
Intragranular				
Tildacerfont (SPN001)	Active ingredient	25.00	50.00	50.00
Lactose Monohydrate, USP/NF, Ph. Eur., JP. (Pharmatose 200M EU)	Diluent	40.25	80.50	80.50
Hydroxypropylcellulose USP/NF, Ph. Eur., JP (Klucel EXF)	Binder	3.00	6.00	6.00
Sodium Lauryl Sulfate, NF/ Ph. Eur./JP (Kolliphor SLS fine)	Surfactant	0.75	1.50	1.50
Microcrystalline Cellulose, NF, Ph.Eur., JP (Avicel PH101)	Diluent	20.00	40.00	40.00
Purified Water, USP, Ph. Eur	Granulating agent	QS*	-	-
Extragranular				
Microcrystalline Cellulose, NF, Ph.Eur., JP (Avicel PH101)	Diluent	5.00	10.00	10.00
Croscarmellose Sodium NF, Ph. Eur., JP (Ac-Di-Sol) SD-711	Disintegrant	4.00	8.00	8.00
Colloidal Silicon dioxide USP/NF, Ph. Eur., JP (Aerosil 200)	Glidant	1.00	2.00	2.00
Magnesium stearate, NF, Ph. Eur., JP (Hyqual 2257)	Lubricant	1.00	2.00	2.00
Total		100.00	200.00	200.00

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

Example 3 – Stability of Crystalline Compositions Comprising Compound 1

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

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

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

Table 3. Stability data under accelerated aging conditions.

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

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

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

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

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

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

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

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

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

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

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

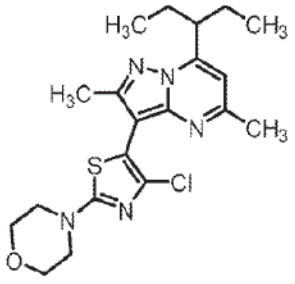
[00227] Samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal prepared in Example 3 are subjected to accelerated aging conditions (40 ± 2 °C /75 ± 5 % relative humidity (RH)) or long-term storage conditions (25 ± 2 °C / 60 ± 5 % RH). Sample stability measurements in each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

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

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

CLAIMS

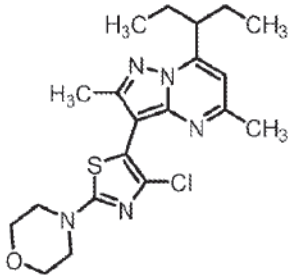
1. A pharmaceutical composition comprising a CRF1 antagonist, wherein the composition is characterized by an X-ray powder diffraction pattern comprising a peak selected from any one or more of 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ.
2. The pharmaceutical composition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



Compound 1

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

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

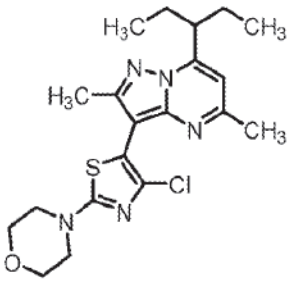


Compound 1

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

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

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



Compound 1,

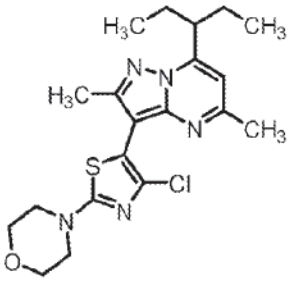
wherein the method comprises:

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

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

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

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



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

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

a diluent in about 5% to about 70%

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

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

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

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

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

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

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

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

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

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

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

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

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

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

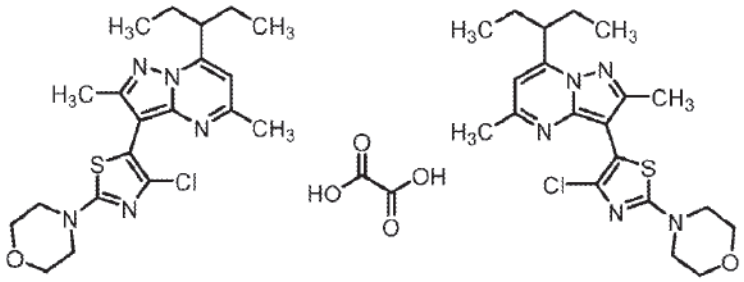
53. The pharmaceutical formulation of claim 52, wherein said granules form is packaged in a capsule.

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

55. A pharmaceutical formulation, comprising:

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

56. A crystalline composition comprising Formula I:



Formula I.

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

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

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

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

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

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

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

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

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

(h) combinations thereof.

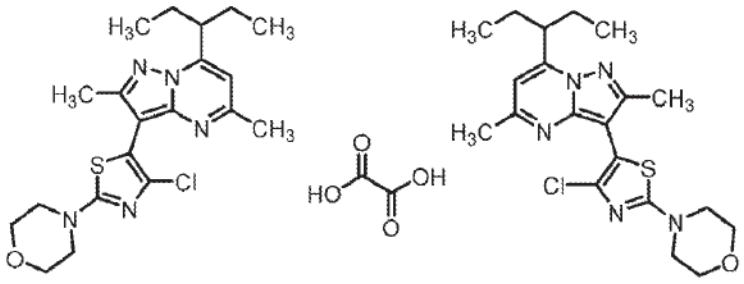
59. The crystalline composition of any one of claim 56, wherein the crystalline composition is characterized by an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray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

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

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

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

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



Formula I,

wherein the method comprises:

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

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

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

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

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

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

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

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

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

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

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

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

FIG. 1

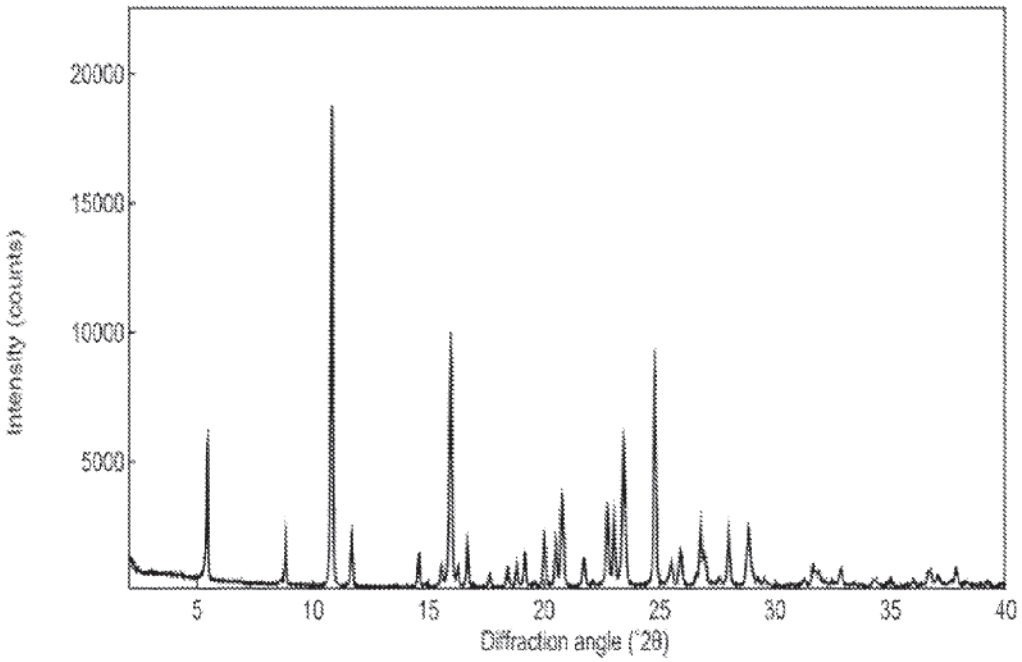

20000
15000
10000
5000
Intensity (counts)
5
10
15
20
25
30
35
40
Diffraction angle (°2θ)

FIG. 2

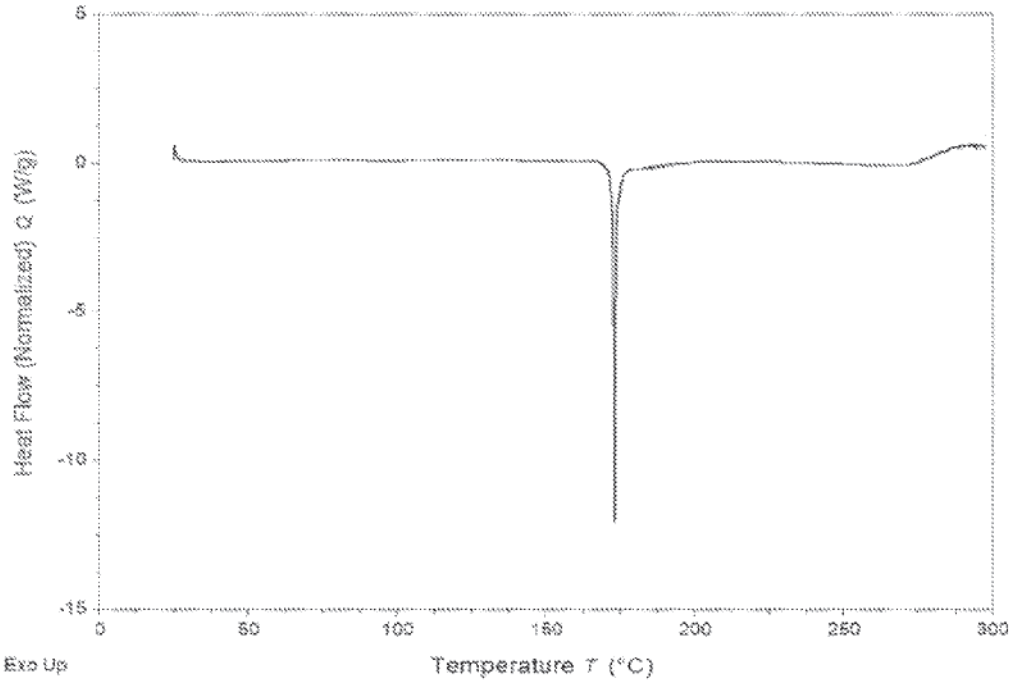

5
0
-5
-10
-15
Heat Flow (Normalized) Q (W/g)
0
50
100
150
200
250
300
Temperature T (°C)
Exo Up

FIG. 3

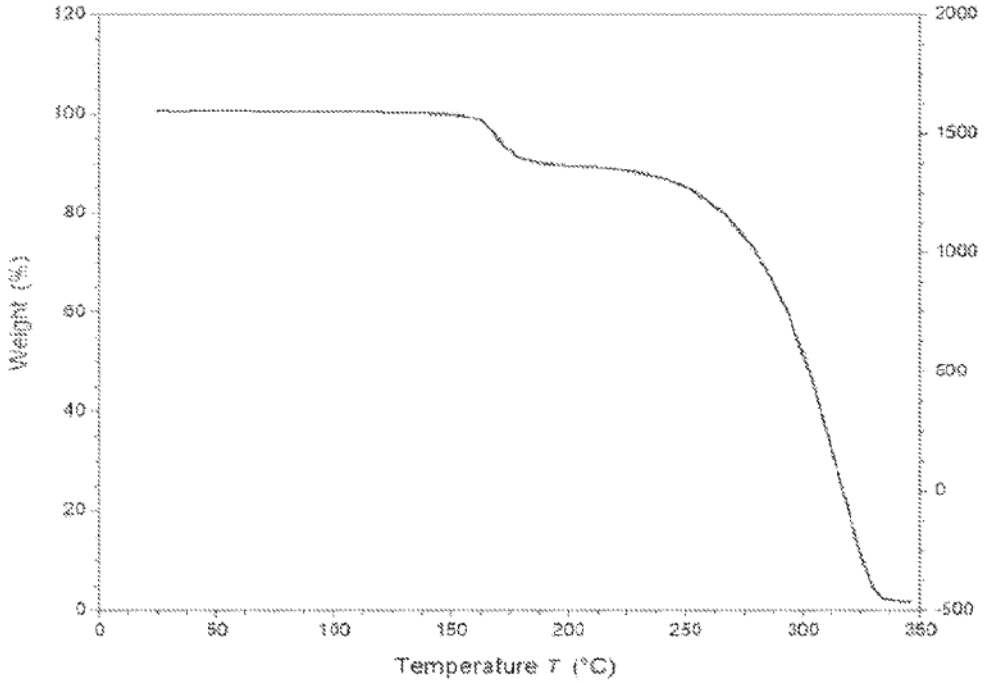

120
100
80
60
40
20
0
Weight (%)
2000
1500
1000
500
0
-500
0
50
100
150
200
250
300
350
Temperature T (°C)

FIG. 4

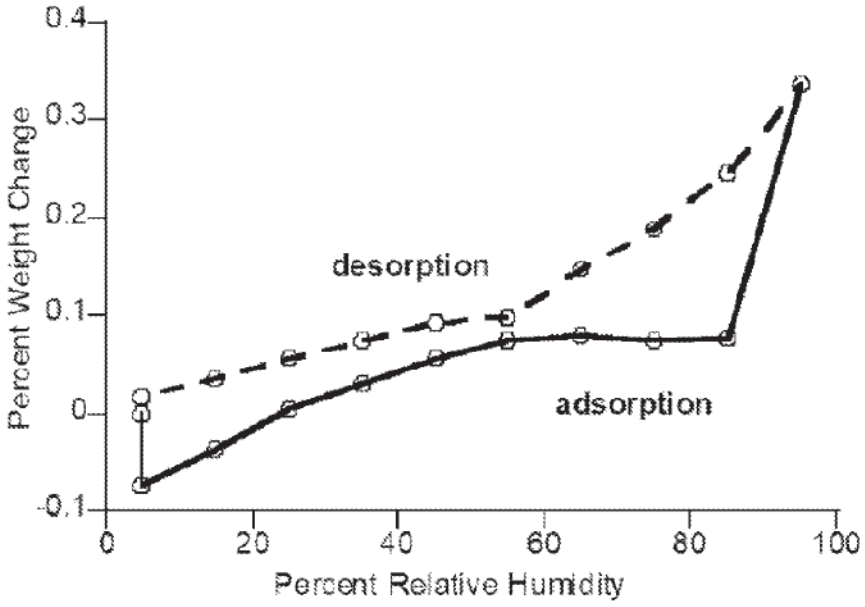

0.4
0.3
0.2
0.1
0
-0.1
Percent Weight Change
desorption
adsorption
0
20
40
60
80
100
Percent Relative Humidity

FIG. 5

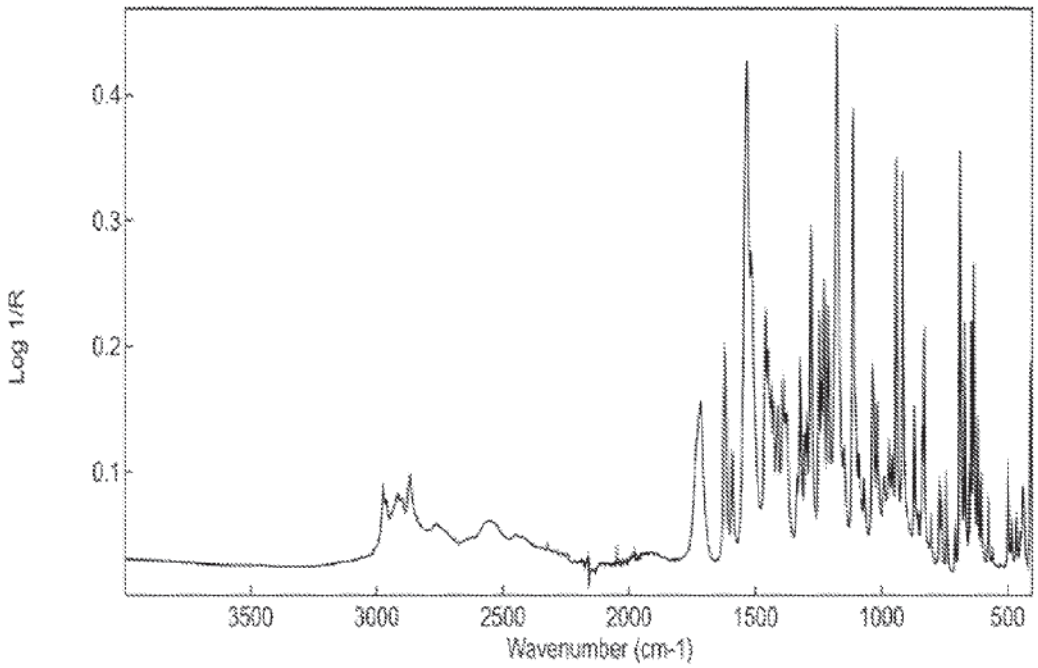

0.4
0.3
0.2
0.1
Log 1/R
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

FIG. 6

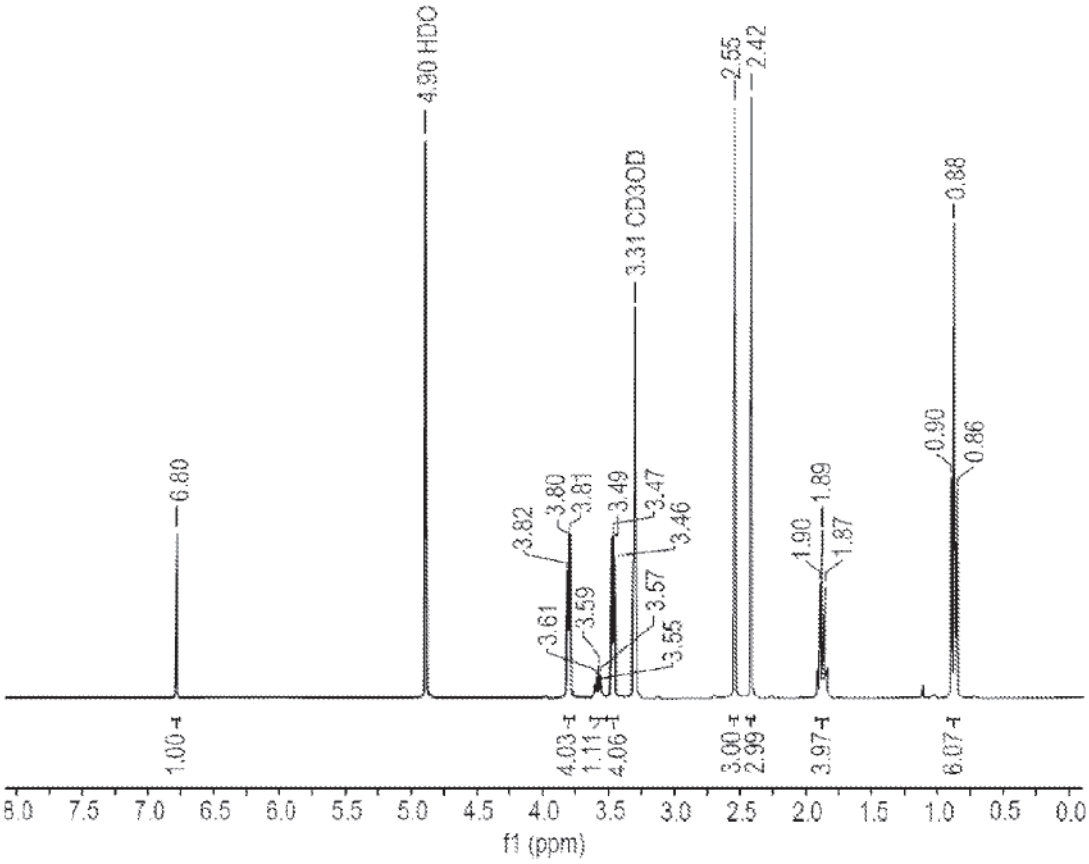
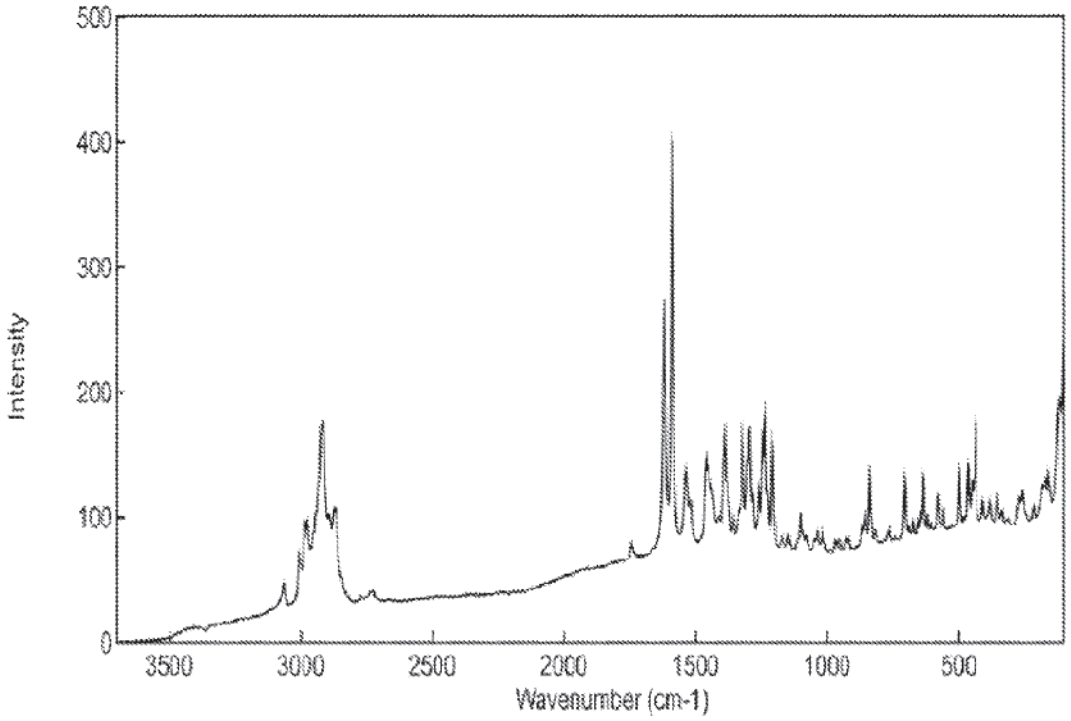

4.90 HDO
3.31 CD3OD
2.55
2.42
0.88
6.80
3.82
3.80
3.81
3.49
3.47
3.46
3.61
3.59
3.57
3.55
1.90
1.89
1.87
0.90
0.86
1.00
4.03
1.11
4.06
3.00
2.99
3.97
6.07
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

FIG. 7


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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/050436

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

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

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

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

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

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

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

See Supplemental Box for Details

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/050436

A. CLASSIFICATION OF SUBJECT MATTER

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

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2023	20 February 2023
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	**Authorised officer** Anthony Lai AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 6283 2642

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

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	**PCT/US2022/050436**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021016208 A1 (SPRUCE BIOSCIENCES, INC.) 28 January 2021 [0125]-[0126]; Examples 2-3	25-55 and 75-105
X	US 2020/0255436 A1 (Spruce Biosciences, Inc.) 13 August 2020 Abstract; [0019]; Example 10-12, Table 12 and 15-16	25-55 and 75-105
X	Sarafoglou K, Barnes CN, Huang M, Imel EA, Madu IJ, Merke DP, Moriarty D, Nakhle S, Newfield RS, Vogiatzi MG, Auchus RJ. Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies. J Clin Endocrinol Metab. 2021 Oct 21;106(11):e4666-e4679. doi: 10.1210/clinem/dgab438. Abstract	25-55 and 75-105
X	WO 2008/036579 A1 (ELI LILLY AND COMPANY) 27 March 2008 Abstract; Example 16	25-55 and 75-105

Supplemental Box

Continuation of: **Box III**

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

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

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

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

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

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

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

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. PCT/US2022/050436

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2021016208 A1	28 January 2021	WO 2021016208 A1	28 Jan 2021
		AR 119442 A1	15 Dec 2021
		AU 2020318970 A1	03 Mar 2022
		BR 112022000956 A2	05 Apr 2022
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		HK 1132505 A1	26 Feb 2010
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		JP 5161226 B2	13 Mar 2013
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		KR 101088239 B1	30 Nov 2011
		MA 30798 B1	01 Oct 2009

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2022/050436**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		MX 2009003125 A	28 May 2009
		MY 146388 A	15 Aug 2012
		NZ 575572 A	28 Oct 2011
		PE 20081377 A1	18 Sep 2008
		RS 51545 B	30 Jun 2011
		TN 2009000095 A1	19 Aug 2010
		TW 200821312 A	16 May 2008
		TW I402269 B	21 Jul 2013
		US 2010222339 A1	02 Sep 2010
		US 8030304 B2	04 Oct 2011

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 3 984 523 A1

(12) EUROPEAN PATENT APPLICATION

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(51) International Patent Classification (IPC):
A61K 9/00 *(2006.01)* ***A61K 31/395*** *(2006.01)*
A61K 31/426 *(2006.01)* ***A61K 31/573*** *(2006.01)*
A61P 5/00 *(2006.01)*

(52) Cooperative Patent Classification (CPC):
(C-Sets available)
A61K 9/0095; A61K 31/426; A61K 31/573; A61P 5/00; C07C 209/52; C07C 249/02; C07C 259/06; C07D 277/42 (Cont.)

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Designated Extension States:
BA ME
Designated Validation States:
KH MA MD TN

(30) Priority: **07.12.2018 US 201862776763 P**
11.03.2019 US 201962816674 P

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
19848938.7 / 3 890 706

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(54) CRF1 RECEPTOR ANTAGONIST, PHARMACEUTICAL FORMULATIONS AND SOLID FORMS THEREOF FOR THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

(57) Provided are methods related to treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine (Formula I), or a pharmaceutically acceptable salt thereof. Further provided are pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

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C07C 209/52;
C07C 249/02

Description

TECHNICAL FIELD

[0001] The present disclosure relates to 4-(2-chloro-4-methoxy5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for the treatment of congenital adrenal hyperplasia (CAH). The present disclosure further relates to pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

BACKGROUND

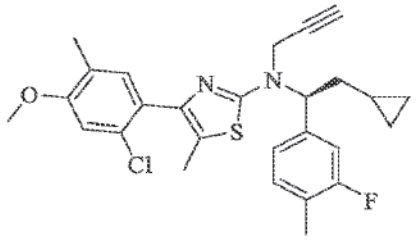
[0002] Classic congenital adrenal hyperplasia (CAH) is a disease that includes a group of autosomal recessive disorders that result in an enzyme deficiency that alters the production of adrenal steroids due to 21-hydroxylase deficiency, a condition that results in little or no cortisol biosynthesis. One clinical manifestation of the absence of cortisol is the lack of feedback inhibition of pituitary adrenocorticotropic hormone (ACTH) secretion. Increased ACTH levels cause adrenal hyperplasia and the enzyme mutation causes a shunting of cortisol precursor steroids to alternate pathways. Most notably, the shunting of androgens leads to virilization and other developmental complications in females and the overaccumulation of ACTH is associated with the formation of testicular adrenal rest tumors in males. In addition, since the same enzyme (21-hydroxylase) is used in the pathway for the biosynthesis of the mineralocorticoids, a number of these patients suffer from aldosterone deficiency which can result in dehydration and death due to salt-wasting. The prevalence of classic 21-hydroxylase deficiency CAH in the US general population, based on newborn screening, has been documented as 1:10,000 to 1:20,800 (Trakakis et al., "An update to 21-hydroxylase deficient congenital adrenal hyperplasia," Gynecol. Endocrinol. (2010) 26(1):63-71; Hertzberg et al., "Birth prevalence rates of newborn screening disorders in relation to screening practices in the United States," J. Pediatr. (2011) 159(4):555-560).

[0003] Pediatric patients from birth through adolescence, and females in particular, appear to be the most vulnerable population of CAH sufferers and represent the subgroup of patients with the greatest unmet medical need (Cheng and Speiser, "Treatment outcomes in congenital adrenal hyperplasia," Adv. Pediatr. (2012) 59(1):269-281; Merke and Poppas, "Management of adolescents with congenital adrenal hyperplasia," Lancet Diabetes Endocrinol. (2013) 1(4):341-352). Excessive androgen production in these younger patients results in early onset puberty and adrenarche, changes in skeletal maturation patterns, short stature caused by premature growth plate fusion, as well as significant hirsutism and acne problems. While survival is properly ensured through steroid replacement strategies based on physiologic dosing of glucocorticoids (e.g., hydrocortisone) and mineralocorticoids (e.g., fludrocortisone), these doses are often inadequate to suppress the accumulating ACTH and overproduction of progestogens and androgens (e.g., 17-hydroxyprogesterone [17-OHP], androstenedione, and testosterone). The uncontrolled symptoms of androgen excess, indeed, have a substantial impact on the day-to-day functioning and development of these patients.

[0004] Currently, exogenous corticosteroids are the standard of care for treating patients with classic CAH. This treatment is used to correct the cortisol deficiency and reduce the excessive ACTH levels and androgen excess. However, the dose and duration of steroid use required to suppress ACTH are typically well above the normal physiological level used for cortisol replacement alone (as in patients with Addison's disease). This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, reduced growth velocity, and decreased bone mineral density in CAH patients (Elnecave et al., "Bone mineral density in girls with classical congenital adrenal hyperplasia due to CYP21 deficiency," J. Pediatr. Endocrinol. Metab. (2008) 21(12):1155-1162; King et al., "Long-term corticosteroid replacement and bone mineral density in adult women with classical congenital adrenal hyperplasia," J. Clin. Endocrinol. Metab. (2006) 91(3):865-869; Migeon and Wisniewski, "Congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Growth, development, and therapeutic considerations," Endocrinol. Metab. Clin. North Am. (2001) 30(1):193-206).

[0005] Corticotropin releasing factor (CRF) is a hypothalamic hormone released directly into the hypophyseal portal vasculature and acts on specific corticotropin releasing factor 1 (CRF1) receptors on corticotropes in the anterior pituitary to stimulate the release of ACTH. Blockade of these receptors has been shown to decrease the release of ACTH in both animals and humans. Therefore, compounds that block CRF1 receptors have the potential to directly inhibit the excessive ACTH release that occurs in CAH and thereby allow for normalization of androgen production while using lower, more physiologic doses of hydrocortisone.

[0006] The compound of Formula (I)



(I)

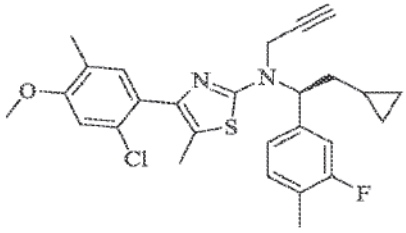
4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, is a selective CRF1 receptor antagonist. The compound of Formula (I) can be prepared according to the methods described in U.S. Patent Nos. 6,586,456 and 8,314,249, each of which is hereby incorporated by reference in its entirety. The compound of Formula (I) is a low solubility compound with low bioavailability. Partially due to its low solubility, attempts at formulating the compound of Formula (I) have proven to be difficult, particularly for formulations suitable for pediatric administration.

[0007] Thus, there is a need for a treatment for CAH that avoids the severe complications associated with corticosteroid therapy. There is also a need for a formulation of the compound of Formula (I) with increased bioavailability and a need for a formulation of the compound of Formula (I) that is suitable for pediatric administration. The formulations and methods of the present invention help address these and other needs.

SUMMARY

[0008] Provided herein is a pharmaceutical composition comprising:

(a) a compound of Formula (I):

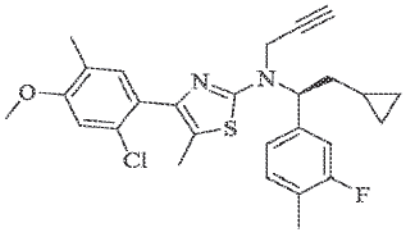


(I)

or a pharmaceutically acceptable salt thereof; and
(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

[0009] Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):

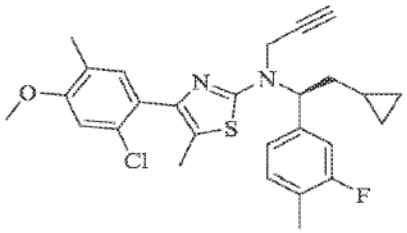


(I)

or a pharmaceutically acceptable salt thereof;
(b) one or more of a sweetener, an anti-oxidant, and a flavor; and
(c) a liquid vehicle.

[0010] Also provided herein is a pharmaceutical composition of the present disclosure (e.g., a pharmaceutical composition in oral solution dosage form of the present disclosure) for use in therapy, for example, for use in any of the methods disclosed herein.

[0011] Provided herein is a method for treating congenital adrenal hyperplasia (CAH) comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

[0012] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject.

[0013] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3- fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject.

[0014] Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

[0015] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

[0016] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic

hormone (ACTH); and (c) androstenedione in the subject.

[0017] In some embodiments, the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the circadian release occurs between the hours of 2 a.m. and 10 a.m.

[0018] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

[0019] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%.

[0020] In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50%.

[0021] In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

[0022] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

[0023] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

[0024] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

[0025] Provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject. In some embodiments, the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

[0026] Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

[0027] Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

[0028] In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

[0029] Provided herein is a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

[0030] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

[0031] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable

salt thereof, in the manufacture of a medicament for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

[0032] In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

[0033] Provided herein is a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

[0034] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

[0035] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3- fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

[0036] Provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

[0037] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

[0038] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

[0039] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

[0040] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

[0041] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

[0042] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

[0043] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

[0044] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

[0045] Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

[0046] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(lS)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

[0047] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the method comprises:

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(lS)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

[0048] In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

[0049] In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

[0050] In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

[0051] In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

[0052] In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

[0053] In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

[0054] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cycloptopyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

[0055] Provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

[0056] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

[0057] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

[0058] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1500 calories per liter with a caloric distribution of about 14.7% protein, about 32% fat and about 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

[0059] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

[0060] In some embodiments, administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

[0061] In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

[0062] Provided herein is a method of reducing glucocorticoid burden in a subject as measured after a time period of administration of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0063] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0064] Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0065] Provided herein is a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

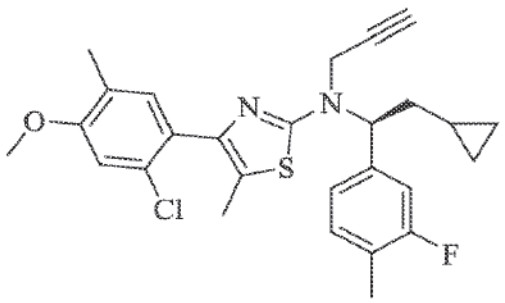
[0066] Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0067] Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

[0068] Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in therapy, for example, for use in any of the methods disclosed herein.

[0069] Also provided herein is use of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(lS)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

[0070] Also provided herein is a spray-dried dispersion containing 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



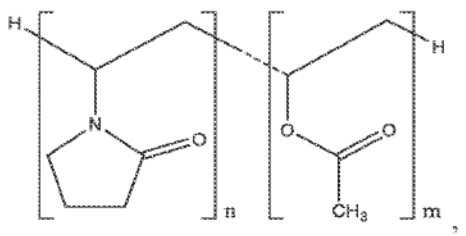
(I)

or a pharmaceutically acceptable salt thereof, and a polymer. In some embodiments, the polymer is selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:9 to about 1:1.

[0071] In some embodiments, the polymer is a neutral polymer. In some embodiment, the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

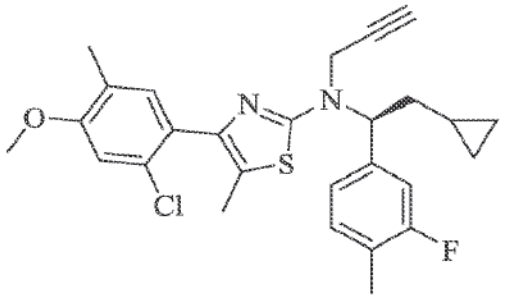
[0072] In some embodiments, the polymer is an enteric polymer. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

[0073] In some embodiments, the polymer is a pyrrolidone polymer. In some embodiments, the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA). In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight. In some embodiments, the copolymer has the structure:



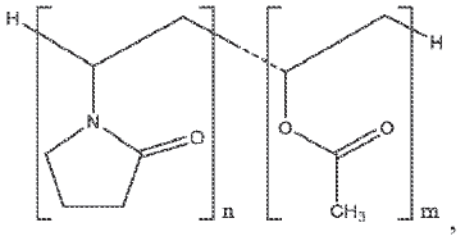
wherein the value of n is about 1 to about 2 times the value of m. In some embodiments, the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m. In some embodiments, the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

[0074] Provided herein is a spray-dried dispersion comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

[0075] In some embodiments of the spray-dried dispersions of the present disclosure, the compound of Formula (I) and the polymer together form homogeneous particles. In some embodiments, the particles have a particle size distribution D_{50} of about 5 μm to about 100 μm. In some embodiments, the particles have a particle size distribution D_{50} of about 10 μm to about 50 μm. In some embodiments, the particles have a particle size distribution D_{50} of about 15 μm to about 30 μm.

[0076] In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is about 1:3.

[0077] In some embodiments, the particles have a residual solvent content less than about 2 wt %. In some embodiments, the particles have a residual solvent content less than about 1 wt %. In some embodiments, the particles have a residual solvent content of about 0.5 wt % or less.

[0078] In some embodiments, the compound of Formula (I) in the dispersion is substantially amorphous.

[0079] Also provided herein is a method for preparing a spray-dried dispersion of the present disclosure, comprising: dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

[0080] In some embodiments, the method comprises removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion. In some embodiments, the spray-dried dispersion is dried with a convection tray dryer. In some embodiments, the organic solvent is acetone.

[0081] In some embodiments, the spray dryer inlet temperature is about 60°C to about 80°C. In some embodiments, the spray dryer inlet temperature is about 72°C.

[0082] In some embodiments, the spray dryer outlet temperature is about 25°C to about 45°C. In some embodiments, the spray dryer outlet temperature is about 35°C.

[0083] In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.2 g/mL. In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.

[0084] In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.3 g/mL. In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.

[0085] Also provided herein is a pharmaceutical composition comprising the spray-dried dispersion of the present disclosure and one or more pharmaceutically acceptable excipients. In some embodiments, the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition. In some embodiments, the spray-dried dispersion is present in an amount of about 40% to 80% w/w of the composition.

[0086] In some embodiments, the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

[0087] In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

[0088] In some embodiments, the pharmaceutical composition is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some

embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the pharmaceutical composition is coated.

[0089] In some embodiments, the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, wherein the spray-dried dispersion has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10.

[0090] Also provided herein is a method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of the present disclosure with one or more pharmaceutically acceptable excipients.

[0091] Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure.

[0092] Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

[0093] Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

[0094] In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state. In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

[0095] In some embodiments, administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20. In some embodiments, the ratio of the Cmax in the fed state to the C_{max} in the fasted state is about 10 to about 20.

[0096] In some embodiments of the disclosed methods, the subject is a pediatric subject.

[0097] Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in therapy, for example, for use in any of the methods disclosed herein.

[0098] Also provided herein is use of a spray-dried dispersion of the present disclosure for manufacture of a medicament for use in any of the methods disclosed herein.

[0099] Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0100] Also provided herein is a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

[0101] Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

[0102] Also provided herein is pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy, for example, for use in any of the methods disclosed herein.

[0103] Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

[0104] Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared

as a spray-dried dispersion.

[0105] Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0106] Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0107] In some embodiments, the subject is a pediatric subject.

[0108] Also provided herein is a method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0109] Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0110] Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

[0111] In some embodiments, the subject is a pediatric subject.

[0112] Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

[0113] Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for use in therapy, for example, for use in any of the methods disclosed herein.

[0114] Also provided herein is use of a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for manufacture of a medicament for use in any of the methods disclosed herein.

[0115] Other features and advantages of the methods, processes, formulations, and uses provided herein will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

[0116]

FIG. 1 shows the dissolution performance of several spray-dried dispersion formulations in 0.5 wt% simulated intestinal fluid (SIF) in phosphate buffered saline (PBS), pH 6.5.

FIG. 2 shows the vertical membrane flux cell integrated in the μDiss Profiler™ used for the membrane flux assay.

FIG. 3 shows non-sink dissolution data for several spray-dried dispersion formulations and the compound of Formula (I) in 0.5 wt% SIF in PBS, pH 6.5.

FIG. 4 is a graph showing membrane flux of 1 mg/mL GB/IB 0.5 wt% SIF doses of the compound of Formula (I) and various spray-dried dispersion formulations over time. The solid lines indicate flux (μg min^{-1} cm^{-2}) and the broken lines indicate concentration (μg/mL) in 0.5% SIF.

FIG. 5 is a flow diagram of the spray drying manufacturing process used to prepare a 1000 g batch of a SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64.

FIGS. 6A and 6B are line graphs showing the pharmacokinetic results of a bioavailability and food effect study in dogs. FIG. 6A shows the results from Cohort 1 and FIG. 6B shows the results from Cohort 2.

FIG. 7 is a flow chart showing the study design of a Phase 1 study of the pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIGS. 8A and 8B are line graphs showing the mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions, respectively, in healthy adult subjects.

FIGS. 9A-9C are spaghetti plots of the pharmacokinetics of the compound of Formula (I) in healthy adult subjects under fasted and fed conditions. FIG. 9A shows the $AUC_{0\text{-tlast}}$ values. FIG. 9B shows the $AUC_{0\text{-}\infty}$ values. FIG. 9C shows the C_{max} values.

FIG. 10 is a flow chart showing the study design of a Phase 1 study of the bioavailability, pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIG. 11 shows the study design of a Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia.

FIGs. 12A and 12B show the arithmetic mean values for adrenocorticotropic hormone (ACTH) (FIG. 12A) and 17-hydroxyprogesterone (17-OHP) (FIG. 12B) for all 8 Cohort 1 subjects plotted at each time point for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 13A and 13B show arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 14A and 14B show the reduction of ACTH at timepoints 8-, 10-, and 12-hours postdose. FIG 14A shows the values for each time point as compared to baseline. FIG. 14B shows the mean values across all three timepoints.

FIGs. 15A and 15B show the reduction of 17-OHP at timepoints 8-, 10-, and 12-hours postdose. FIG 15A shows the values for each time point as compared to baseline. FIG. 15B shows the mean values across all three timepoints.

FIGs. 16A and 16B show the reduction of androstenedione at timepoints 8-, 10-, and 12-hours postdose. FIG 16A shows the values for each time point as compared to baseline. FIG. 16B shows the mean values across all three timepoints.

FIG. 17A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 17B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 17C: shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 18A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 18B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 18C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 19A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 19B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 19C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 20 is a scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I).

FIG. 21 is an alternative scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I).

FIGs. 22A and 22B show a scheme showing the manufacturing process for forming SDD granules of the compound of Formula (I).

FIG. 23 is a scheme showing the manufacturing process for forming 50 mg/nL liquid formulation 1 of the compound of Formula (I).

FIG. 24 is a scheme showing the manufacturing process for forming 50 mg/nL liquid formulation 2 of the compound of Formula (I).

FIG. 25 is an XRPD spectrum of the compound of Formula (I) free base crystalline form I.

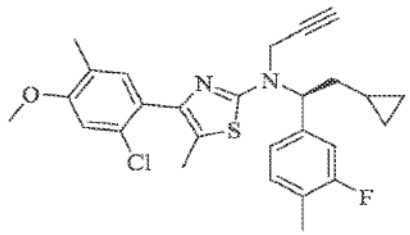
FIG. 26 is a DSC spectrum of the compound of Formula (I) free base crystalline form I.

FIG. 27 is an XRPD spectrum of the compound of Formula (1) tosylate crystalline form 1.

FIG. 28 is a DSC and TGA spectrum of the compound of Formula (I) tosylate crystalline form 1.

DETAILED DESCRIPTION

[0117] As described herein, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, is a selective CRF1 receptor antagonist that has been found to be effective treating congenital adrenal hyperplasia. Specifically, the compound of Formula (I) has been found to effectively reduce several biomarkers associated with congenital adrenal hyperplasia.

[0118] Newborn screening for CAH is performed by immunoassay to measure 17-OHP levels in heel-stick capillary blood specimens obtained within the first 72 hours of life. The blood sample is analyzed for 17-OHP by commercially available dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA; PerkinElmer, Waltham Massachusetts) (White et al., J. Pediatr. 163:10-12 (2013)). Second-tier screening tests utilizing biochemical and molecular genetic testing methods, performed between 8 and 14 days of life, are employed by nine states in the United States and strongly recommended by an additional 5 states. The biochemical method includes immunoassay with organic solvent extraction or liquid chromatography followed by tandem mass spectrometry to measure steroid ratios of 17-OHP, androstenedione, and 21-deoxycortisol to cortisol *(see, e.g.,* Speiser et al., Int. J. Pediatr. Endocrinol. 2010:494173, 2010). The genetic screen looks for *CYP21A2* mutations that are associated with CAH. While not widely employed in the U.S., the addition of a second screening could potentially improve the sensitivity of the overall screening process, where sensitivity of the first screen alone is approximately 72%.

[0119] In absence of results from the newborn screening, female infants with classical CAH are typically identified due to the presence of ambiguous genitalia. Males have normal genitalia at birth and therefore are not diagnosed unless newborn screening is conducted or other medical complications come to attention. Infants who are not initially diagnosed with CAH and suffer from the salt-wasting form of the disease are later diagnosed in the setting of poor weight gain, vomiting, hyperkalemia and hyponatremia within the first few weeks of life.

[0120] Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women and to inhibit testicular adrenal rest tumors in men. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

[0121] The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of iatrogenic Cushing's syndrome due to glucocorticoid overtreatment in an effort to adequately suppress androgen production, or Addisonian syndrome due to under-treatment.

[0122] Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione, testosterone, renin activity, and electrolytes. Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance *(see, e.g.,* Kim et al., Semin. Reprod. Med. 27(4):316-21 (2009)). A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes *(see, e.g.,* Finkielstain et al., J. Clin. Endocrinol Metab. 97(12):4429-38 (2012)).

[0123] Treatment of CAH includes efforts to normalize the cortisol deficiency with glucocorticoids (usually hydrocor-

tisone in children but often more potent agents with narrow therapeutic indices, such as dexamethasone, in adults) and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients *(see, e.g.,* Elnecave et al., J. Pediatr. Endocrinol. Metab. 21:1155-62 (2008); King et al., J. Clin. Endocrinol. Metab. 91(3):8656-59 (2006); Migeon et al., Endocrinol. Metab. Clin. North Am. 30:193-206 (2001)). Recently, best practices for the clinical management of congenital adrenal hyperplasia were published in the *Journal of Clinical Endocrinology and Metabolism* (Speiser, P.W., et al. J. Clin. Endocrinol Metab. November 2018, 103(11): 1-46). This article is incorporated by reference in its entirety.

[0124] Corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide. CRF has been found to produce profound alterations in endocrine, nervous, and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), β-endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (see, *e.g.,* Vale et al., Science 213:1394-1397,1981). Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the CRF_1 receptor, a member of the class B family of G-protein coupled receptors.

[0125] Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF_1 receptor binding activity and which are capable of antagonizing the CRF_1 receptor remains a desirable goal and has been the subject of ongoing research and development for the treatment of anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.

[0126] The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21-hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-hydroxyprogesterone (17-OHP). Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21-hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically cortisol and aldosterone. Cortisol is a critical negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

Definitions

[0127] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0128] The term "about" preceding a value for DSC, TGA, or T_g, which are reported as degrees Celsius, have an allowable variability of ±5°C. In all other instances, unless otherwise specified, the term "about" preceding a stated value includes the stated value and also includes ±20% of the stated value, and includes more specifically values of ±10%, ±5%, ±2%, and ±1% of the stated value.

[0129] To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that when a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

[0130] "Room temperature" or "RT" refers to the ambient temperature of a typical laboratory, which is typically around 25°C.

[0131] "Spray-drying" refers to the method of producing a dry powder from a solution or slurry. The solution or slurry is atomized or rapidly dried with a hot gas, e.g., air or nitrogen, that causes the solvent to evaporate quickly and uniformly. A "spray-dried dispersion" refers to the powder obtained from the spray-drying process.

[0132] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, co-solvents, complexing agents, dispersion media, coatings, antibacterial and antifungal agents, isotonic

and absorption delaying agents, and the like, which are not biologically or otherwise undesirable. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic formulations is contemplated. Supplementary active ingredients can also be incorporated into the fonnulations. In addition, various excipients, such as are commonly used in the art, can be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (2010); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 12th Ed., The McGraw-Hill Companies.

[0133] "Subject," as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate. In some embodiments, the subject is a human.

[0134] In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having congenital adrenal hyperplasia (CAH). In some embodiments, the subject is suspected of having CAH. In some embodiments, the subject has a clinical record indicating that the subject has CAH (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein). In some embodiments, the subject is a pediatric subject.

[0135] The term "pediatric subject" as used herein refers to a subject under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman et al., Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph et al., Rudolph's Pediatrics, 21st Ed. New York: McGraw-Hill, 2002; and Avery et al., Pediatric Medicine, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

[0136] As used herein, the terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0137] The term "preventing," as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

[0138] The term "administration" or "administering" refers to a method of giving a dosage of a compound or pharmaceutical formulation to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian. The preferred method of administration can vary depending on various factors, e.g., the components of the pharmaceutical formulation, the site of the disease, and the severity of the disease.

[0139] As used herein, "therapeutically effective amount" is an amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or an amount of a pharmaceutical composition comprising the compound of Formula (I), which is sufficient to achieve the desired effect and can vary according to the nature and severity of the disease condition, and the potency of the compound. A therapeutic effect is the relief, to some extent, of one or more of the symptoms of the disease, and can include curing a disease. "Curing" means that the symptoms of active disease are eliminated. However, certain long-term or permanent effects of the disease can exist even after a cure is obtained (such as, e.g., extensive tissue damage).

[0140] The term "amorphous" means a solid in a solid state that is a non-crystalline state. Amorphous solids are disordered arrangements of molecules and therefore possess no distinguishable crystal lattice or unit cell and consequently have no definable long range ordering. The solid state form of a solid may be determined by polarized light microscopy, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), or other standard techniques known to those of skill in the art.

[0141] As used herein, "time of day window" refers to a period of time defined by a window start time and a window stop time. These times all refer to local times where a sample was taken. The phrase "same time of day window" when

referring to samples taken from the subject mean, e.g., that a sample taken at 8:15 a.m. and a sample taken at 9:15 a.m. are considered to be taken in the same time of day window of, e.g., 2 a.m. to 10 a.m. or 6 a.m. to 10 a.m.

Methods

[0142] The present disclosure relates to methods of treating congenital adrenal hyperplasia (CAH). The methods include administering to a subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0143] Provided herein is a method of treating congenital adrenal hyperplasia (CAH) comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof to normalize or partially normalize levels of biomarkers associated with congenital adrenal hyperplasia. In some embodiments, normalizing or partially normalizing levels of biomarkers comprises reducing levels of elevated biomarkers or increasing levels of depressed biomarkers as compared to subject without CAH.

[0144] Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers associated with congenital adrenal hyperplasia. In some embodiments, the biomarkers are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

[0145] In some embodiments, the reduction in level of any of the biomarkers (e.g., any of 17-OHP, ACTH, and androstenedione) is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. A day prior to administering the compound of Formula (I) applies to a subject that has not previously been administered the compound of Formula (I) within at least the past 24 hours.

[0146] In some embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 2 a.m. and 10 a.m. In other embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 6 a.m. and 10 a.m.

[0147] In some embodiments of any of the methods disclosed herein, the compound of Formula (I), or a pharmaceutically acceptable salt, is administered to the subject at nighttime or administration prior to sleep (i.e., bedtime administration). In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered six to eight hours prior to the circadian release of the biomarker. Administration prior to the circadian release may be adapted for shift workers (*e.g.,* those who work at night and sleep during the day), in which case administration will not necessarily occur at nighttime. Administration is therefore dependent upon the expected circadian release of the biomarker, and can vary depending upon the individual's (*i.e.*, subject, patient) particular work and sleep patterns.

[0148] In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%. In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

[0149] In some embodiments, the level of 17-hydroxyprogesterone is reduced to a level within the range of 17-hydroxyprogesterone expected for a subject without CAH, i.e., less than 1,000 ng/dL or less than 200 ng/dL.

[0150] In some embodiments of the methods provided herein, the level of adrenocorticotropic hormone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50%.

[0151] In some embodiments of the methods provided herein, the level of adrenocorticotropic hormone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about

55% to about 90%, or about 60% to about 90% from pre-administration levels.

[0152] In some embodiments, the level of adrenocorticotropic hormone is reduced to a level within the range of adrenocorticotropic hormone expected for a subject without CAH.

[0153] In some embodiments of the methods provided herein, the level of androstenedione is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

[0154] In some embodiments of the methods provided herein, the level of androstenedione is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

[0155] In some embodiments, the level of androstenedione is reduced to a level within the range of androstenedione expected for a subject without CAH, i.e., less than 200 ng/dL.

[0156] Also provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce one or more biomarker of CAH in a subject, e.g. reduce the androstenedione in the subject. Growth impairment can refer to, e.g., accelerated height velocity, accelerated weight velocity, and/or accelerated bone age.

[0157] Provided herein is a method for reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

[0158] Provided herein is a method for reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

[0159] Also provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. The long-term effects of glucocorticoid treatment are well documented in the art (see, e.g., Oray, M. et al. (2016): Long-term effect of glucocorticoids, Expert Opinion on Drug Safety. DOI: 10.1517/14740338.2016.1140743). Such side effects are associated with every biological system, e.g., musculoskeletal (e.g., osteoporosis, avascular necrosis of bone, and myopathy), endocrine and metabolic (e.g., hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression), gastrointestinal (e.g., gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis), cardiovascular (e.g., hypertension, coronary heart disease, ischemic heart disease, heart failure), dermatologic (e.g., dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, and hair loss), neuropsychiatric (e.g., mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, and delirium), ophthalmologic (e.g., cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, and central serous chorioretinopathy), and immunologic (e.g., suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections).

[0160] Accordingly, in some embodiments, the side effects of glucocorticoid treatment are selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, reactivation of latent infections, and any combination thereof.

[0161] Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

(i)measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii)analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii)administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject

is determined to have elevated levels of the one or more biomarkers.

[0162] In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

[0163] In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

[0164] In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

[0165] In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

[0166] In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

[0167] In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

[0168] In some embodiments of the methods of the present disclosure, the compound of Formula (I) is administered at an amount equivalent to from about 25 mg to about 150 mg of the compound of Formula (I) free base. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at an amount equivalent to about 50 mg or about 100 mg of the compound of Formula (I) free base.

[0169] In some embodiments of the methods disclosed herein, compound of Formula (I) is administered in the free base form.

[0170] In some embodiments of the methods disclosed herein, the compound of Formula (I) is administered once daily.

[0171] Also provided herein is a method of treating CAH in a pediatric subject. The methods include administering to a pediatric subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject is a neonate. In some embodiments, the pediatric subject is an infant. In some embodiments, the pediatric subject is a child. In some embodiments, the pediatric subject is an adolescent.

[0172] In some embodiments of the methods of the present disclosure, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject in a fed state. The term "fed state," as used herein, refers to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof from about 1 hour before consumption of food or a nutritional composition to about 1 hour after consumption of food or a nutritional composition. The term "fasted state," as used herein, refers to a gap of at least two hours between consumption of food or a nutritional composition and administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with food or a nutritional composition, such as a nutritional supplement or formula, a meal replacement beverage, a liquid dietary supplement, or a high caloric liquid meal. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour before the subject has consumed food or a nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour after the subject has consumed food or a nutritional composition. Examples of suitable nutritional compositions include, but are not limited to, infant formulas, dietary supplements, dietary substitutes, and rehydration compositions. In some embodiments, the food is a product containing concentrated calories and protein. In some embodiments, the nutritional composition is a composition utilized for enteral and parenteral supplementation for infants, specialty infant formulas, supplements for the elderly, and supplements for those with gastrointestinal difficulties and/or malabsorption. Adult and pediatric nutritional formulas are well known in the art and are commercially available (e.g., Similac®, Ensure®, Jevity® and Alimentum® from Ross Products Division, Abbott Laboratories, Columbus, Ohio).

[0173] In some embodiments, the nutritional composition is in liquid form. The energy density of the nutritional compositions, when in liquid form, can range from about 0.6 Kcal to about 3 Kcal per mL. In some embodiments, the nutritional composition is in solid or powdered form. When in solid or powdered form, the nutritional supplements can contain from

about 1.2 to more than 9 Kcals per gram, such as about 3 to 7 Kcals per gram.

[0174] In some embodiments, the nutritional composition is a meal replacement bar. Examples include PowerBar®, Glucerna® bars, Choice DM® bars, Ensure® bars, and Boost® bars. In some embodiments, the nutritional composition is a nutrition shake or meal replacement beverage. Commercially available examples include the Ensure® branded adult products (such as Ensure® Original, Ensure® Plus, Ensure® Enlive, Ensure® High Protein, Ensure® Clear, and Ensure® Light), Glucerna®, Choice DM®, Slim Fast®, Pediasure®, Glytrol®, and Resource®. In some embodiments, the nutritional composition is Ensure® Plus. In some embodiments, the nutritional composition is vanilla-flavored Ensure® Plus. Ensure Plus® is a high calorie liquid dietary supplement that contains 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

[0175] In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

[0176] In some embodiments of the methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject before administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject at the same time as administration of the nutritional composition.

[0177] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject, followed by administration of the nutritional composition. In some embodiments, the nutritional composition is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60 minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered within 30 minutes of administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

[0178] In some embodiments, the nutritional composition is administered to the subject, followed by administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered within 30 minutes of administering the nutritional composition. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

[0179] In some embodiments of the methods, a food effect is observed between administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof in a fed state versus a fasted state. The term "food effect," as used herein, refers to the relative difference in AUC (area under the curve AUC(0-t) and/or $AUC_{(0-\infty)}$) or C_{max} (maximum plasma concentration or peak plasma concentration) of an active substance, when the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally to a subject, concomitantly with food or in a fed state as compared to the same values when the same compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in a fasted state. The food effect (F) is calculated as:

$$F\% = [(X_{fasted} - X_{fed}) / X_{fasted}] \times 100$$

where X_{fed} and X_{fasted} are the values of AUC ($AUC_{(0-t)}$ and/or $AUC_{(0-\infty)}$) or C_{max} in the fed and fasted state, respectively. In some embodiments, an increased, or positive, food effect is observed when the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to a subject in a fed state. In some embodiments, administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in an increased, or positive, food effect, whereby an increased C_{max} and/or AUC are observed when administered orally in the fed state as compared to the fasting state.

[0180] In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20.

[0181] In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values.

[0182] In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 1.5 to about 3 times higher in the fed stated compared to the fasted state. In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10,6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is 1.5 to 3 times higher in the fed stated compared to the fasted state. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 2 times higher in the fed stated compared to the fasted state. In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 10 to about 20.

[0183] In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a meal. In some embodiments, the meal is a high fat, high caloric meal. In some embodiments, the meal is a low fat, low caloric meal. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered within approximately 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

[0184] In some embodiments, the fed state is with a high fat meal. In some embodiments, the fed state is with a low fat meal. The FDA has provided draft guidelines regarding high fat and low fat meals ("Assessing the Effects of Food on Drugs in INDs and NDAs - Clinical Pharmacology Considerations Guidance for Industry," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February 2019, Clinical Pharmacology). Table 1 shows test meal definitions provided by the FDA guidance.

Table 1

Meal Type	Total Kcal	Fat		
		Kcal	Grams	Percent
High-Fat	800-1000	500-600	55-65	50
Low-Fat	400-500	100-125	11-14	25

[0185] The composition of a high fat meal provided by the FDA guidance is depicted in Table 2.

Table 2. Composition of a High Fat Meal*

Total Calories	800-1000
Calories from Protein	150
Calories from Carbohydrates	250
Calories from Fat	500-600

(continued)

An Example of a High Fat Breakfast	• Two eggs fried in butter • Two strips of bacon • Two slices of toast with butter • Four ounces of hash brown potatoes • Eight ounces of whole milk
*50 percent of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained.	

[0186] The composition of a low fat meal provided by the FDA guidance is depicted in Table 3.

Table 3. Composition of a Low Fat Meal

Total Calories	400-500
Fat (g)	250
Percent Calories from Fat	25
An Example of a Low Fat Breakfast*	• Eight ounces milk (1 percent fat) • One boiled egg • One packet flavored instant oatmeal made with water
*This low-fat breakfast contains 387 calories and has 10 grams of fat.	

[0187] In some embodiments, a high fat meal contains 800-1000 total Kcal and 500-600 fat Kcal. In some embodiments, a low fat meal contains 400-500 total Kcal and 100-125 fat Kcal.

[0188] Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion. In some embodiments, the subject is a pediatric subject.

[0189] Also provided herein is a method of improving oral bioavailability of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion.

[0190] In some embodiments of the methods provided herein, the subject is a pediatric subject.

[0191] Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition is a lipidic semi-solid formulation. In some embodiments, the pharmaceutical composition is a liquid formulation. In some embodiments, the pharmaceutical composition is administered to the subject in a fed state.

[0192] Also provided herein is a pharmaceutical composition of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject. In some embodiments, the subject is in a fed state.

[0193] In some embodiments, the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

[0194] In some embodiments, the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the

fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1.5 to 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1.5 to 3.

[0195] In some embodiments, the subject is a pediatric subject.

[0196] In some embodiments, the pharmaceutical composition is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1.5 to 3. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of 1.5 to 3.

[0197] In some embodiments, the pharmaceutical composition is administered to the subject with a meal. In some embodiments, the meal is a high fat meal. In some embodiments, the meal is a low fat meal. In some embodiments, the pharmaceutical composition is administered within about 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

[0198] In some embodiments, administering the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound

of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1.5 to 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1.5 to 3.

[0199] For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

[0200] For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

[0201] For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

Reduction in glucocorticoid burden, adrenal androgens and precursors

[0202] Glucocorticoids are a class of corticosteroids, which are a class of steroid hormones. Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor that is present in almost every vertebrate animal cell. In some embodiments, the subject is concurrently receiving a dose of a glucocorticoid. In some embodiments, the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate. In some embodiments, the glucocorticoid is cortisol (hydrocortisone). In some embodiments, the glucocorticoid is cortisone. In some embodiments, the glucocorticoid is prednisone. In some embodiments, the glucocorticoid is dexamethasone.

[0203] In some embodiments, the glucocorticoid dose is measured in hydrocortisone equivalents. In some embodiments, the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents. Any glucocorticoid can be given in a dose that provides approximately the same glucocorticoid effects as normal cortisol production; this is referred to as physiologic, replacement, or maintenance dosing.

[0204] In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m^2/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m^2/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m^2/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0205] In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0206] In some embodiments, the glucocorticoid dose concurrently given to the subject is a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2 to about 16 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 12 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 5 to about 11 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 6 to about 10 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 7 to about 9 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 9 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 8 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 12 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is less than about 8 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15 or about 16 mg/m^2/day, or within a range defined by any of the preceding values.

[0207] In some embodiments, the glucocorticoid dose concurrently given to the subject is at the upper limit of normal of a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the upper limit of normal is 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, or about 3.0 times the normal physiological dose, or within a range defined by any of the preceding values.

[0208] In some embodiments, the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the compound of Formula (I), or a

pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0209] In some embodiments, the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0210] In some embodiments, the glucocorticoid dose of the subject is reduced within a range defined by any of the preceding values.

[0211] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In

some embodiments, the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0212] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0213] In some embodiments, the level of 17-hydroxyprogesterone of the subject is reduced within a range defined by any of the preceding values.

[0214] In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0215] In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0216] In some embodiments, the level of adrenocorticotropic hormone of the subject is reduced within a range defined by any of the preceding values.

[0217] In some embodiments, the level of androstenedione is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration

of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0218] In some embodiments, the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0219] In some embodiments, the level of androstenedione of the subject is reduced within a range defined by any of the preceding values.

[0220] In some embodiments, the level of testosterone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0221] In some embodiments, the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0222] In some embodiments, the level of testosterone of the subject is reduced within a range defined by any of the preceding values.

[0223] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal and the level of androstenedione is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0224] In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0225] In some embodiments, the level of 17-hydroxyprogesterone and androstenedione of the subject is reduced within a range defined by any of the preceding values.

[0226] In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0227] In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0228] In some embodiments, the quality of life as measured by the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) in the subject is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) is relative to the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) results prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0229] In some embodiments, fatigue is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in fatigue is relative to the fatigue prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0230] In some embodiments, sleep is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in sleep is relative to the sleep prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0231] In some embodiments, insulin resistance is reduced in the subject after a time period of administration of the

compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of insulin resistance is relative to the insulin resistance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0232] In some embodiments, glucose tolerance is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in glucose tolerance is relative to the glucose tolerance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0233] In some embodiments, glucose control is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in glucose control is relative to the glucose control prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0234] In some embodiments, lipid levels reflecting dyslipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0235] In some embodiments, lipid levels reflecting hyperlipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0236] In some embodiments, bone mineral density is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone mineral density is relative to the bone mineral density prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0237] In some embodiments, bone turnover is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone turnover is relative to the bone turnover prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0238] In some embodiments, fat mass is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in fat mass is relative to the fat mass prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0239] In some embodiments, body weight is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in body weight is relative to the body weight prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0240] In some embodiments, central obesity is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in central obesity is relative to the central obesity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0241] In some embodiments, blood pressure is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in blood pressure is relative to the blood pressure prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0242] In some embodiments, the severity of hirsutism is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in the severity of hirsutism is relative to the severity of hirsutism prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0243] In some embodiments, menstrual cyclicity is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in menstrual cyclicity is relative to the menstrual cyclicity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0244] In some embodiments, control of testicular adrenal rest tumor is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in control of testicular adrenal rest tumor is relative to the control of testicular adrenal rest tumor prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0245] In some embodiments, fertility is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in fertility is relative to the fertility prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0246] In some embodiments, gonadotropin levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in gonadotropin levels is relative to the gonadotropin levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0247] In some embodiments, progesterone levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in progesterone

levels is relative to the progesterone levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0248] In some embodiments, semen levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in semen levels is relative to the semen levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0249] In some embodiments, LH (luteinizing hormone) levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in LH levels are relative to the LH levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0250] In some embodiments, the time period of administration is at least about 4 weeks. In some embodiments, the time period of administration is at least about 24 weeks. In some embodiments, the time period of administration is at least about one year. In some embodiments, the time period of administration is at least 4 weeks. In some embodiments, the time period of administration is at least 24 weeks. In some embodiments, the time period of administration is at least one year. In some embodiments, the time period of administration is less than about 1 day. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6 or 7 days, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 weeks, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, or within a range of any of the preceding values. It is understood that comparative measurements occur preferably during the morning.

[0251] In some embodiments, the subject is a pediatric subject. In some embodiments, the pediatric subject is less than or equal to six years old. In some embodiments, the pediatric subject is greater than six years old and less than eleven years old. In some embodiments, the pediatric subject is greater than ten years old and less than fifteen years old. In some embodiments, the pediatric subject is greater than fourteen years old and less than nineteen years old.

[0252] In some embodiments, the subject is an adult subject. In some embodiments, the subject is over eighteen years old. In some embodiments, the subject is female. In some embodiments, the subject is male.

[0253] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described herein. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 9. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 11. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 12. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 13. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

[0254] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt described herein.

[0255] For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

[0256] For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

[0257] For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

p-Toluenesulfonic Acid Salt

[0258] In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt thereof is 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

[0259] In some embodiments, the 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt is a crystalline salt. In some embodiments, the p-toluenesulfonic acid crystalline salt has Form 1.

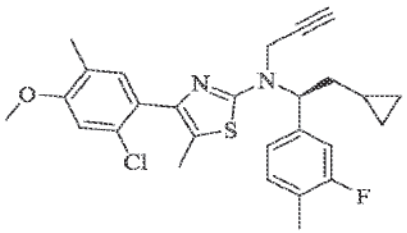
[0260] In some embodiments, the p-toluenesulfonic acid crystalline salt has an X-ray powder diffraction pattern as substantially shown in Figure 27. In some embodiments, the p-toluenesulfonic acid crystalline salt has a DSC thermogram substantially as depicted in Figure 28. In some embodiments, the p-toluenesulfonic acid crystalline salt has a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.

[0261] In some embodiments, the p-toluenesulfonic acid crystalline salt has at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta (± 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

Lipidic Semi-Solid Formulation

[0262] Provided herein is a lipidic semi-solid formulation, which is a pharmaceutical composition comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and
(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

[0263] In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

[0264] In some embodiments, the pharmaceutical composition comprises an oily phase vehicle. An oily phase vehicle is a solvent that is poorly miscible with water. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 20 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35 wt% to about 45 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 39 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 wt% of the oily phase vehicle, or within a range of any of the preceding values.

[0265] In some embodiments, the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the oily phase vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides are Labrafac TM Lipophile WL1349. In some embodiments, the medium-chain triglycerides are Miglyol 812N.

[0266] In some embodiments, the pharmaceutical composition comprises an emulsifying agent. An emulsifying agent is a compound or substance that acts as a stabilizer for emulsions. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 20 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises

about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the emulsifying agent, or within a range of any of the preceding values.

[0267] In some embodiments, the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the emulsifying agent is propylene glycol dicaprylate/dicaprate. In some embodiments, the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

[0268] In some embodiments, the pharmaceutical composition comprises a nonionic surfactant. A nonionic surfactant is a substance with a hydrophilic head and a hydrophobic tail that has no charge that is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 19 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the nonionic surfactant, or within a range of any of the preceding values.

[0269] In some embodiments, the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides. In some embodiments, the nonionic surfactant is lauroyl polyoxyl-32 glycerides. In some embodiments, the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

[0270] In some embodiments, the pharmaceutical composition comprises a solubilizing agent. A solubilizing agent is a solvent that assists with solubilizing the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 11 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the solubilizing agent, or within a range of any of the preceding values.

[0271] In some embodiments, the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer. In some embodiments, the solubilizing agent is vitamin E polyethylene glycol succinate. In some embodiments, the vitamin E polyethylene glycol succinate is Kolliphor® TPGS. In some embodiments, the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

[0272] In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) an oily phase vehicle;
(c) an emulsifying agent;
(d) a nonionic surfactant; and
(e) a solubilizing agent.

[0273] In some embodiments, the pharmaceutical composition comprises:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 35 wt% to about 45 wt% of an oily phase vehicle;
(c) about 15 wt% to about 25 wt% of an emulsifying agent;
(d) about 15 wt% to about 25 wt% of a nonionic surfactant; and
(e) about 5 wt% to about 15 wt% of a solubilizing agent.

[0274] In some embodiments, the pharmaceutical composition comprises:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 39 wt% of an oily phase vehicle;
(c) about 20 wt% of an emulsifying agent;

(d) about 19 wt% of a nonionic surfactant; and
(e) about 11 wt% of a solubilizing agent.

[0275] In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) a medium-chain triglycerides component;
(c) a propylene glycol dicaprylate/dicaprate component;
(d) a lauroyl polyoxyl-32 glycerides component; and
(e) a vitamin E polyethylene glycol succinate component.

[0276] In some embodiments, the pharmaceutical composition comprises:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) about 35 wt% to about 45 wt% of medium-chain triglycerides;
(c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;
(d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and
(e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

[0277] In some embodiments, the pharmaceutical composition comprises:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) about 39 wt% of medium-chain triglycerides;
(c) about 20 wt% of propylene glycol dicaprylate/dicaprate;
(d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and
(e) about 11 wt% of vitamin E polyethylene glycol succinate.

[0278] In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 15 to about 40 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 26 to about 30 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 5 to about 25 centipoise at about 60 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 14 to about 18 centipoise at about 60 °C.

[0279] In some embodiments, the pharmaceutical composition does not comprise a combination of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

[0280] In some embodiments, the pharmaceutical composition does not comprise at least one of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

[0281] In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in crystalline form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in amorphous form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I) as a free base. In some embodiments, the crystalline form of the compound of Formula (I) is of Form I.

[0282] In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg to about 150 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 25 mg, based on the weight of the free base.

[0283] In some embodiments, the pharmaceutical composition is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the dosage form is coated.

[0284] Some embodiments provide a method for preparing the pharmaceutical composition, comprising:

(a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;
(b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

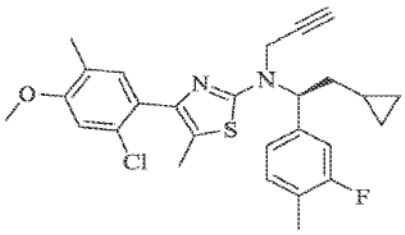
[0285] In some embodiments, the method further comprises:

(d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and
(e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

Liquid Formulations

[0286] Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;
(b) one or more of a sweetener, an anti-oxidant, and a flavor; and
(c) a liquid vehicle.

[0287] In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

[0288] In some embodiments, the pharmaceutical composition comprises a sweetener. A sweetener is a formulation component added to improve taste. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.15 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the sweetener, or within a range of any of the preceding values.

[0289] In some embodiments, the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and avantame. In some embodiments, the sweetener is saccharin.

[0290] In some embodiments, the pharmaceutical composition comprises an anti-oxidant. An anti-oxidant is a formulation component included to improve stability by preventing oxidation. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.17 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the anti-oxidant, or within a range of any of the preceding values.

[0291] In some embodiments, the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated

hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid. In some embodiments, the anti-oxidant is butylated hydroxytoluene.

[0292] In some embodiments, the pharmaceutical composition comprises a flavor. A flavor is a formulation component added to mask taste through aromatics. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 0.5 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05 w/v% to about 0.2 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.10 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19 or 0.2 w/v% of the flavor, or within a range of any of the preceding values.

[0293] In some embodiments, the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor. In some embodiments, the flavor is FONA orange flavor.

[0294] A liquid vehicle is a solvent capable of dissolving or partially dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the purposes of delivery as an oral dosing solution. In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 99.9 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90 w/v% to about 99 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 92 w/v% to about 97 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 94.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 w/v% of the liquid vehicle, or within a range of any of the preceding values.

[0295] In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

[0296] In some embodiments, the pharmaceutical composition further comprises a surfactant. A surfactant is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10 w/v% to about 30 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 20 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 w/v% of the surfactant, or within a range of any of the preceding values.

[0297] In some embodiments, the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters. In some embodiments, the surfactant is oleoyl polyoxyl-6 glycerides. In some embodiments, the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

[0298] In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 90 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70 w/v% to about 80 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 75 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 74.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 w/v% of the liquid vehicle, or within a range of any of the preceding values.

[0299] In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

[0300] In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) a sweetener;
(c) an anti-oxidant;
(d) a flavor; and
(e) a liquid vehicle.

[0301] In some embodiments, the pharmaceutical composition further comprises a surfactant.

[0302] In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
(d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and
(e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

[0303] In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of a sweetener;
(c) about 0.17 w/v% of an anti-oxidant;
(d) about 0.1 w/v% of a flavor; and
(e) about 94.6 w/v% of a liquid vehicle.

[0304] In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
(d) about 0.05 w/v% to about 0.2 w/v% of a flavor;
(e) about 15 w/v% to about 25 w/v% of a surfactant; and
(f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

[0305] In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of a sweetener;
(c) about 0.17 w/v% of an anti-oxidant;
(d) about 0.1 w/v% of a flavor;
(e) about 20 w/v% of a surfactant; and
(f) about 75 w/v% of a liquid vehicle.

[0306] In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) saccharin;
(c) butylated hydroxytoluene;
(d) FONA orange flavor; and
(e) medium-chain triglycerides.

[0307] In some embodiments, the pharmaceutical composition further comprises oleoyl polyoxyl-6 glycerides.

[0308] In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and

(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

[0309] In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of saccharin;
(c) about 0.17 w/v% of butylated hydroxytoluene;
(d) about 0.1 w/v% of FONA orange flavor; and
(e) about 94.6 w/v% of medium-chain triglycerides.

[0310] In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;
(e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and
(f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

[0311] In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of saccharin;
(c) about 0.17 w/v% of butylated hydroxytoluene;
(d) about 0.1 w/v% of FONA orange flavor;
(e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and
(f) about 75 w/v% of medium-chain triglycerides.

[0312] In some embodiments, the pharmaceutical composition comprises the compound of Formula (I) as a free base.

[0313] In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg/mL, based on the weight of the free base.

[0314] In some embodiments, the liquid pharmaceutical composition has a viscosity between about 1 to about 50 centipoise at about 25 °C.

[0315] Some embodiments provide a method for preparing a pharmaceutical composition comprising:

(a) mixing a liquid vehicle with a sweetener;
(b) mixing the mixture of step (a) with an anti-oxidant and a flavor;
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and
(d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

[0316] In some embodiments, step (a) of the method comprises mixing a liquid vehicle with a sweetener and a surfactant.

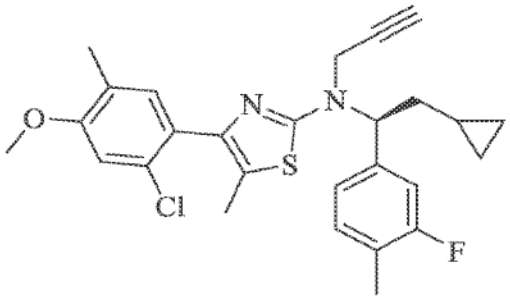
Spray-dried dispersions

[0317] The methods and uses of the present disclosure may comprise administering a spray-dried dispersion (SDDs) of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-

ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and to the use of the SDDs in the treatment of congenital adrenal hyperplasia (CAH).

[0318] In some embodiments, concentration and bioavailability enhancement in an aqueous environment of a low-solubility drug in a spray-dried dispersion is achieved if the SDD exhibits one or more properties, including, for example: (1) the solid dispersion is substantially homogeneous; (2) the drug is substantially amorphous; (3) the SDD has a relatively high drug loading; and (4) the SDD has a low residual solvent content. In some embodiments, the dispersion, when administered to an aqueous environment, provides at least a temporary dissolved drug concentration in the aqueous environment that is greater than the solubility of the crystalline form of the drug in the same environment. The aqueous environment can be, for example, an *in vitro* environment, such as a dissolution test media (e.g., phosphate buffered saline (PBS) solution), or an *in vivo* environment, such as the gastrointestinal (GI) tract of an animal, for example, a human. In some embodiments, the aqueous environment is the lower GI tract, such as the small intestine and large intestine.

[0319] Provided in the present disclosure is a spray-dried dispersion that contains a polymer and a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof. In some embodiments, the SDD includes a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9.

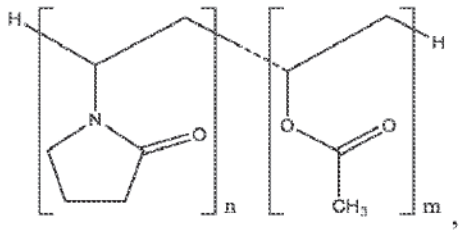
[0320] In some embodiments, the polymer is a neutral polymer. For example, the polymer does not contain any charged functional groups. In some embodiments, the neutral polymer is a cellulosic polymer. For example, the cellulosic polymer can be a polymer with at least one ester- and/or ether-linked substituent in which the polymer has a degree of substitution of at least 0.05 for each substituent. Examples of suitable neutral polymers include, but are not limited to, hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

[0321] In some embodiments, the polymer is an enteric polymer. An "enteric polymer," as used herein, is a polymeric substance that is substantially insoluble and/or substantially stable under acidic conditions exhibiting a pH of less than about 7 and which is substantially soluble or can decompose under conditions exhibiting a pH of about 7 or more. Examples of suitable enteric polymers include, but are not limited to, carboxymethyl ethyl cellulose (CMEC), cellulose acetate phthalate (CAP), cellulose acetate succinate (CAS), methylcellulose phthalate, hydroxymethyl ethyl cellulose phthalate, hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate succinate (HP-MCAS), polyvinyl alcohol phthalate, polyvinyl butyrate phthalate, polyvinyl acetal phthalate, a copolymer of vinyl acetate/maleic anhydride, a copolymer of vinylbutylether/maleic anhydride, a copolymer of styrene/maleic acid monoester, a copolymer of methyl acrylate/methacrylic acid, a copolymer of styrene/acrylic acid, a copolymer of methyl acrylate/methacrylic acid/octyl acrylate, a copolymer of methacrylic acid/methyl methacrylate, an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, a methacrylic copolymer, and mixtures thereof. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer. In some embodiments, the enteric polymer is a Eudragit® polymer sold by Evonik Industries (Essen, Germany). In some embodiments, the enteric polymer is an amino methacrylate copolymer. In some embodiments, the amino methacrylate copolymer is Eudragit® E PO/100. In some embodiments, the enteric polymer is an ammonioalkyl methacrylate copolymer. In some embodiments, the ammonioalkyl methacrylate copolymer is Eudragit® RLPO. In some embodiments, the enteric polymer is a methacrylic copolymer. In some embodiments, the methacrylic copolymer is Eudragit® L100 or Eudragit® S100.

[0322] In some embodiments, the polymer is a pyrrolidone polymer. For example, the pyrrolidone polymer can be a vinyl pyrrolidone polymer, such as polyvinyl pyrrolidone (PVP) or polyvinyl pyrrolidone vinyl acetate (PVP/VA), including

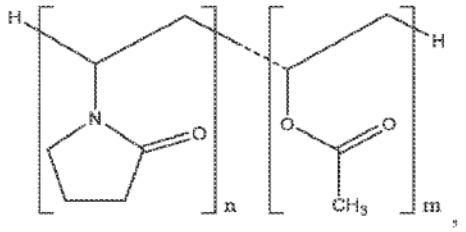
homopolymers and copolymers of PVP and homopolymers and copolymers of N-vinyl pyrrolidone. In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the PVP/VA is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70 to about 70:30 by weight, such as about 40:60 to about 60:40 by weight, or about 45:55 to about 55:45 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70, about 35:65, about 40:60, about 45:55, about 50:50, about 55:45, about 60:40, about 65:35, or about 70:30 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

[0323] In some embodiments, the pyrrolidone polymer has the structure:



where the value of n is about 1 to about 2 times the value of m. For example, the value of n can be about 1, about 1.05, about 1.1, about 1.15, about 1.16, about 1.2, about 1.25, about 1.3, about 1.35, about 1.4, about 1.45, about 1.5, about 1.55, about 1.6, about 1.65, about 1.7, about 1.75, about 1.8, about 1.85, about 1.9, about 1.95, or about 2 times the value of m, or a value within a range defined by any of the preceding values. In some embodiments, the value of n is about 1.16 times the value of m. In some embodiments, the copolymer is copovidone, and the value of n is about 1.16 times the value of m.

[0324] In some embodiments, the pyrrolidone polymer has the structure:



where the value of n is 1 to 2 times the value of m. For example, the value of n can be 1, 1.05, 1.1, 1.15, 1.16, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2 times the value of m, or a value within a range defined by any of the preceding values. In some embodiments, the value of n is 1.16 times the value of m. In some embodiments, the copolymer is copovidone, and the value of n is 1.16 times the value of m.

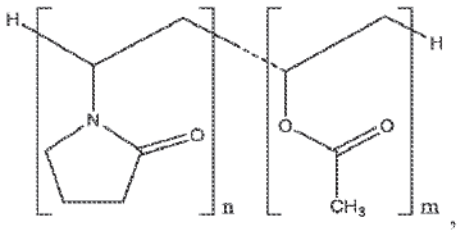
[0325] In some embodiments, the polymer used in the disclosed SDDs is present in an amount sufficient to increase the maximum drug concentration of the amorphous form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the environment of use (e.g., aqueous environment) relative to a control composition that contains an equivalent amount of a crystalline form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, but without polymer. In some embodiments, once the SDD is introduced into an environment of use (e.g., aqueous environment), the polymer increases the aqueous concentration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, relative to the control composition. It is to be understood that the control composition is free from solubilizers or other components that would materially affect the solubility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is in solid form in the control composition.

[0326] In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be about 1:1 to about 1:8, about 1:1 to about 1:7, about 1:1 to about 1:6, about 1:1 to about 1:5, about 1:1 to about 1:4, about 1:1 to about 1:3, about 1:1 to about 1:2, about 1:1 to about 1:1.5, about 1:1.5 to about 1:9, or about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9, about 1:8, about 1:7.5, about 1:7, about 1:6, about 1:5, about 1:4, about 1:3, about 1:2.5, about 1:2, about 1:1.5, or about

1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.

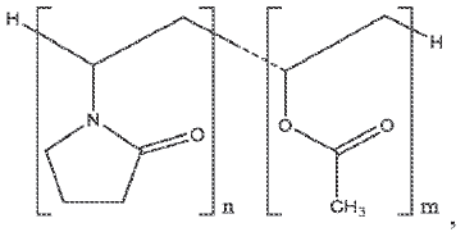
[0327] In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from 1:1 to 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be 1:1 to 1:8, 1:1 to 1:7, 1:1 to 1:6, 1:1 to 1:5, 1:1 to 1:4, 1:1 to 1:3, 1:1 to 1:2, 1:1 to 1:1.5, 1:1.5 to 1:9, or 1:2.5 to 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9, 1:8,1:7.5,1:7,1:6,1:5,1:4,1:3,1:2.5, 1:2, 1:1.5, or 1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.

[0328] In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is about 1 to about 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from about 1:1 to about 1:9.

[0329] In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is 1 to 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from 1:1 to 1:9.

[0330] In some embodiments of the SDDs, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer together form homogeneous particles. In some embodiments, the particles are a substantially homogeneous composition that includes the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer. As used herein, "substantially homogeneous" means that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dispersed as homogeneously as possible throughout the polymer and can be thought of as a solid solution of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, dispersed in the polymer. While the dispersion can have some concentrated domains of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the dispersion itself has a single glass transition temperature (T_g) which demonstrates that the dispersion is substantially homogeneous. This contrasts with a simple physical mixture of pure amorphous particles of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and pure amorphous polymer particles, which generally displays two distinct T_gS, one of the compound of Formula (I), or a pharmaceutically acceptable salt

thereof, and one of the polymer. "T_g," as used herein, is the characteristic temperature where a glassy material, upon gradual heating, undergoes a relatively rapid (e.g., 10 to 100 seconds) physical change from a glass state to a rubber state.

[0331] In some embodiments, the particles have a particle size distribution (D-value, D_{50}), of about 5 μm to about 100 μm, such as about 5 μm to about 95 μm, about 5 μm to about 90 μm, about 5 μm to about 85 μm, about 5 μm to about 80 μm, about 5 μm to about 75 μm, about 5 μm to about 70 μm, about 5 μm to about 65 μm, about 5 μm to about 60 μm, about 5 μm to about 55 μm, about 5 μm to about 50 μm, about 5 μm to about 45 μm, about 5 μm to about 40 μm, about 5 μm to about 35 μm, about 5 μm to about 30 μm, about 5 μm to about 25 μm, about 5 μm to about 20 μm, about 5 μm to about 15 μm, about 5 μm to about 10 μm, about 10 μm to about 100 μm, about 10 μm to about 95 μm, about 10 μm to about 90 μm, about 10 μm to about 85 μm, about 10 μm to about 80 μm, about 10 μm to about 75 μm, about 10 μm to about 70 μm, about 10 μm to about 65 μm, about 10 μm to about 60 μm, about 10 μm to about 55 μm, about 10 μm to about 50 μm, about 10 μm to about 45 μm, about 10 μm to about 40 μm, about 10 μm to 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In some embodiments, the D_{50} is about 5 μm, about 10 μm, about 15 μm, about 16 μm, about 20 μm, about 25 μm, about 30 μm, about 35 μm, about 40 μm, about 45 μm, about 50 μm, about 55 μm, about 60 μm, about 65 μm, about 70 μm, about 75 μm, about 80 μm, about 85 μm, about 90 μm, about 95 μm, or about 100 μm. In some embodiments, the D_{50} is about 10 μm, about 11 μm, about 12 μm, about 13 μm, about 14 μm, about 15 μm, about 16 μm, about 17 μm, about 18 μm, about 19 μm, or about 20 μm, or a value within a range defined by any of the preceding values. In some embodiments, the Dso value is about 16 μm. The Dso value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and

disc centrifugation.

[0332] In some embodiments, the particles have a particle size distribution (D-value, D_{50}), of 5 μm to 100 μm, such as 5 μm to 95 μm, 5 μm to 90 μm, 5 μm to 85 μm, 5 μm to 80 μm, 5 μm to 75 μm, 5 μm to 70 μm, 5 μm to 65 μm, 5 μm to 60 μm, 5 μm to 55 μm, 5 μm to 50 μm, 5 μm to 45 μm, 5 μm to 40 μm, 5 μm to 35 μm, 5 μm to 30 μm, 5 μm to 25 μm, 5 μm to 20 μm, 5 μm to 15 μm, 5 μm to 10 μm, 10 μm to 100 μm, 10 μm to 95 μm, 10 μm to 90 μm, 10 μm to 85 μm, 10 μm to 80 μm, 10 μm to 75 μm, 10 μm to 70 μm, 10 μm to 65 μm, 10 μm to 60 μm, 10 μm to 55 μm, 10 μm to 50 μm, 10 μm to 45 μm, 10 μm to 40 μm, 10 μm to 35 μm, 10 μm to 30 μm, 10 μm to 25 μm, 10 μm to 20 μm, 10 μm to 15 μm, 15 μm to 100 μm, 15 μm to 95 μm, 15 μm to 90 μm, 15 μm to 85 μm, 15 μm to 80 μm, 15 μm to 75 μm, 15 μm to 70 μm, 15 μm to 65 μm, 15 μm to 60 μm, 15 μm to 55 μm, 15 μm to 50 μm, 15 μm to 45 μm, 15 μm to 40 μm, 15 μm to 35 μm, 15 μm to 30 μm, 15 μm to 25 μm, 15 μm to 20 μm, 20 μm to 100 μm, 20 μm to 95 μm, 20 μm to 90 μm, 20 μm to 85 μm, 20 μm to 80 μm, 20 μm to 75 μm, 20 μm to 70 μm, 20 μm to 65 μm, 20 μm to 60 μm, 20 μm to 55 μm, 20 μm to 50 μm, 20 μm to 45 μm, 20 μm to 40 μm, 20 μm to 35 μm, 20 μm to 30 μm, 20 μm to 25 μm, 25 μm to 100 μm, 25 μm to 95 μm, 25 μm to 90 μm, 25 μm to 85 μm, 25 μm to 80 μm, 25 μm to 75 μm, 25 μm to 70 μm, 25 μm to 65 μm, 25 μm to 60 μm, 25 μm to 55 μm, 25 μm to 50 μm, 25 μm to 45 μm, 25 μm to 40 μm, 25 μm to 35 μm, 25 μm to 30 μm, 30 μm to 100 μm, 30 μm to 95 μm, 30 μm to 90 μm, 30 μm to 85 μm, 30 μm to 80 μm, 30 μm to 75 μm, 30 μm to 70 μm, 30 μm to 65 μm, 30 μm to 60 μm, 30 μm to 55 μm, 30 μm to 50 μm, 30 μm to 45 μm, 30 μm to 40 μm, 30 μm to 35 μm, 35 μm to 100 μm, 35 μm to 95 μm, 35 μm to 90 μm, 35 μm to 85 μm, 35 μm to 80 μm, 35 μm to 75 μm, 35 μm to 70 μm, 35 μm to 65 μm, 35 μm to 60 μm, 35 μm to 55 μm, 35 μm to 50 μm, 35 μm to 45 μm, 35 μm to 40 μm, 40 μm to 100 μm, 40 μm to 95 μm, 40 μm to 90 μm, 40 μm to 85 μm, 40 μm to 80 μm, 40 μm to 75 μm, 40 μm to 70 μm, 40 μm to 65 μm, 40 μm to 60 μm, 40 μm to 55 μm, 40 μm to 50 μm, 40 μm to 45 μm, 45 μm to 100 μm, 45 μm to 95 μm, 45 μm to 90 μm, 45 μm to 85 μm, 45 μm to 80 μm, 45 μm to 75 μm, 45 μm to 70 μm, 45 μm to 65 μm, 45 μm to 60 μm, 45 μm to 55 μm, 45 μm to 50 μm, 50 μm to 100 μm, 50 μm to 95 μm, 50 μm to 90 μm, 50 μm to 85 μm, 50 μm to 80 μm, 50 μm to 75 μm, 50 μm to 70 μm, 50 μm to 65 μm, 50 μm to 60 μm, 50 μm to 55 μm, 55 μm to 100 μm, 55 μm to 95 μm, 55 μm to 90 μm, 55 μm to 85 μm, 55 μm to 80 μm, 55 μm to 75 μm, 55 μm to 70 μm, 55 μm to 65 μm, 55 μm to 60 μm, 60 μm to 100 μm, 60 μm to 95 μm, 60 μm to 90 μm, 60 μm to 85 μm, 60 μm to 80 μm, 60 μm to 75 μm, 60 μm to 70 μm, 60 μm to 65 μm, 65 μm to 100 μm, 65 μm to 95 μm, 65 μm to 90 μm, 65 μm to 85 μm, 65 μm to 80 μm, 65 μm to 75 μm, 65 μm to 70 μm, 70 μm to 100 μm, 70 μm to 95 μm, 70 μm to 90 μm, 70 μm to 85 μm, 70 μm to 80 μm, 70 μm to 75 μm, 75 μm to 100 μm, 75 μm to 95 μm, 75 μm to 90 μm, 75 μm to 85 μm, 75 μm to 80 μm, 80 μm to 100 μm, 80 μm to 95 μm, 80 μm to 90 μm, 80 μm to 85 μm, 85 μm to 100 μm, 85 μm to 95 μm, 85 μm to 90 μm, 90 μm to 100 μm, 90 μm to 95 μm, or 95 μm to 100 μm. In some embodiments, the D_{50} is 5 μm, 10 μm, 15 μm, 16 μm, 20 μm, 25 μm, 30 μm, 35 μm, 40 μm, 45 μm, 50 μm, 55 μm, 60 μm, 65 μm, 70 μm, 75 μm, 80 μm, 85 μm, 90 μm, 95 μm, or 100 μm. In some embodiments, the Dso is 10 μm, 11 μm, 12 μm, 13 μm, 14 μm, 15 μm, 16 μm, 17 μm, 18 μm, 19 μm, or 20 μm, or a value within a range defined by any of the preceding values. In some embodiments, the D_{50} value is 16 μm. The Dso value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and disc centrifugation.

[0333] The SDDs of the present disclosure have a low residual solvent content. "Residual solvent content," as used herein, refers to the amount of solvent present in the SDD following spray drying, immediately upon exit from the spray dryer. The presence of solvent in the SDD lowers the glass transition temperature (T_g) of the dispersion. In some embodiments, mobility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the SDD and its propensity to phase separate and crystallize decreases as the amount of residual solvent in the SDD decreases. In some embodiments, the SDDs have a residual solvent content of not more than about 10 wt%, such as not more than about 5 wt%, or not more than about 1 wt%. For example, the SDDs have a residual solvent content of about 2 wt%, about 1.9 wt%, about 1.8 wt%, about 1.7 wt%, about 1.6 wt%, about 1.5 wt%, about 1.4 wt%, about 1.3 wt%, about 1.2 wt%, about 1.1 wt%, about 1 wt%, about 0.9 wt%, about 0.8 wt%, about 0.7 wt%, about 0.6 wt%, about 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than about 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than about 1 wt%. In some embodiments, the SDDs have a residual solvent content of about 0.5 wt% or less. In some embodiments, the SDDs have a residual solvent content of not more than 10 wt%, such as not more than 5 wt%, or not more than 1 wt%. For example, the SDDs may have a residual solvent content of 2 wt%, 1.9 wt%, 1.8 wt%, 1.7 wt%, 1.6 wt%, 1.5 wt%, 1.4 wt%, 1.3 wt%, 1.2 wt%, 1.1 wt%, 1 wt%, 0.9 wt%, 0.8 wt%, 0.7 wt%, 0.6 wt%, 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than 1 wt%. In some embodiments, the SDDs have a residual solvent content of 0.5 wt% or less.

[0334] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the spray-dried dispersion is substantially amorphous. As used herein, "substantially amorphous" means that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in amorphous form is at least 60 wt% and that the amount of crystalline form present does not exceed 20 wt%. In some embodiments, the compound of Formula (I),

or a pharmaceutically acceptable salt thereof, in the dispersion is "almost completely amorphous," meaning that at least 90 wt% of the drug is amorphous, or that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the crystalline form does not exceed 10 wt%. Amounts of crystalline drug can be measured by powder X-ray diffraction (PXRD), scanning electron microscope (SEM) analysis, differential scanning calorimetry (DSC), polarized light microscopy (PLM), or any other standard quantitative or qualitative measurement used to detect crystalline material. Without wishing to be bound by any theory, it is believed that the amorphous, or non-crystalline form, in combination with the polymer, leads to greater ease of dissolution and absorption in the desired location, for example, the intestines, resulting in enhanced bioavailability as compared to a crystalline form of the compound of Formula (I) without polymer.

Process for preparing spray-dried dispersions

[0335] Provided in the present disclosure are methods for preparing a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof, such as the SDDs described herein. In some embodiments, the method includes dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer. In some embodiments, the product obtained by spray-drying is dried to remove the solvent or solvent mixture. In some embodiments, the organic solvent is acetone.

[0336] The SDDs disclosed herein can be obtained by spray-drying a mixture comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, one or more polymer(s), and an appropriate solvent or solvent mixture. Spray-drying involves atomization of a liquid mixture containing, for example, a solid and a solvent or solvent mixture, and removal of the solvent or solvent mixture. Atomization can be done, for example, through a two-fluid or pressure or electrosonic nozzle, or on a rotating disk.

[0337] Spray-drying converts a liquid feed to a dried particulate form. In some embodiments, spray-drying involves the atomization of a liquid feed solution into a spray of droplets and contacting the droplets with hot air or gas in a drying chamber. The composition to be spray-dried can be any solution, coarse suspension, slurry, colloidal dispersion, or paste that can be atomized using the selected spray-drying apparatus. In some embodiments, the composition is a solution that is clear and free of undissolved solids. In some embodiments, the sprays are produced by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. Commercially available types of apparatus can be used to conduct the spray-drying. For example, commercial spray dryers are manufactured by Buchi Ltd. and Niro (e.g., the PSD line of spray driers manufactured by Niro). Techniques and methods for spray-drying can also be found in Perry's Chemical Engineering Handbook, 6th Ed., R. H. Perry, D. W. Green & J. O. Maloney, eds., McGraw-Hill Book Co. (1984); and Marshall, "Atomization and Spray-Drying" 50, Chem. Eng. Prog. Monogr. Series 2 (1954).

[0338] In some embodiments, the spray-drying is conducted with an inlet temperature of from about 40°C to about 100°C, for example, from about 60°C to about 80°C, or from about 70°C to about 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 70°C, about 72°C, about 75°C, about 80°C, about 85°C, about 90°C, about 95°C, or about 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 60°C to about 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 61°C, about 63°C, about 65°C, about 67°C, about 69°C, about 71°C, about 73°C, about 75°C, about 77°C, about 79°C, about 81°C, about 83°C, or about 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 72°C.

[0339] In some embodiments, the spray-drying is conducted with an inlet temperature of from 40°C to 100°C, for example, from 60°C to 80°C, or from 70°C to 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 40°C, 45°C, 50°C, 55°C, 60°C, 70°C, 72°C, 75°C, 80°C, 85°C, 90°C, 95°C, or 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 60°C to 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 61°C, 63°C, 65°C, 67°C, 69°C, 71°C, 73°C, 75°C, 77°C, 79°C, 81°C, 83°C, or 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 72°C.

[0340] In some embodiments, the spray-drying is conducted with an outlet temperature of from about 20°C to about 75°C, for example, from about 25°C to about 50°C, or from about 30°C to about 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 20°C, about 25°C, about 30°C, about 35°C, about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 65°C, about 70°C, or about 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is about 25°C to about 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 24°C, about 26°C, about 28°C, about 30°C, about 32°C, about 34°C, about 36°C, about 38°C, about 40°C, about 42°C, about 44°C, or about 46°C, or within a range

defined by any of the preceding values. In some embodiments, the outlet temperature is about 35°C.

[0341] In some embodiments, the spray-drying is conducted with an outlet temperature of from 20°C to 75°C, for example, from 25°C to 50°C, or from 30°C to 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 20°C, 25°C, 30°C, 35°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, or 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 25°C to 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 24°C, 26°C, 28°C, 30°C, 32°C, 34°C, 36°C, 38°C, 40°C, 42°C, 44°C, or 46°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 35°C.

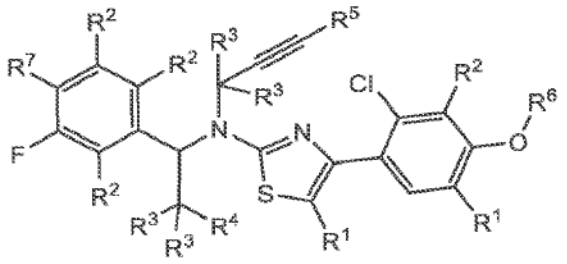
[0342] In some embodiments, the method involves removing the organic solvent after formation of the spray-dried dispersion. In some embodiments, the organic solvent is removed by drying the SDD. In some embodiments, a secondary drying process, such as fluidized bed drying, vacuum drying, tray drying, microwave drying, rotary drum drying or biconical vacuum drying is used to remove or reduce residual solvents, such as the organic solvent, to pharmaceutically acceptable levels. In some embodiments, the SDD is dried with a convection tray dryer.

[0343] In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than about 0.2 g/mL, or less than about 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of about 0.19 g/mL, about 0.18 g/mL, about 0.17 g/mL, about 0.16 g/mL, about 0.15 g/mL, about 0.14 g/mL, about 0.13 g/mL, about 0.12 g/mL, about 0.11 g/mL, about 0.1 g/mL, about 0.09 g/mL, about 0.08 g/mL, about 0.07 g/mL, about 0.06 g/mL or about 0.05 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than 0.2 g/mL, or less than 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of 0.19 g/mL, 0.18 g/mL, 0.17 g/mL, 0.16 g/mL, 0.15 g/mL, 0.14 g/mL, 0.13 g/mL, 0.12 g/mL, 0.11 g/mL, 0.1 g/mL, 0.09 g/mL, 0.08 g/mL, 0.07 g/mL, 0.06 g/mL or 0.05 g/mL, or within a range defined by any of the preceding values. The term "bulk density," as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

[0344] In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than about 0.3 g/mL, or less than about 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of about 0.29 g/mL, about 0.28 g/mL, about 0.27 g/mL, about 0.26 g/mL, about 0.25 g/mL, about 0.24 g/mL, about 0.23 g/mL, about 0.22 g/mL, about 0.21 g/mL, about 0.2 g/mL, or about 0.19 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than 0.3 g/mL, or less than 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of 0.29 g/mL, 0.28 g/mL, 0.27 g/mL, 0.26 g/mL, 0.25 g/mL, 0.24 g/mL, 0.23 g/mL, 0.22 g/mL, 0.21 g/mL, 0.2 g/mL, or 0.19 g/mL, or within a range defined by any of the preceding values. The term "tap density" or "tapped density," as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

Deuterated Compounds

[0345] Also disclosed herein are compounds having the structure of the following formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently $C(R^A)_3$;
each R^A is independently hydrogen or deuterium;
each R^2 is independently hydrogen or deuterium;

each R^3 is independently hydrogen or deuterium;
R^4 is

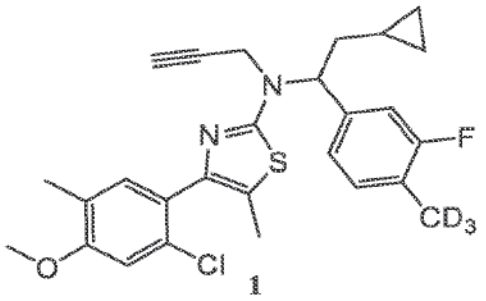


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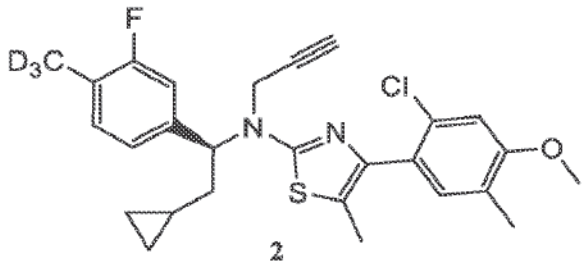
R^5 is hydrogen or deuterium;
R^6 is $C(R^A)_3$; and
R^7 is $C(R^B)_3$, wherein at least one of R^A, R^B, R^2, R^3 and R^5 is deuterium.

[0346] With regard to the compounds provided herein, when a particular atomic position is designated as having deuterium or "D" or "d", it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of, in certain embodiments, at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation) at each designated deuterium position.

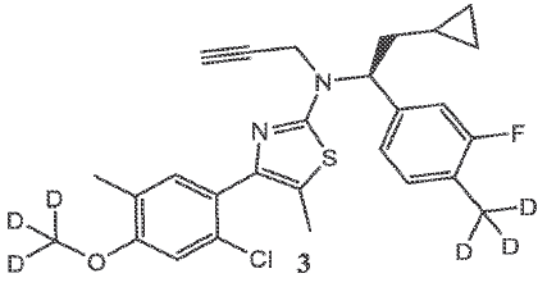
[0347] In some embodiments, the compound of Formula (II) may be one of the following, or a pharmaceutically acceptable salt thereof:



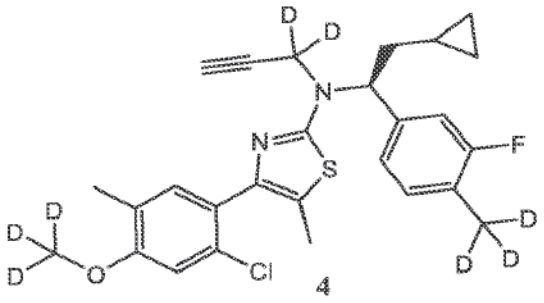
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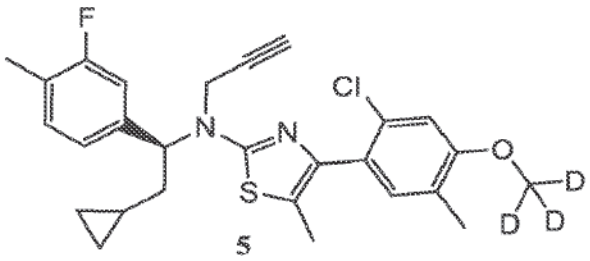
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Pharmaceutical compositions

[0348] The methods and uses disclosed herein can comprise administering the compound of Formula (I) as a pharmaceutical composition.

[0349] In some embodiments of the methods described herein, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition further comprising one or more pharmaceutically acceptable excipients.

[0350] Also provided herein is a pharmaceutical composition comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein.

[0351] In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that does not comprise a spray-dried dispersion of the compound of Formula (I), as specified, e.g., in Example 1. Accordingly, in some embodiments, the pharmaceutical composition does not comprise any of the following polymers: hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); HPMCAS-M; and methyl methacrylate copolymer (1:1) (Eudragit® L100).

[0352] In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is not the reference formulation described in Example 9. Accordingly, in some embodiments, the pharmaceutical composition does not comprise at least three of the excipients selected from caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicrapolate/dicaprate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

[0353] In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 9. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 11. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 12. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 13.

[0354] In some embodiments, the pharmaceutical compositions include a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0355] In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 20% to about 90% w/w of the composition, such as about 20% to about 85%,

about 20% to about 80%, about 20% to about 75%, about 20% to about 70%, about 20% to about 65%, about 20% to about 60%, about 20% to about 55%, about 20% to about 50%, about 20% to about 45%, about 20% to about 40%, about 20% to about 35%, about 20% to about 30%, about 20% to about 25%, about 25% to about 90%, about 25% to about 85%, about 25% to about 80%, about 25% to about 75%, about 25% to about 70%, about 25% to about 65%, about 25% to about 60%, about 25% to about 55%, about 25% to about 50%, about 25% to about 45%, about 25% to about 40%, about 25% to about 35%, about 25% to about 30%, about 30% to about 90%, about 30% to about 85%, about 30% to about 80%, about 30% to about 75%, about 30% to about 70%, about 30% to about 65%, about 30% to about 60%, about 30% to about 55%, about 30% to about 50%, about 30% to about 45%, about 30% to about 40%, about 30% to about 35%, about 35% to about 90%, about 35% to about 85%, about 35% to about 80%, about 35% to about 75%, about 35% to about 70%, about 35% to about 65%, about 35% to about 60%, about 35% to about 55%, about 35% to about 50%, about 35% to about 45%, about 35% to about 40%, about 40% to about 90%, about 40% to about 85%, about 40% to about 80%, about 40% to about 75%, about 40% to about 70%, about 40% to about 65%, about 40% to about 60%, about 40% to about 55%, about 40% to about 50%, about 40% to about 45%, about 45% to about 90%, about 45% to about 85%, about 45% to about 80%, about 45% to about 75%, about 45% to about 70%, about 45% to about 65%, about 45% to about 60%, about 45% to about 55%, about 45% to about 50%, about 50% to about 90%, about 50% to about 85%, about 50% to about 80%, about 50% to about 75%, about 50% to about 70%, about 50% to about 65%, about 50% to about 60%, about 50% to about 55%, about 55% to about 90%, about 55% to about 85%, about 55% to about 80%, about 55% to about 75%, about 55% to about 70%, about 55% to about 65%, about 55% to about 60%, about 60% to about 90%, about 60% to about 85%, about 60% to about 80%, about 60% to about 75%, about 60% to about 70%, about 60% to about 65%, about 65% to about 90%, about 65% to about 85%, about 65% to about 80%, about 65% to about 75%, about 65% to about 70%, about 70% to about 90%, about 70% to about 85%, about 70% to about 80%, about 70% to about 75%, about 75% to about 90%, about 75% to about 85%, about 75% to about 80%, about 80% to about 90%, about 80% to about 85%, or about 85% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 60% to about 80% w/w of the composition. In some embodiments, the SDD is present in an amount of about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

[0356] In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 20% to 90% w/w of the composition, such as 20% to 85%, 20% to 80%, 20% to 75%, 20% to 70%, 20% to 65%, 20% to 60%, 20% to 55%, 20% to 50%, 20% to 45%, 20% to 40%, 20% to 35%, 20% to 30%, 20% to 25%, 25% to 90%, 25% to 85%, 25% to 80%, 25% to 75%, 25% to 70%, 25% to 65%, 25% to 60%, 25% to 55%, 25% to 50%, 25% to 45%, 25% to 40%, 25% to 35%, 25% to 30%, 30% to 90%, 30% to 85%, 30% to 80%, 30% to 75%, 30% to 70%, 30% to 65%, 30% to 60%, 30% to 55%, 30% to 50%, 30% to 45%, 30% to 40%, 30% to 35%, 35% to 90%, 35% to 85%, 35% to 80%, 35% to 75%, 35% to 70%, 35% to 65%, 35% to about 60%, 35% to 55%, 35% to 50%, 35% to 45%, 35% to 40%, 40% to 90%, 40% to 85%, 40% to 80%, 40% to 75%, 40% to 70%, 40% to 65%, 40% to 60%, 40% to 55%, 40% to 50%, 40% to 45%, 45% to 90%, 45% to 85%, 45% to 80%, 45% to 75%, 45% to 70%, 45% to 65%, 45% to 60%, 45% to 55%, 45% to 50%, 50% to 90%, 50% to 85%, 50% to 80%, 50% to 75%, 50% to 70%, 50% to 65%, 50% to 60%, 50% to 55%, 55% to 90%, 55% to 85%, 55% to 80%, 55% to 75%, 55% to 70%, 55% to 65%, 55% to 60%, 60% to 90%, 60% to 85%, 60% to 80%, 60% to 75%, 60% to 70%, 60% to 65%, 65% to 90%, 65% to 85%, 65% to 80%, 65% to 75%, 65% to 70%, 70% to 90%, 70% to 85%, 70% to 80%, 70% to 75%, 75% to 90%, 75% to 85%, 75% to 80%, 80% to 90%, 80% to 85%, or about 85% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 60% to 80% w/w of the composition. In some embodiments, the SDD is present in an amount of 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

[0357] In some embodiments of the pharmaceutical compositions disclosed herein (e.g., a composition including an SDD), the pharmaceutically acceptable excipient is selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

[0358] In some embodiments, the pharmaceutical composition includes a filler. In some embodiments, the filler is selected from among binders, diluents, disintegrants, glidants, surfactants, and combinations thereof.

[0359] In some embodiments, the filler include saccharides (e.g., sugars, starch, and cellulose), gelatin, calcium carbonate, and synthetic polymers (e.g., polyvinylpyrrolidone, polyethylene glycol, and poloxamers (e.g., Poloxamer 188, a copolymer of polyoxyethylene and polyoxypropylene)). Exemplary fillers include, but are not limited to, glucose,

sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (e.g., Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 μm to about 500 μm) or Parteck® M 100 (mannitol with an average particle size of less than 212 μm)), a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a polymethacrylate, dibasic calcium phosphate, magnesium stearate, calcium stearate, sodium stearate, stearic acid, hydrogenated vegetable oils, a mineral oil, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, sodium acetate, aliginic acid, alginates (e.g., sodium alginate), calcium silicate, and ion exchange resins. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 μm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 μm)), methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethylcellulose. Exemplary fillers include cross-linked polyvinylpyrrolidone such as with an average particle size of 90 μm to 130 μm) or with an average particle size of 10 μm to 30 μm). Other fillers known to those of skill in the art are also contemplated as being useful when formulated in the pharmaceutical compositions described herein.

[0360] In some embodiments, the filler is a binder. Binders include agents that hold the active pharmaceutical ingredient (e.g., spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof) and inactive ingredients together in a cohesive mix. Exemplary binders include, but are not limited to, glucose, sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 μm to about 500 μm), Parteck® M 100 (mannitol with an average particle size of less than 212 μm)), gelatin, gum tragacanth, acacia mucilage, a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a polymethacrylate, and sodium starch glycolate. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 μm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 μm)), cellulose ethers, methyl cellulose, ethyl cellulose, croscarmellose sodium, sodium carboxy methyl cellulose starches, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose. Exemplary polyvinylpyrrolidone fillers include cross-linked polyvinylpyrrolidone such as Kollidon® CL (crospovidone with an average particle size of 90 μm to 130 μm) or Kollidon® CL-SF (crospovidone with an average particle size of 10 μm to 30 μm). Other binders known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

[0361] In some embodiments, the filler is a diluent. Suitable diluents include, but are not limited to, lactose, mannitol, isomalt, sucrose, dextrose, and sorbitol.

[0362] In some embodiments, the filler is a disintegrant. Disintegrants include any agent that promotes breakup of the formulation in an aqueous environment, for example, to promote more rapid release of the active pharmaceutical ingredient (e.g., the compound of Formula (I), or a pharmaceutically acceptable salt thereof). Exemplary disintegrants include, but are not limited to, starch and modified starches, such as corn starch, potato starch, sodium starch glycolate or croscarmellose sodium, alginic acid, alginates, such as sodium alginate, polyvinylpyrrolidone, bentonite, methylcellulose, agar, carboxymethylcellulose, crospovidone, acid-carbonate effervescent systems, such as citric acid with bicarbonate salts, and ion exchange resins. Other disintegrants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

[0363] In some embodiments, the pharmaceutical composition comprises a disintegrant. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 30 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 5 w/w% to about 15 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 10 w/w% of the disintegrant. In some embodiments, the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate. In some embodiments, the disintegrant is croscarmellose sodium.

[0364] In some embodiments, the filler is a glidant. Glidants can be used to improve the flowability of a powder or granules or both. Glidants include, but are not limited to, silicone dioxide, such as colloidal silicon dioxide or hydrated silicon dioxide, magnesium silicate, magnesium aluminometasilicate, talc, starch, calcium silicate, light anhydrous silicic acid, and silicon dioxide aerogels.

[0365] In some embodiments, the pharmaceutical composition comprises a glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 5 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.67 w/w% of the glidant. In some embodiments, the glidant is selected from calcium silicate, silicon dioxide, and talc. In some embodiments, the glidant is calcium silicate.

[0366] In some embodiments, the filler is a surfactant, wetting agent, solubilizer, or combination thereof. Examples include, but are not limited to, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., Tween®), polyoxyethylene stearates, sodium dodecylsulfate, tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton). Other examples

include, but are not limited to, poloxamers such as Pluronic® F68, F127, and F108, which are block copolymers of ethylene oxide and propylene oxide, and polyxamines such as Tetronic® 908 (also known as Poloxamine® 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (available from BASF), dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol® OT, which is a dioctyl ester of sodium sulfosuccinic acid (available from American Cyanimid), Duponol® P, which is a sodium lauryl sulfate (available from DuPont), Triton® X-200, which is an alkyl aryl polyether sulfonate (available from Rohm and Haas), Tween® 20 and Tween® 80, which are polyoxyethylene sorbitan fatty acid esters (available from ICI Specialty Chemicals), Carbowax™ 3550 and 934, which are polyethylene glycols (available from Union Carbide), Crodesta™ F-110, which is a mixture of sucrose stearate and sucrose distearate, and Crodesta™ SL-40 (both available from Croda Inc.), and SA90HCO, which has the chemical formula $C_{18}H_{37}$-$CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$.

[0367] In some embodiments, the pharmaceutical composition comprises a filler. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 99 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 90 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 75.5 w/w% of the filler. In some embodiments, the filler is selected from mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof. In some embodiments, the filler is a combination of mannitol and microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 80 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 60 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 50 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 10 w/w% to about 30 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 20 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

[0368] In some embodiments, the pharmaceutical composition includes a lubricant. Lubricants are agents added to pharmaceutical formulations to reduce friction during processing and prevent ingredients from clumping together. Exemplary lubricants include, but are not limited to, talc, starch, magnesium stearate, calcium stearate, sodium stearate, zinc stearate, stearic acid, vegetable stearin, adipic acid, waxy fatty acids, such as glyceryl behenate, a hydrogenated vegetable oil, a mineral oil, a polyethylene glycol, lycopodium, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium chloride, sterotex, glycerol monostearate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, and sodium acetate. Other lubricants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

[0369] In some embodiments, the pharmaceutical composition comprises a lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 10 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.5 w/w% of the lubricant. In some embodiments, the pharmaceutical lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc. In some embodiments, the lubricant is sodium stearyl fumarate.

[0370] In some embodiments, the pharmaceutical composition comprises:

(a) the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;
(b) a glidant;
(c) a filler; and
(d) a disintegrant.

[0371] In some embodiments, the pharmaceutical composition comprises:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;
(b) about 0.1 w/w% to about 1 w/w% of a glidant;
(c) about 50 w/w% to about 90 w/w% of a filler; and
(d) about 5 w/w% to about 0.2 w/w% of a disintegrant.

[0372] In some embodiments, the pharmaceutical composition comprises:

(a) about 13 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;

(b) about 0.67 w/w% of a glidant;
(c) about 75.5 w/w% of a filler; and
(d) about 10 w/w% of a disintegrant.

[0373] In some embodiments, the pharmaceutical composition comprises:

(a) the spray-dried dispersion of Example 3;
(b) calcium silicate;
(c) a combination of mannitol and microcrystalline cellulose; and
(d) croscarmellose sodium.

[0374] In some embodiments, the pharmaceutical composition comprises:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;
(b) about 0.1 w/w% to about 1 w/w% of calcium silicate;
(c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and
(d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.

[0375] In some embodiments, the pharmaceutical composition comprises:

(a) about 13 w/w% of the spray-dried dispersion of Example 3;
(b) about 0.67 w/w% of calcium silicate;
(c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and
(d) about 10 w/w% of croscarmellose sodium.

[0376] Additional excipients can be included in the pharmaceutical formulations of the present disclosure. Further examples of excipients include, but are not limited to, pigments, colorants, flavoring agents, preservatives, and sweeteners. Flavors and colors can be added to improve the taste or appearance of a formulation. Examples of preservatives used in pharmaceutical compositions are aromatic alcohols, such as benzyl or phenol alcohol, antioxidants such as vitamin A, vitamin E, vitamin C, and selenium, amino acids such as cysteine and methionine, citric acid and sodium citrate, or synthetic preservatives such as methyl paraben and propyl paraben. Sweeteners can be added to make the ingredients more palatable, especially in chewable tablets or liquids like syrups.

[0377] Also provided are methods for preparing a pharmaceutical composition, such as a pharmaceutical composition of the present disclosure. In some embodiments, the method includes combining the spray-dried dispersion described herein with one or more pharmaceutically acceptable excipients, e.g., a pharmaceutically acceptable excipient described herein.

[0378] In some embodiments, the method for preparing the pharmaceutical composition comprises:

(a) blending the spray-dried dispersion described herein, with a glidant;
(b) further blending the blend of step (a) with a filler and a disintegrant;
(c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;
(d) further blending the intragranular blend of step (c);
(e) compaction of the intragranular blend of step (d) via roller compaction to form granules; and
(f) milling of ribbon from roller compaction into granules of step (e).

[0379] In some embodiments, the spray-dried dispersion is the spray-dried dispersion described in Example 3.

[0380] The pharmaceutical compositions of the present disclosure are formulated for oral administration. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media can be employed. For solid oral preparations such as, for example, powders, capsules, caplets, gelcaps, and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

[0381] Oral pharmaceutical dosage forms can be solid, gel, or liquid. In some embodiments, the dosage form is a solid dosage form. In some embodiments, the solid dosage form is a pill, tablet, capsule, caplet, gelcaps, granules, powder, sachet, melting strip, or melting film. In some embodiments, the solid dosage form is coated. In some embodiments, the

coating is an enteric coating, a sugar coating, or a film coating. In some embodiments, the solid dosage form is a coated particle, coated tablet, enterocoated tablet, or enterocoated capsule. In some embodiments, the solid dosage form is a pill or tablet. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric coated, sugar coated or film coated. In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a powder, solution, or suspension (e.g., in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides), or is encapsulated in a capsule (gelatin or cellulose base capsule). Capsules can be hard or soft gelatin capsules, while granules and powders can be provided in non-effervescent or effervescent form with a combination of other ingredients known to those skilled in the art.

[0382] The pharmaceutical compositions of the present disclosure can contain, per dosage unit, e.g., tablet, capsule, powder, and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

[0383] In some embodiments, the pharmaceutical compositions of the present disclosure are formulated in unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg in the unit dosage form. For example, about 5 mg to about 175 mg, about 5 mg to about 150 mg, about 5 mg to about 125 mg, about 5 mg to about 100 mg, about 5 mg to about 75 mg, about 5 mg to about 50 mg, about 5 mg to about 25 mg, about 25 mg to about 200 mg, about 25 mg to about 175 mg, about 25 mg to about 150 mg, about 25 mg to about 125 mg, about 25 mg to about 100 mg, about 25 mg to about 75 mg, about 25 mg to about 50 mg, about 50 mg to about 200 mg, about 50 mg to about 175 mg, about 50 mg to about 150 mg, about 50 mg to about 125 mg, about 50 mg to about 100 mg, about 50 mg to about 75 mg, about 75 mg to about 200 mg, about 75 mg to about 175 mg, about 75 mg to about 150 mg, about 75 mg to about 125 mg, about 75 mg to about 100 mg, about 100 mg to about 200 mg, about 100 mg to about 175 mg, about 100 mg to about 150 mg, about 100 mg to about 125 mg, about 125 mg to about 200 mg, about 125 mg to about 175 mg, about 125 mg to about 150 mg, about 150 mg to about 200 mg, about 150 mg to about 175 mg, or about 175 mg to about 200 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg to about 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg, about 10 mg, about 25 mg, about 35 mg, about 50 mg, about 65 mg, about 75 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg in the unit dosage form.. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg to 250 mg in the unit dosage form. For example, 5 mg to 175 mg, 5 mg to 150 mg, 5 mg to 125 mg, 5 mg to 100 mg, 5 mg to 75 mg, 5 mg to 50 mg, 5 mg to 25 mg, 25 mg to 200 mg, 25 mg to 175 mg, 25 mg to 150 mg, 25 mg to 125 mg, 25 mg to 100 mg, 25 mg to 75 mg, 25 mg to 50 mg, 50 mg to 200 mg, 50 mg to 175 mg, 50 mg to 150 mg, 50 mg to 125 mg, 50 mg to 100 mg, 50 mg to 75 mg, 75 mg to 200 mg, 75 mg to 175 mg, 75 mg to 150 mg, 75 mg to 125 mg, 75 mg to 100 mg, 100 mg to 200 mg, 100 mg to 175 mg, 100 mg to 150 mg, 100 mg to 125 mg, 125 mg to 200 mg, 125 mg to 175 mg, 125 mg to 150 mg, 150 mg to 200 mg, 150 mg to 175 mg, or 175 mg to 200 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 25 mg to 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 75 mg to 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg, 10 mg, 25 mg, 35 mg, 50 mg, 65 mg, 75 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 100 mg in the unit dosage form. In some embodiments, the pharmaceutical compositions of the present disclosure are formulated as a tablet. In some embodiments, the tablet is coated. In some embodiments, the pharmaceutical compositions of the present disclosure are formulated as capsules. In some embodiments, the pharmaceutical compositions are in sachet form. In some embodiments, the pharmaceutical compositions are in granule form.

[0384] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 100 mg, based on the weight of the

free base.

[0385] In some embodiments, the pharmaceutical composition is administered in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0386] In some embodiments, the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0387] The daily dosage of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition as described in the present disclosure can be varied over a wide range from about 1.0 mg to about 10,000 mg per adult human per day, or higher, or any range therein. For oral administration, the compositions can be provided in the form of tablets containing, for example, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2.5 mg, about 5.0 mg, about 10.0 mg, about 15.0 mg, about 25.0 mg, about 50.0 mg, about 75.0 mg, about 100 mg, about 150 mg, about 200 mg, about 250 or about 500 milligrams of the compound of Formula (I), or pharmaceutically acceptable salt thereof, for the symptomatic adjustment of the dosage to the subject to be treated. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from about 0.1 mg/kg to about 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from about 0.5 mg/kg to about 500 mg/kg, about 1.0 mg/kg to about 250 mg/kg, about 0.1 mg/kg to about 100 mg/kg, about 0.1 mg/kg to about 50.0 mg/kg of body weight per day, about 0.1 mg/kg to about 15.0 mg/kg of body weight per day, about 0.5 mg/kg to about 7.5 mg/kg of body weight per day, or any amount to range therein. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from 0.1 mg/kg to 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from 0.5 mg/kg to 500 mg/kg, 1.0 mg/kg to 250 mg/kg, 0.1 mg/kg to 100 mg/kg, 0.1 mg/kg to 50.0 mg/kg of body weight per day, 0.1 mg/kg to 15.0 mg/kg of body weight per day, 0.5 mg/kg to 7.5 mg/kg of body weight per day, or any amount to range therein. A pharmaceutical composition as provided herein can be administered on a regimen of 1 to 4 times per day or in a single daily dose.

[0388] In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 25 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 50 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 75 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 100 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 150 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 200 mg, based on the weight of the free base.

[0389] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 100 mg, based on the weight of the free base.

[0390] In some embodiments, the daily dose of the pharmaceutical composition is about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 150 mg of the compound of Formula (I),

or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0391] In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0392] In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0393] In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof, twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

[0394] Factors associated with the particular subject being treated, including subject age, weight, diet, and time of administration, can result in the need to adjust dosages. In some embodiments, the subject is a human adult. In some embodiments, the subject is a pediatric subject.

[0395] One skilled in the art will recognize that both *in vivo* and *in vitro* trials using suitable, known, and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder. One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy subjects and/or those suffering from a given disorder, can be completed according to methods well known in the clinical and medical arts. For example, determining proper dosages for pediatric subjects can be determined using known methods, including weight, age, and models such as Simcyp® Pediatric Simulation modeling (CERTARA, Princeton, N.J.) which can be used to establish a pharmacokinetic approach for dosing that takes into account subject age, ontogeny of the clearance pathways that a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and body surface area (BSA).

[0396] In some embodiments, the pharmaceutical compositions of the present disclosure are stable for at least 3 months. In some embodiments, the pharmaceutical compositions are stable for at least 6 months. In some embodiments, the pharmaceutical compositions are stable for at least 9 months. In some embodiments, the pharmaceutical compositions are stable for at least 12 months. For example, the compositions do not exhibit a change (e.g., greater than 5%) in appearance, pH, percent impurities, activity (as measured by in vitro assays), or osmolarity over time, e.g., at least 3 months, 6 months, 9 months, or at least 12 months as compared to the original composition after manufacturing. In some embodiments, the pharmaceutical compositions do not exhibit a significant change, as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in one or more of appearance, pH, percent impurities, activity (as measured by *in vitro* assays), or osmolarity over time, e.g., at least 12 months as compared to the original pharmaceutical composition after manufacturing.

Kits

[0397] Also provided are kits. Typically, a kit includes one or more pharmaceutical compositions as described herein, e.g., a pharmaceutical composition containing, e.g., a spray-dried dispersion as described in Examples 1-4, or the formulation described in Example 9. In certain embodiments, a kit can include one or more delivery systems, e.g., for delivering or administering the pharmaceutical composition as provided herein, and directions for use of the kit (e.g., instructions for treating a subject). In some embodiments, the kit can include a pharmaceutical composition as described herein and a label that indicates that the contents are to be administered to a subject with congenital adrenal hyperplasia. The actual dose of the compound of Formula (I), or pharmaceutically acceptable salt thereof, provided herein depends on the specific formulation, the weight of the patient, and on the condition to be treated.

EXAMPLES

Example 1: Spray-dried dispersion formulations containing the compound of Formula (I) and various polymers

Spray-dried** dispersion **formulations

[0398] A series of spray-dried dispersion (SDD) formulations containing the compound of Formula (I) and a polymer were prepared. The SDD formulations included: (1) 10% compound of Formula (I)/90% hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); (2) 25% compound of Formula (I)/75% HPMCAS-L; (3) 40% compound of Formula (I)/60% HPMCAS-L; (4) 25% compound of Formula (I)/75% polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); (5) 25% compound of Formula (I)/60% Cabosil (fumed silica)/15% HPMCAS-L; (6) 25% compound of Formula (I)/75% HPMCAS-M; and (7) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100).

[0399] The PVP/VA polymer was a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate with a ratio of 60:40 by weight 1-vinyl-2-pyrrolidone:vinyl acetate with an average molecular weight of 45,000-70,000 (copovidone, sold as Kollidon® VA 64, BASF, Florham Park, NJ). The HPMCAS was a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose that was either grade L (HPMCAS-L), with an acetyl content of 5-9%, a succinoyl content of 14-18%, a methoxyl content of 20-24%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan); or grade M (HPMCAS-M), with an acetyl content of 7-11%, a succinoyl content of 10-14%, a methoxyl content of 21-25%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan).

Dissolution performance

[0400] Dissolution performance of several of the SDD formulations described above was tested (see FIG. 1). 1000 μgA/mL of each SDD was tested in 0.5 wt% simulated intestinal fluid (SIF) in PBS, pH 6.5. Samples were tested at 5, 10, 20, 45, 90, and 1200 minutes. A lipid formulation containing 10% of the compound of Formula (I) was used as a control. The results are shown in Table 4, below.

Table 4. Dissolution data of various SDDs

Sample	C_{max90} (μg/mL)	AUC_{90} (min*μg/mL)	C_{mix90} (μg/mL)	$Ultra_{90}$ (μg/mL)	C_{1200} (μg/mL)	$Ultra_{1200}$ (μg/mL)
2	762	66,080	743	210	671	166
4	322	27,330	306	109*	268	199
6	718	62,240	708	202	632	217
7	742	60,600	742	113*	674	194
Control	802	69,580	800	253	799	270
*Large variability between replicates, high value discarded						

Non-sink dissolution

[0401] A membrane flux assay was performed (see, e.g., Stewart et al., Mol. Pharm. (2017) 14:2032-2046) and non-sink dissolution data was collected for several of the SDD formulations described above and compared to the compound

of Formula (I) and several reference formulations, including a semi-solid lipidic formulation (Reference Formulation 1) and two self-emulsifying drug delivery system (SEDDS) formulations (Reference Formulations 2 and 3). The components of the Reference Formulations are shown in Table 5, below, and include, in addition to the compound of Formula (I), caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicrapolate/dicaprate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

Table 5. Reference formulations (capsules)

Formulation (mg/caps)	Ref. Formulation 1	Ref. Formulation 2	Ref. Formulation 3
Formula (I)	50.0	50.0	50.0
Labrafac® Lipophile	196.0	100.0	100.0
Labrafac® PG	102.0	-	-
Labrafil® M 1944 CS	-	135.0	46.0
Polysorbate 20	-	-	89.9
Kolliphor® RH 40	-	-	100.0
Kolliphor® HS 15	-	165.0	-
Gelucire® 44/14	95.0	-	-
TPGS	57.0	-	65.0
Transcutol®	-	50.0	50.0
Total	500.0	500.0	500.0

[0402] The assay measured the flux across simulated gastric and intestinal walls via UV spectroscopy (μDiss ProfilerTM, Pion Inc., Billerica, MA). Briefly, the assay was performed as follows. A vertical membrane flux cell consisting of a donor compartment and a receiver compartment, and separated by an Accurel PP 1E (55% porous, 100 μm thickness) polypropylene membrane (3M, Maplewood, MN) (FIG. 2), was impregnated with 50 μL of Pion GIT-0 lipid solution consisting of 20% w/w phospholipid dissolved into dodecane (Pion Inc., Billerica, MA) and attached to the receiver vessel. Both the donor and receiver compartments were agitated by magnetic stirring. The receiver compartment contained a plastic spacer and grating to elevate the stir bar above the membrane. Samples were introduced to the donor vessel by pre-weighing directly into the donor vessel and subsequently adding dissolution medium. Once the dissolution medium was added to the donor vessel, the receiver vessel was inserted into the donor vessel and suspended vertically 5 mm above the donor compartment by a plastic sleeve. For this assay, the simulated gastric (feed) media was 0.1 N HCl, pH 2 and included 200 μgA/mL of each SDD, and the simulated intestinal (receiver) media was 0.5 wt% SIF in PBS, pH 6.5 and included 100 μgA/mL of each SDD. The temperature for the assay was maintained at 44.5°C. UV probes (10 mm path length) connected to a Rainbow UV spectrometer (Pion Inc.) system were used to determine the apparent drug concentration in the receiver vessels. Samples of the donor compartment were removed with a disposable pipet for centrifugation followed by HPLC and DLS analysis of the supernatant. The results are shown in FIG. 3 and Table 6, below.

Table 6. Non-sink dissolution data

Sample	C_{maxGB} (μg/mL)	$C_{max90\ IB}$ (μg/mL)	$AUC_{4\text{-}90IB}$ (min*μg/mL)	C_{90} (μg/mL)	$Ultra_{90}$ (μg/mL)	C_{1200} (μg/ML)
Formula (I)	0	1	10	0	0	3
1	6	80	6,800	80	79	90
2	17	74	6,240	73	73	86
4	6	4	200	4	5	36
5	23	55	3,180	55	54	83
6	35	71	6,070	71	77	83

(continued)

Sample	C_{maxGB} (μg/mL)	$C_{max90\ IB}$ (μg/mL)	$AUC_{4\text{-}90IB}$ (min*μg/mL)	C_{90} (μg/mL)	$Ultra_{90}$ (μg/mL)	C_{1200} (μg/ML)
Ref. Formulation 1	205	109	9,050	109	-	-
Ref. Formulation 2	249	120	10,160	120	-	-
Ref. Formulation 3	218	107	9,100	107	-	-

[0403] The membrane flux of 1 mg/mL gastric barrier/intestinal barrier (GB/IB) 0.5 wt% SIF doses of the compound of Formula (I) and spray-dried dispersions (2) 25% compound of Formula (I)/75% HPMCAS-L and (4) 25% compound of Formula (I)/75% PVP/VA 64 were also determined. The results are shown in FIG. 4 as receiver concentration vs. time and flux vs. time (smoothed derivative of receiver concentration x volume/surface area).

Example 2: Characterization of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% of a polyvinyl pyrrolidone vinyl acetate (PVP/VA) polymer

SDD stability screening

[0404] Several of the SDDs described in Example 1 were tested for chemical and physical stability. Wet SDD stability studies were performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 7 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

Table 7. Wet SDD stability data

Retention time (min)			11.04	16.79	17.26	30.94	32.26			
Relative retention time			0.34	0.52	0.53	0.96	1.00			
	Storage temp	Timepoint						Total impurities	Potency (mgA/g)	Std Dev
Ref. Std.						0.37	99.63	0.37		
Formula (I)						0.26	99.74	0.26		
Sample 1		initial		0.13	0.16	0.25	99.46	0.54	100	1.3
	5°C	1 week		0.03	0.03	0.26	99.69	0.31	99	0.0
		2 weeks		0.12	0.16	0.28	99.45	0.55	99	0.5
	25°C	1 week		0.03	0.04	0.26	99.67	0.33	99	0.3
		2 weeks		0.21	0.27	0.28	99.24	0.76	98	0.8
Sample 2		initial	<LOQ	0.07	0.08	0.26	99.59	0.41	247	0.3
	5°C	1 week	<LOQ	0.02	0.03	0.26	99.70	0.30	248	1.3
		2 weeks	<LOQ	0.22	0.27	0.27	99.24	0.76	246	0.3
	25°C	1 week	<LOQ	0.02	0.03	0.26	99.69	0.31	248	0.9
		2 weeks	<LOQ	0.23	0.28	0.26	99.23	0.77	246	1.4

LOQ = limit of quantification

[0405] Solution stability studies were also performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 8 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

Table 8. SDD solution stability data

Retention time (min)			31.51	32.26	
Relative retention time			0.97	1.00	
	Storage temp	**Timepoint**			**Total impurities**
Ref. Std.			0.74	99.26	0.74
Formula (I)			0.26	99.74	0.26
Sample 1		initial	0.33	99.67	0.33
	5°C	2 weeks	0.29	99.71	0.29
	25°C	2 weeks	0.38	99.62	0.38
Sample 2		initial	0.25	99.75	0.25
	5°C	2 weeks	0.26	99.74	0.26
	25°C	2 weeks	0.33	99.67	0.33

[0406] Stability studies were also performed for the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64, with samples stored at both 5°C (closed with desiccant), 25°C (60% RH, closed with desiccant), and 30°C (65% RH, closed with desiccant). Measurements were taken after storage for 1 month, 2 months, 3 months, 6 months, and 12 months. No change in purity was observed after 12 months of storage. The results are shown in Table 9 below. The column with a retention time of 30.2 min correlates with the compound of Formula (I).

Table 9. SDD stability data

Retention time (min)			28.7	30.2		
Relative retention time			0.95	1.00		
	Storage conditions	**Timepoint**			**Total impurities**	**Potency (mgA/g)**
Crystalline Formula (I)			0.26	99.74	0.26	1001

(continued)

	Storage conditions	Timepoint			Total impurities	Potency (mgA/g)
Sample 4 (25% Formula (I):75% PVP/VA 64)		initial	0.26	99.74	0.26	245
	5°C (closed w/ desiccant)	1 month	0.25	99.75	0.25	247
		2 months	0.25	99.75	0.25	244
		3 months	0.26	99.74	0.26	246
		6 months	0.25	99.75	0.25	245
		12 months	0.25	99.75	0.25	248
	25°C/60% RH (closed with desiccant)	1 month	0.25	99.75	0.25	245
		2 months	0.25	99.75	0.25	247
		3 months	0.25	99.75	0.25	246
		6 months	0.25	99.75	0.25	242
		12 months	0.25	99.75	0.25	245
	30°C/65% RH (closed with desiccant)	1 month	0.25	99.75	0.25	249
		2 months	0.25	99.75	0.25	242
		3 months	0.25	99.75	0.25	246
		6 months	0.25	99.73	0.25	243
		12 months	0.25	99.75	0.25	242

[0407] While Samples 1 and 2 showed degradation after about 2 weeks of storage, the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64 (Sample 4) was found to be both chemically and physically stable and was further screened and characterized as described below.

25% Formula (I)/75% PVP/VA 64 SDD process parameter screening manufacture Round 1

[0408] The 25% Formula (I)/75% PVP/VA 64 SDD was prepared on a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The manufacturing summary is shown in Table 10, below.

Table 10. Manufacturing summary of process parameters

Formulation	25% Formula (I):75% PVP/VA 64
Solids Loading (wt%)	10
Batch Size (kg)	1.5
Solvent	Acetone
Atomizer (Pressure Swirl)	SK 80-16
Solution Flow-rate (g/min)	160
Atomization Pressure (psig)	480
Inlet Temperature (°C)	94
Outlet Temperature (°C)	40
Calculated Outlet Acetone Saturation (% RS)	6.2
Dry Yield (%)	73

[0409] Based on the 73% yield observed in the first round of process screening, three sprays were performed to investigate the effect of reducing solution throughput and outlet temperature on product yield. All sprays were conducted

at a reduced flow-rate of 110 g/min. The outlet temperature was varied at 40°C (Lot A), 35°C (Lot B), and 30°C (Lot C). The outlet temperature was decreased while maintaining a low outlet acetone saturation to increase the difference between the chamber outlet temperature and the wet SDD T_g, thus improving product yields. The spray dryer chamber and outlet ductwork were cleaned between all manufactures. A manufacturing summary is shown in Table 11.

Table 11. Manufacturing summary for process parameters (1.5 kg batch size)

Description	Low Flow-Rate	Low Flow-Rate/Low Outlet Temperature	Low Flow-Rate/Lower Outlet Temperature
Lot	A	B	C
Solids Loading (wt%)	10	10	10
Batch Size (kg)	1.5	1.5	1.5
Solvent	Acetone	Acetone	Acetone
Atomizer (Pressure Swirl)	Steinen A75	Steinen A75	Steinen A75
Solution Flow-Rate (g/min)	110	110	110
Atomization Pressure (psig)	275	285	285
Inlet Temperature (°C)	79	72	63
Outlet Temperature (°C)	40	35	30
Calculated Outlet Acetone Saturation (% RS)	4.3	5.2	6.4
Calculated wet SDD T_g (°C)	72	71	69
Dry Yield (%)	55	80	43

[0410] The conditions used for Lot B were found to give the highest yield. One additional spray was then performed at the same processing conditions as Lot B while increasing the batch size from 1.5 kg to 3.5 kg to evaluate process consistency and to determine if product yield would continue to improve over time. The averaged process conditions for this lot are shown in Table 12.

Table 12. Manufacturing summary of process parameters (1.5 kg and 3.5 kg batch sizes)

Description	Low Flow-Rate/Low Outlet Temperature	Low Flow-Rate/Low Outlet Temperature/Larger Batch Size
Lot	B	D
Solids Loading (wt%)	10	10
Batch Size (kg)	1.5	3.5
Solvent	Acetone	Acetone
Atomizer (Pressure Swirl)	Steinen A75	Steinen A75
Solution Flow-Rate (g/min)	110	110
Atomization Pressure (psig)	285	285
Inlet Temperature (°C)	72	72
Outlet Temperature (°C)	35	35
Calculated Outlet Acetone Saturation (% RS)	5.2	5.2
Calculated wet SDD T_g (°C)	71	71
Dry Yield (%)	80	84

[0411] The 1.5 kg batch size (Lot D) was sprayed with an 84% yield compared to the 80% yield of the 3.5 kg batch (Lot B).

25% Formula (I)/75% PVP/VA 64 SDD process parameter screening characterisation

[0412] The 25% Formula (I)/75% PVP/VA 64 SDDs manufactured to evaluate processing parameters were characterized for powder properties, performance, and physical and chemical properties. Testing included particle size distribution by Malvern, determination of bulk and tapped density, microcentrifuge dissolution, modulated differential scanning calorimetry (mDSC), powder x-ray diffraction (PXRD), scanning electron microscope (SEM), and assay and related substances. The results did not show any significant differences between the lots.

[0413] The particle size distribution (PSD) and tabulated powder properties data of the 25% Formula (I)/75% PVP/VA 64 SDDs are shown in Table 13. All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have a very similar PSD with a D_{50} of approximately 16 μm. All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have low bulk and tapped densities.

Table 13. Powder properties of process parameter screening PVP/VA-64 SDDs

Sample	Lot	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	$D_{(3,2)}$ (μm)	$D_{(4,3)}$ (μm)	Span	Bulk density (g/mL)	Tapped density (g/mL)
40°C Outlet	A	5	15	34	8	17	1.93	0.12	0.25
35°C Outlet	B	5	16	36	9	19	1.97	0.11	0.23
30°C Outlet	C	5	15	32	7	17	1.86	0.12	0.27
35°C Outlet, 3.5 kg batch	D	5	16	38	9	19	1.98	0.12	0.24

[0414] The 3.5 kg batch size lot was analyzed and compared to process parameter Lot A. Dissolution performance was similar for each of these lots. Dissolution was rapid to C_{max} and high free drug was sustained through 90 minutes. These data are shown in Table 14.

Table 14. Dissolution performance of Lot A (1.5 kg batch size) vs. Lot D (3.5 kg batch size)

Sample	C_{max90} (μg/mL)	AUC_{90} (min*μg/mL)	C_{90} (μg/mL)	$Ultra_{90}$ (μg/mL)
Lot A	447	37,740	437	319
Lot D	437	37,120	433	301

[0415] The 25% Formula (I)/75% PVP/VA 64 SDDs were also evaluated by DSC, PXRD, and SEM. The DSC thermograms showed a single T_g at 84°C, indicating homogeneous dispersions. PXRD diffractograms showed no evidence of crystals in the SDDs. SEM images showed inflated sphere morphology with some broken particles and some very small particles.

[0416] Additional testing on Lot B was carried out, which included assessing the chemical/physical stability of both spray solution and SDD prior to secondary drying (wet SDD) to establish maximum in-process hold times. Residual acetone concentration as a function of secondary drying time in a convection tray dryer was also evaluated to nominate tray drying conditions to ensure the SDD is dried below International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for acetone.

[0417] Residual acetone content as a function of drying time was assessed by drying wet SDD in a tray dryer and collecting samples over a 24-hour period. Wet SDD was dried at 40°C/15% relative humidity (RH) and was observed to dry below ICH acetone guidelines (0.5 wt%, 5000 ppm) by four hours.

[0418] Spray solution hold time was determined by making up a representative solution that contained 2.5 wt% compound of Formula (I), 7.5 wt% PVP/VA 64, and 90 wt% acetone. These solutions were analyzed initially for related substances. and then aged at 5°C and 25°C. Aliquots were taken and analyzed for related substances periodically for 14 days. Results showed no change in impurity profile at either condition through 14 days.

[0419] Wet SDD was analyzed for impurities after storage at 5°C and 25°C for 1 and 2 weeks and compared to the impurity profiles of the ingoing compound of Formula (I) and the SDD that was secondarily dried immediately after spray drying. The impurity profiles were similar to that of the initial dried sample and the ingoing compound of Formula (I) through 2 weeks of storage.

[0420] The wet SDD stability samples were characterized for physical stability by DSC, PXRD, and SEM. DSC thermograms showed a single T_g at 81°C, indicative of a homogeneous dispersion with no phase separation. The PXRD diffractograms did not show any evidence of crystals after storage at either condition. SEM images showed a typical morphology of mostly inflated spheres with some broken particles.

Example 3: Preparation of a 1000 g batch of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64

[0421] A 1000 g batch of the spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64 was prepared as described in Example 2 for the 1.5 kg and 3.5 kg batches. Briefly, acetone (90% (w/w) of the total mixture) was added to the mixing tank followed by the addition of 250.0 g of the compound of Formula (I) (2.5% (w/w) of the total mixture). The mixture was mixed for 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids. The PVP/VA 64 (750.0 g, 7.5% (w/w) of the total mixture) was then added and the mixture was stirred for an additional 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids.

[0422] The solution was pumped and atomized in a drying chamber. The spray-dried dispersions were prepared in a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The inlet temperature was set at 75°C (varied between 60°C-90°C). The outlet temperature was set at 35°C (varied between 32°C-38°C). The feed pressure was set at 280 psig (varied between 230-330 psig). The feed rate was set at 110 g/min (varied between 90-130 g/min). The spray dried powder was then dried in a convection tray dryer with a bed depth of ≤ 2.5 cm at 40°C (±5°C) and 15% relative humidity (±10%) for 24 hours under amber light. The residual acetone after drying was < 0.5 wt% (5000 ppm). FIG. 5 is a flow diagram of the manufacturing process.

Example 4: Preparation of spray-dried dispersion formulations of the compound of Formula (I) for clinical use

[0423] The spray-dried dispersion (SDD) containing 25% compound of Formula (I) and 75% PVP/VA 64, prepared as described above, was formulated as a suspension or a capsule for clinical use.

Suspension preparation

[0424] A suspension that contained 50 mg of the SDD was prepared as follows. A 30 mL amber dosing bottle was tared on a balance. 200.0 mg SDD (50 mgA) ± 5% was then weighed into the dosing bottle. Using a 10-mL syringe, 5.0 mL of water (purified, USP) was added to the dosing bottle and the bottle was capped and shaken moderately for 30 seconds. The SDD suspension was stored in an amber vial at 2-8°C prior to use, and dosed within 24 hours of preparation.

Capsule preparation

[0425] An empty hard gelatin capsule, size 0 (Capsugel, Morristown, NJ), was placed on a balance and the weight was recorded. 200.0 mg SDD (50 mgA) ± 5% was then weighed onto weigh paper or an equivalent. All contents were transferred to the capsule using a ProFunnel device for Size 0 capsules. The filled capsule was placed on the balance and the weight was recorded. The weight of the empty capsule was subtracted from the filled weight, ensuring that the weight of the SDD within the capsule was 200.0 mg SDD ± 5%, or from 190.0 mg to 210.0 mg. The capsule was securely closed with the head, assuring it clicked into place. The capsules were stored in an amber vial at 2-8°C prior to use, and were dosed within 24 hours of preparation.

Example 5: Dog relative bioavailability and food effect study

[0426] Four spray-dried dispersions (SDDs), formulated in 0.25% methylcellulose as a suspension, were prepared: (1) 25% compound of Formula (I)/75% HPMCAS-L; (2) 10% compound of Formula (I)/90% HPMCAS-L; (3) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100); and (4) 25% compound of Formula (I)/75% PVP/VA 64. A clinical capsule formulation was prepared as a reference formulation (Reference Formulation 1 from Table 5, above).

[0427] Dogs (two cohorts, six dogs in each) were dosed in six sessions, including fasted state sessions and fed sessions (high fat diet), with 50 mg dose of one of the SDDs or reference per dog in a 3-way crossover design. Each session had a 3-day washout in between. All formulations were well tolerated. The study design is shown in Table 15, below.

Table 15. Study design

Cohort 1	Session 1 (Fasted)	Session 2 (Fed)	Session 3 (Fasted)	Session 4 (Fed)	Session 5 (Fasted)	Session 6 (Fed)
Dog 1001	Reference	Reference	SDD 1	SDD 1	SDD 2	SDD 2
Dog 1002	Reference	Reference	SDD 1	SDD 1	SDD 2	SDD 2
Dog 2001	SDD 1	SDD 1	SDD 2	SDD 2	Reference	Reference
Dog 2002	SDD 1	SDD 1	SDD 2	SDD 2	Reference	Reference
Dog 3001	SDD 2	SDD 2	Reference	Reference	SDD 1	SDD 1
Dog 3002	SDD 2	SDD 2	Reference	Reference	SDD 1	SDD 1
Cohort 2	**Session 1 (Fasted)**	**Session 2 (Fed)**	**Session 3 (Fasted)**	**Session 4 (Fed)**	**Session 5 (Fasted)**	**Session 6 (Fed)**
Dog 4001	Reference	Reference	SDD 3	SDD 3	SDD 4	SDD 4
Dog 4002	Reference	Reference	SDD 3	SDD 3	SDD 4	SDD 4
Dog 5001	SDD 3	SDD 3	SDD 4	SDD 4	Reference	Reference
Dog 5002	SDD 3	SDD 3	SDD 4	SDD 4	Reference	Reference
Dog 6001	SDD 4	SDD 4	Reference	Reference	SDD 3	SDD 3
Dog 6002	SDD 4	SDD 4	Reference	Reference	SDD 3	SDD 3

[0428] The area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), the apparent terminal half-life ($t_{½}$), and the time to achieve maximum plasma concentration (t_{max}) were calculated. Results are shown in Table 16, below, and in FIGS. 6A and 6B.

Table 16. Pharmacokinetic results

Cohort	Form	Fasted [Mean (%CV)]		Fed [Mean (%CV)]		Ratio of Fed/Fasted [Mean (%CV)]	
		C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max}	AUC
1 (N=4) *	Ref	652 (55.5)	5170 (69.4)	3650 (19.5)	20100 (22)	6.9 (48)	5.5 (69.2)
	SDD 1	524 (62.7)	2870 (62.9)	5760 (25.6)	22800 (14.6)	15.4 (66.9)	8 (89.6)
	SDD 2	487 (45.7)	3950 (26.4)	4220 (27.4)	18100 (26.8)	16.5 (40.7)	6.3 (34.6)

(continued)

Cohort	Form	Fasted [Mean (%CV)]		Fed [Mean (%CV)]		Ratio of Fed/Fasted [Mean (%CV)]	
		C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max}	AUC
2 (N=6)	Ref	854 (40.2)	5520 (59.1)	4220 (27.4)	18100 (26.8)	5.8 (46.5)	4.1 (49.2)
	SDD 3	453 (28.3)	2830 (21.6)	5320 (13.5)	23800 (26.1)	12.6 (30.3)	8.6 (22.2)
	SDD 4	353 (20.1)	1840 (21.9)	3060 (20.7)	17200 (20.5)	8.9 (29.3)	8.4 (46.1)
*Animals 2001 and 2002 were excluded from summary statistics due to emesis in all 3 fed sessions, which resulted in notably lower exposures							

[0429] The results showed that $t_{1/2}$ and t_{max} were similar among the formulations, and comparable between the fed and fasted states. Under the fed state with a high fat meal, exposures increased and inter-animal variability decreased. The food effect was more notable with the spray-dried dispersion formulations, especially for peak exposure (C_{max}).

[0430] Compared to the reference form, SDD 4 (25% compound of Formula (I)/75% PVP/VA 64) appeared to have lower inter-animal variability, lower exposures under the fasted state, and slightly lower C_{max} but relatively comparable AUC in the fed state.

Example 6: Phase 1 study to evaluate the pharmacokinetics, effect of food on pharmacokinetics, and safety of the compound of Formula (I) in healthy adult subjects

[0431] The present study was designed to evaluate the pharmacokinetics (PK) of the compound of Formula (I) as well as to evaluate the effect of a fed condition on the PK of the compound of Formula (I). The 50 mg dose was chosen for this study because it was within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study were: to evaluate the PK of the compound of Formula (I) 50 mg in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg.

Study Design

[0432] This was a Phase 1, open-label, randomized, 2-period crossover study of the PK and the effect of food on the PK of the compound of Formula (I) in 16 healthy male and female adult subjects, 18 to 55 years of age.

[0433] After providing informed consent, subjects were screened for eligibility to participate in the study up to 28 days prior to Day 1 of treatment period 1. Eligible subjects were admitted to the clinical unit on Day -1 and randomized to 1 of the 2 treatment sequences (16 subjects [8 males and 8 females]; see Table 17, below). On Day 1 of each treatment period, subjects received a single dose of the compound of Formula (I) 50 mg under fasted or fed conditions. There were 21 days between doses.

Table 17. Treatment sequences

Treatment sequence	Treatment period I	Treatment period 2
1	Formula (I) - fasted	Formula (I) - fed
2	Formula (I) - fed	Formula (I) - fasted

[0434] Subjects were required to fast for at least 4 hours before check-in on Day -1. In the fasted condition, subjects were required to fast overnight for at least 10 hours prior to dosing and continued to fast for an additional 4 hours after dosing. In the fed condition, subjects were required to fast overnight for at least 10 hours and then ingest a liquid dietary supplement with study drug (liquid dietary supplement was consumed within 30 minutes) and not consume any other food for 4 hours after dosing. During both treatment periods, water was not permitted for 1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing. Vanilla-flavored Ensure Plus® was used as the liquid dietary supplement.

[0435] On Day 1 of each treatment period, subjects were dosed with the compound of Formula (I) 50 mg. Blood samples were collected for PK analysis over a period of 36 hours during the in-house stay. Subjects remained in the

unit on the day of dosing and were discharged on Day 2 of each treatment period, following completion of all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects returned to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1, subjects arrived at the site and had Day 21 assessments completed in the evening, and they stayed overnight at the site and began Day 1 of treatment period 2 the following day. A final follow-up study visit was conducted on Day 22 of treatment period 2 (21 ± 2 days after treatment period 2 dosing) or upon early termination.

[0436] During each treatment period, blood samples for PK analysis were collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

[0437] Safety assessments (including clinical safety laboratory tests, vital sign measurements, physical examinations, and electrocardiograms (ECGs)) were conducted at scheduled times throughout the study. Adverse events (AEs) and the use of concomitant medications were monitored throughout the study. FIG. 7 illustrates the study design.

*Test **product,** dose **and mode of administration***

[0438] The compound of Formula (I) was supplied as an encapsulated, lipidic semi-solid containing 50 mg of the compound of Formula (I) as free base equivalent for oral administration. Subjects swallowed a single capsule with approximately 240 mL of water in the fasted condition. Subjects swallowed a single capsule with a liquid dietary supplement (Ensure Plus® [237 mL container]) with up to an additional 120 mL of water in the fed condition.

Duration of treatment

[0439] The duration of study participation for each adult subject was approximately 10 weeks, including up to 28 days of screening, 2 days of dosing separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 2.

Criteria for Evaluation

Pharmacokinetics

[0440] The following plasma PK parameters were calculated for the compound of Formula (I):

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours ($AUC_{0\text{-}24}$)
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)
- Molar AUC ratio of the hydroxylated metabolite of the compound of Formula (I) to the parent drug the compound of Formula (I)

[0441] The following plasma PK parameters were calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

Safety

[0442] Safety was monitored throughout the study and included the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

Statistical Methods

[0443] Pharmacokinetic parameters were calculated using noncompartmental methods and summarized by condition (fed or fasted) using descriptive statistics. Two-sided 90% confidence intervals were calculated for the ratio under the fed condition vs. under the fasted condition for $AUC_{0-\infty}$, $AUC_{0\text{-tlast}}$, and C_{max} for the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I).

[0444] Safety data were summarized with descriptive statistics.

Pharmacokinetics

***Pharmacokinetic** assessments*

[0445] PK plasma samples for analyses of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were collected at the following times during each treatment period:

- Day 1: within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5,6, 7, 8, 9, 10, 12, and 16 hours after dosing.
- Day 2: approximately 24 and 36 hours after dosing.
- Day 8: approximately 168 hours after dosing.
- Day 15: approximately 336 hours after dosing.
- Approximately 504 hours after dosing (for treatment period 1, this sample was collected in the morning at least 30 minutes prior to the predose sample on Day 1 of treatment period 2).
- Final study visit for subjects who terminate early: 1 sample.

[0446] Blood samples on Day 1 were collected within 5 minutes of the scheduled sampling times (other than the predose sample). Blood samples on Days 2, 8, and 15 were collected within 2 hours of the scheduled sampling time. The 504 hour blood sample for treatment period 2 had a ± 2-day window. A PK sample was to be collected from subjects who terminated early. The exact time of sampling in hour and minutes was recorded.

Bioanalytical methods

[0447] Plasma samples were analyzed for the compound of Formula (I) and for its hydroxylated metabolite by in Ventiv Health, Princeton NJ, in compliance with Good Laboratory Practice (GLP) and relevant Standard Operating Procedures (SOPs).

[0448] The concentrations of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were quantified in plasma samples according to validated methods using tandem mass spectrometry in positive ion mode. This method was validated for the analysis of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) in 25.0 μL dipotassium ethylenediaminetetraacetic acid (K_2-EDTA) human plasma samples over concentration ranges of 5.00 to 2500 ng/mL and 0.500 and 250 ng/mL, respectively. All analytical results were within acceptable limits. Incurred sample reanalysis (ISR) was successfully conducted in this study for both analytes.

Results

Pharmacokinetic results

[0449] Eight male and eight female subjects were enrolled. The mean age was 37.1 years (range, 21 to 55 years). The majority of subjects were White (93.8%) and of Hispanic ethnicity (81.3%). The mean weight at screening was 160.28 lbs (range, 102.0 to 222.2 lbs) and mean BMI was 25.50 kg/m^2 (range, 20.7 to 30.5 kg/m^2). The randomization was well balanced with respect to demographics and baseline characteristics.

[0450] All 16 subjects were included in the safety analysis set. No subjects were excluded from the safety analysis set and no subject had his or her PK data excluded from analysis.

[0451] The mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions are presented in FIGS. 8A and 8B, respectively. The compound of Formula (I) was slowly absorbed after oral administration in both fasted and fed conditions. Mean plasma concentrations were lower in the fasted than in the fed condition.

[0452] PK parameters for the compound of Formula (I) after treatment with the compound of Formula (I) under fasted and fed conditions are summarized in Table 18, below, where AUC_{0-24}=area under the plasma concentration vs. time curve from 0 to 24 hours, AUCo-t_{bu}t=AUC from 0 hours to last measurable concentration, $AUC_{0-\infty}$=AUC from 0 hours

extrapolated to infinity, CL/F=apparent systemic clearance after oral administration, CV=coefficient of variation, C_{max}=maximum plasma concentration, CV(%)=coefficient of variation, max=maximum, min=minimum, MRT=apparent mean residence time, PK=pharmacokinetic, SD=standard deviation, $t_{½}$=apparent terminal half-life, T_{lag}=delay time between time of dosing and time of appearance of measurable test article, t_{max}=time to maximum plasma concentration, VZ/F=apparent volume of distribution during the terminal phase after oral administration.

[0453] The PK data for t_{max}, T_{lag}, $t_{½}$, MRT, and Vz/F were rounded to 2 significant figures and all other parameters (AUC_{0-24}, $AUC_{0-tlast}$, $AUC_{0-\infty}$, C_{max}, and CL/F) were rounded to 3 significant figures. The last significant figure was rounded up if the digit to the right of it was ≥5, and was rounded down if the digit to the right of it was ≤4.

Table 18. Summary of Formula (I) PK parameters (safety analysis set)

Parameter Statistic	Fasted Formula (I) (50 mg) (N=16)	Fed Formula (I) (50 mg) (N=15)
AUC_{0-24} (ng×hr/mL) Mean (SD) Geometric CV%	5590 (2230) 32.7	9950 (2540) 26.2
$AUC_{0-tlast}$ (ng×hr/mL) Mean (SD) Geometric CV%	8020 (5110) 53.6	16200 (5450) 39.7
$AUC_{0-\infty}$ (ng×hr/mL) Mean (SD) Geometric CV%	9440 (2990) [n=7] 39.7	17800 (4990) [n=12] 28.1
C_{max} (ng/mL) Mean (SD) Geometric CV%	731 (301) 36.6	1550 (392) 24.2
t_{max} (hours) Median (min, max)	6.0 (3.0, 6.0)	5.0 (3.0, 6.0)
T_{lag} (hours) Mean (SD)	0.63 (0.22)	0.94 (0.37)
$t_{½}$ (hours) Mean (SD) Geometric CV%	33 (17) [n=7] 99	42 (6.8) [n=12] 15
MRT (hours) Mean (SD) Geometric CV%	28 (11) [n=7] 49	30 (5.0) [n=12] 16
CL/F (L/hr) Mean (SD) Geometric CV%	6.0 (2.7) [n=7] 40	3.0 (0.82) [n=12] 28
VZ/F (L) Mean (SD) Geometric CV%	240 (120) [n=7] 67	180 (57) [n=12] 30

[0454] As seen in Table 18, above, administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean C_{max} of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{½}$ (42 vs. 33 hours), a slightly shorter median t_{max} (5.0 vs. 6.0 hours), and a higher mean $AUC_{0-\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ngxhr/mL). The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0-tlast}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% confidence interval (CI) bounds for both C_{max} (187.4% and 255.1%, respectively) and $AUC_{0-tlast}$ (182.9% and 253.1%, respectively) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure.

[0455] Frequency distribution of T_{lag} and t_{max} values are presented in Table 19 and Table 20, respectively. Spaghetti plots for the compound of Formula (I) $AUC_{0-tlast}$, $AUC_{0-\infty}$ and C_{max} are shown in FIGS. 9A, 9B, and 9C, respectively.

Table 19. Frequency distribution of plasma Formula (I) T_{lag} values by treatment (safety analysis set)

T_{lag} (hr)	Statistic	Fasted (Formula (I) 50 mg) (N=16)	Fed (Formula (I) 50 mg) (N=15)
0.50	n (%)	11 (68.8%)	3 (20.0%)
0.53	n (%)	1 (6.3%)	0 (0.0%)
0.55	n (%)	0 (0.0%)	1 (6.7%)
1.00	n (%)	4 (25.0%)	8 (53.3%)
1.02	n (%)	0 (0.0%)	1 (6.7%)
1.03	n (%)	0 (0.0%)	1 (6.7%)
2.00	n (%)	0 (0.0%)	1 (6.7%)

Table 20. Frequency distribution of plasma Formula (I) T_{max} values by treatment (safety analysis set)

T_{max} (hr)	Statistic	Fasted (Formula (I) 50 mg) (N=16)	Fed (Formula (I) 50 mg) (N=15)
3.00	n (%)	1 (6.3%)	2 (13.3%)
4.02	n (%)	1 (6.3%)	0 (0.0%)
5.00	n (%)	4 (25.0%)	8 (53.3%)
5.03	n (%)	0 (0.0%)	1 (6.7%)
5.05	n (%)	0 (0.0%)	1 (6.7%)
6.00	n (%)	10 (62.5%)	2 (13.3%)
6.02	n (%)	0 (0.0%)	1 (6.7%)

[0456] The compound of Formula (I) was slowly absorbed after oral administration in the fasted and fed conditions. In the fasted condition, the mean compound of Formula (I) C_{max} was approximately 53% lower than in the fed condition (731 vs. 1550 ng/mL). Due to a prolonged elimination phase, $t_{½}$ values and therefore, $AUC_{0-\infty}$ values could not be determined for some the compound of Formula (I) concentration-time profiles. Mean $AUC_{0-\infty}$ was approximately 47% lower in the fasted condition than in the fed condition (9440 vs. 17800 ngxhr/mL) for those subjects for whom $AUC_{0-\infty}$ could be determined. Mean $AUC_{0-tlast}$ was approximately 50% lower in the fasted condition than in the fed condition (8020 vs. 16200 ngxhr/mL). Median t_{max} was slightly longer in the fasted condition than in the fed condition (6.0 vs. 5.0 hours) and mean $t_{½}$ was shorter in the fasted condition than in the fed condition (33 vs. 42 hours) for those subjects for whom a $t_{½}$ could be determined. Variability in the compound of Formula (I) PK (geometric CV%) for AUC, C_{max}, $t_{½}$, and MRT was lower in the fed condition compared with the fasted condition.

[0457] The geometric mean ratios and associated 90% CIs for $AUC_{0-tlast}$ and C_{max} for the compound of Formula (I) after treatment with the compound of Formula (I) for the fed vs. fasted condition are provided in Table 21, below, where $AUC_{0-tlast}$= AUC from 0 hours to last measurable concentration, C_{max}=maximum plasma concentration, and PK=pharmacokinetic.

Table 21. Formula (I) geometric mean ratios for PK exposure parameters under fed vs. fasted conditions (safety analysis set)

Parameter	Ratio[a] (%) (Fed vs. Fasted Condition)	90% Confidence Interval[b]
$AUC_{0-tlast}$ (ngxhr/mL)	215.2	182.9,253.1
C_{max} (ng/mL)	218.6	187.4,255.1
[a] Ratio of geometric least-squares means was based on a mixed model using log-transformed (base 10) data. [b] The 90% confidence interval for geometric mean ratio was based on least-squares means using log-transformed (base 10) data.		

[0458] The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0-tlast}$ for the fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both C_{max} (187.4%, 255.1%) and $AUC_{0-tlast}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Due to the missing $AUC_{0-\infty}$ values, the food effect on overall exposure was not assessed using $AUC_{0-\infty}$ values.

Conclusion

[0459] Administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean C_{max} of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{½}$ (42 vs. 33 hours), a slightly shorter median t_{max} (5.0 vs. 6.0 hours), and a higher mean $AUC_{0-\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ngxhr/mL). The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0-tlast}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approx-

imately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both C_{max} (187.4%, 255.1%) and $AUC_{0\text{-}tlast}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Similar results were observed with the hydroxylated metabolite of the compound of Formula (I). Overall, these results indicate that the compound of Formula (I) 50 mg was well tolerated in healthy subjects when administered under fasted or fed conditions and that the total AUC and C_{max} were increased when the compound of Formula (I) was taken with food.

Example 7: Phase 1 study to evaluate the relative bioavailability, effect of food on pharmacokinetics, and safety of formulations of the compound of Formula (I) in healthy adult subjects

[0460] A Phase 1 study to compare the relative bioavailability of a 50 mg dose of different formulations of the compound of Formula (I) as well as to evaluate the effect of fasting and fed conditions on the pharmacokinetics (PK) of the compound of Formula (I) was designed. The 50 mg dose was chosen for this study because it is within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study are: to evaluate the PK and compare the relative bioavailability of the compound of Formula (I) 50 mg formulations in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg formulations; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg formulations.

Study Design

[0461] This is a Phase 1, open-label, randomized, three-period crossover study of the relative bioavailability and the effect of food on the PK of the compound of Formula (I) 50 mg in healthy adult subjects. During treatment period 1 and treatment period 2, subjects will receive a single dose of the compound of Formula (I) 50 mg administered as an encapsulated, lipidic semi-solid (reference) and 1 of 2 different spray-dried dispersion (SDD) test formulations (suspension or capsule) under fed conditions, and during treatment period, three subjects will receive the same SDD test formulation under fasted conditions.

[0462] A total of 36 healthy adult subjects will be randomized to 1 of 4 treatment sequences (9 subjects per sequence; approximately equal distribution of males and females per sequence; see Table 22, below). There will be 21 days between each dose.

Table 22. Treatment sequences

Treatment sequence	Treatment period 1 (Fed)	Treatment period 2 (Fed)	Treatment period 3 (Fasted)
1	Reference	SDD suspension	SDD suspension
2	SDD suspension	Reference	SDD suspension
3	Reference	SDD capsule	SDD capsule
4	SDD capsule	Reference	SDD capsule

[0463] After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days prior to Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1, and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During treatment periods 1 and 2, subjects will fast overnight for at least 10 hours and then ingest a liquid dietary supplement (vanilla-flavored Ensure Plus®, 237 mL container) with the study drug and not consume any other food for 4 hours after dosing. During treatment period 3, subjects will fast overnight for at least 10 hours prior to dosing and continue to fast for an additional 4 hours after dosing. During all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing.

[0464] On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 50 mg and have blood samples collected for PK analysis. Subjects will complete a taste satisfaction questionnaire after study drug ingestion on Day 1 of treatment period 3 (only for subjects who receive the SDD suspension under the fasted condition). Subjects will remain in the unit on the day of dosing and will be discharged on Day 2 of each treatment period, following completion of all required procedures, including collection of the 36-hour PK sample. On the mornings of Days 8 and 15 of each treatment period, subjects will return to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1 and treatment period 2, subjects will arrive at the site and have Day 21 assessments completed, and they will stay overnight at the site and begin Day 1 of treatment period 2 or treatment period 3 the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 3 (21 $\pm$ 2 days after treatment period 3 dosing) or upon early termination.

[0465] Blood samples for PK analysis and safety assessments will be collected/conducted at scheduled times throughout the study. The study design schematic is shown in FIG. 10.

Duration of treatment

[0466] The expected duration of study participation for each healthy adult subject will be approximately 13 weeks, including up to 28 days of screening, 3 doses each separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 3.

Test ***product,*** *dose,* ***and mode*** *of* ***administration***

[0467] The compound of Formula (I) will be supplied as two different test formulations for oral administration: as powder in bottles for constitution into a suspension (20 mL) and as powder-filled capsules. The compound of Formula (I) test formulations will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow the study drug with a liquid dietary supplement (Ensure Plus® [237 mL container]) with an additional 100 mL of water (SDD capsule formulation) or with an additional 80 mL of water (SDD suspension formulation) during treatment period 1 or 2. Subjects must swallow the study drug with 330 mL of water (SDD capsule formulation) or 310 mL of water (SDD suspension formulation) during treatment period 3.

Reference therapy, dose, and mode of administration

[0468] The compound of Formula (I) reference formulation (encapsulated, lipidic semi-solid formulation) will be supplied as capsules for oral administration. The compound of Formula (I) reference capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow a single capsule with a liquid dietary supplement (Ensure Plus [237 mL container]) with an additional 100 mL of water during treatment period 1 or 2.

Criteria for Evaluation

Pharmacokinetics

[0469] Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

[0470] The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to the time of the last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration curve extrapolated from 0 hours to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)
- Molar AUC ratio of primary metabolite(s) to the parent drug the compound of Formula (I)

[0471] The following plasma PK parameters will be calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

Other assessment

[0472] A taste satisfaction questionnaire will be administered.

Safety ***assessments***

[0473] Safety will be monitored throughout the study and will include the following assessments:

- AEs
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiogram (ECG)

Statistical methods

[0474] Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by formulation using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test formulation (SDD suspension and SDD capsule) vs. the reference formulation for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and metabolites under fed conditions. Further, two-sided 90% confidence intervals will be calculated for the ratio of each test formulation under fasted conditions vs. under fed conditions for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and metabolites.

[0475] Safety and taste satisfaction questionnaire data will be summarized with descriptive statistics.

Results

Pharmacokinetic results

[0476] Pharmacokinetic results are shown in Tables 23-26, below.

Table 23: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set - SDD Suspension Group)

			Compound of Formula (I) Plasma Concentration	
Parameter (units) Statistic		**Reference Capsule (Fed) (N=18)**	**SDD Suspension (Fed) (N=18)**	**SDD Suspension (Fasted) (N=18)**
$AUC_{0-tlast}$ (ng×hr/mL)				
	Mean (SD)	16600 (7880)	5980 (3960)	737 (417)
	Geom CV(%)	46.8	72.8	68.7
$AUC_{0-\infty}$ (ng×hr/mL)				
	Mean	17400 (8010)	6500 (4180)	893 (480)
	Geom CV(%)	45.4	71.7	60.1
C_{max} (ng/mL)				
	Mean (SD)	1480 (506)	672 (323)	72.3 (44.9)
	Geom CV(%)	32.1	57.9	57.5
t_{max} (hr)				
	Median (min, max)	5.0 (3.0, 6.0)	5.0 (5.0, 10)	7.0 (5.0, 12)
T_{lag} (hr)				
	Mean (SD)	1.0 (0.31)	0.85 (0.29)	1.2 (0.65)
$t_{½}$ (hr)				
	Mean (SD)	50 (20)	19 (6.1)	9.0 (0.46)
	Geom CV(%)	140	93	23
MRT (hr)				
	Mean (SD)	36 (43)	23 (24)	17 (2.9)
	Geom CV(%)	84	62	18
CL/F (L/hr)				

(continued)

		Compound of Formula (I) Plasma Concentration	
Parameter (units) Statistic	**Reference Capsule (Fed) (N=18)**	**SDD Suspension (Fed) (N=18)**	**SDD Suspension (Fasted) (N=18)**
Mean (SD)	3.4 (1.4)	11 (8.0)	80 (54)
Geom CV(%)	45	72	63
Vz/F (L)			
Mean (SD)	180 (260)	210 (140)	970 (560)
Geom CV(%)	93	77	53
T_{last} (hr)			
Mean (SD)	170 (140)	77 (110)	31 (7.6)
Geom CV(%)	120	92	30

Table 24: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set - SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
$AUC_{0\text{-tlast}}$ (ngxhr/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	32.2	(26.4%, 39.4%)
$AUC_{0\text{-}\infty}$	SDD Suspension (Fed) vs. Reference Capsule (Fed)	33.5	(27.7%, 40.6%)
C_{max} (ng/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	42.2	(34.8%, 51.2%)
$AUC_{0\text{-tlast}}$ (ngxhr/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.4	(3.4%, 5.7%)
$AUC_{0\text{-}\infty}$	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	5.0	(3.8%, 6.5%)
C_{max} (ng/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.5	(3.8%, 5.4%)

Table 25: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set - SDD Capsule Group)

		Compound of Formula (I) Plasma Concentration	
Parameter (units) Statistic	**Reference Capsule (Fed) (N=18)**	**SDD Capsule (Fed) (N=18)**	**SDD Capsule (Fasted) (N=17)**
$AUC_{0\text{-tlast}}$ (ng×hr/mL)			
Mean (SD)	19500 (7960)	9470 (4670)	1840 (1650)
Geom CV (%)	50.4	48.0	78.7
$AUC_{0\text{-}\infty}$ (ng×hr/mL)			
Mean	20100 (7850)	10000 (4610)	2120 (1830)
Geom CV (%)	47.1	44.9	73.7

(continued)

		Compound of Formula (I) Plasma Concentration		
Parameter (units) Statistic		**Reference Capsule (Fed) (N=18)**	**SDD Capsule (Fed) (N=18)**	**SDD Capsule (Fasted) (N=17)**
C_{max} (ng/mL)				
	Mean (SD)	1770 (494)	1110 (449)	143 (110)
	Geom CV (%)	25.7	44.5	74.1
t_{max} (hr)				
	Median (min,max)	5.0 (5.0, 8.0)	5.0 (3.0, 6.0)	7.0 (6.0, 12)
T_{lag} (hr)				
	Mean (SD)	1.0 (0.38)	1.3 (0.49)	1.2 (0.88)
$t_{½}$ (hr)				
	Mean (SD)	35 (18)	26 (20)	14 (11)
	Geom CV (%)	69	98	49
MRT (hr)				
	Mean (SD)	28 (12)	25 (14)	21 (9.2)
	Geom CV (%)	45	55	31
CL/F (L/hr)				
	Mean (SD)	3.0 (1.5)	5.9 (2.4)	36 (18)
	Geom CV (%)	47	45	74
Vz/F (L)				
	Mean (SD)	130 (61)	190 (140)	630 (380)
	Geom CV (%)	47	75	72
T_{last} (hr)				
	Mean (SD)	170 (96)	100 (89) 44 (32)	
	Geom CV (%)	91	100	39

Table 26: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set - SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
$AUC_{0\text{-tlast}}$	SDD Capsule (Fed) vs. Reference Capsule (Fed)	48.2	(41.4%, 56.1%)
$AUC_{0\text{-}\infty}$ (ngxhr/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	49.7	(43.1%, 57.2%)

(continued)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
C_{max} (ng/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	59.8	(51.7%, 69.2%)
$AUC_{0\text{-tlast}}$ (ngxhr/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	8.0	(5.7%, 11.2%)
$AUC_{0\text{-}\infty}$ (ngxhr/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	9.0	(6.6%, 12.4%)
C_{max} (ng/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	6.7	(4.9%, 9.2%)

Example 8: Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia

[0477] A Phase 2 study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of the compound of Formula (I) in adult subjects with classic congenital adrenal hyperplasia (CAH) was designed. The objectives of the study are: to assess the safety and tolerability of two ascending doses of the compound of Formula (I) in adult subjects with CAH; to evaluate the effect of repeated doses of the compound of Formula (I) on endogenous levels of PD biomarkers in adult subjects with CAH; and to evaluate plasma exposures following repeated doses of the compound of Formula (I) administered nightly.

[0478] The lower dose strength selected for this study, the compound of Formula (I) 50 mg, was well tolerated in both single and repeat-dose safety and PK studies in healthy volunteers. Doses up to 100 mg were also well tolerated in both single-dose and repeat-dose Phase 1 studies in healthy volunteers, and importantly, in a large Phase 2 study in non-elderly female and male subjects with major depressive disorder receiving the compound of Formula (I) during an 8-week, double-blind treatment period. Furthermore, the anticipated steady state exposures with the selected the compound of Formula (I) doses, using the predicted C_{max} and AUC, are within the acceptable safety margins defined by the nonclinical toxicology studies that have been conducted to date.

Study Design

[0479] A Phase 2, open-label, multiple-dose, dose-escalation study to assess the safety, tolerability, PK, and PD of the compound of Formula (I) in approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH was designed. The study will include a sequential-cohort design with four compound of Formula (I) dose cohorts: 50 mg and 100 mg, with each dose administered for 14 consecutive days:

- Cohort 1: compound of Formula (I) 50 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 2: compound of Formula (I) 100 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 3: compound of Formula (I) 100 mg once daily with the evening meal at approximately 1900 hours.
- Cohort 4: compound of Formula (I) 100 mg twice daily with breakfast at approximately 0700 hours and with the evening meal at approximately 1900 hours.

[0480] There will be an approximate 2-week period to evaluate safety and tolerability data before proceeding from Cohort 1 to Cohort 2. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects). Table 27 below depicts the dose cohorts, doses, and number of subjects per cohort.

Table 27. Dose cohorts, doses, and number of subjects

Cohort	Compound of Formula (I) Dose	Approximate Dosing Time(s)	Number of Subjects
1	50 mg	2200 hours	8-10
2	100 mg	2200 hours	8-10

(continued)

Cohort	Compound of Formula (I) Dose	Approximate Dosing Time(s)	Number of Subjects
3	100 mg	1900 hours	8-10
4	100 mg	0700 and 1900 hours	Up to 8

[0481] Subjects will be screened for eligibility to participate in the study for up to approximately 3 weeks (Days -28 to -8). Subjects who reenroll and have had a stable medication regimen for CAH since their last visit in this study do not have to undergo screening; those who reenroll and have had a change to their medication regimen for CAH must undergo a second screening visit. During screening, subjects will provide a single blood sample in the morning between 0700 and 1000 hours (prior to first morning dose of hydrocortisone) to determine their 17-hydroxyprogesterone (17-OHP) levels for study entry.

[0482] Eligible subjects who have a screening 17-OHP level ≥1,000 ng/dL will be admitted to the study center for 1 night and have baseline serial PD samples collected over a 24-hour period beginning in the evening of Day -7. Baseline serial PD samples will be collected at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

[0483] Subjects within each dose cohort will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for CYP21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (the compound of Formula (I) 50 or 100 mg) will be administered at approximately 2200 hours for Cohorts 1 and 2 and at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours for Cohorts 3 and 4. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

[0484] Subjects in Cohorts 1 and 2 will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for cytochrome P450 (CYP) 21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (compound of Formula(I) 50 mg or 100 mg) will be administered at approximately 2200 hours. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 12-hour post-dose PK/PD samples are collected (at approximately 1000 hours) on Day 2 and after the 16-hour post-dose PK/PD samples are collected (at approximately 1400 hours) on Day 15. Subjects will be discharged from the study center the evening on Days 2 and 15 following completion of all study-related procedures for those days. Prior to this discharge on Day 2, study drug will be administered at the study center at approximately 2200 hours. Study drug will then be selfadministered nightly at home at approximately 2200 hours on Days 3 to 13. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 3 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center.

[0485] Subjects in Cohorts 3 and 4 will have a blood sample collected on Day 1 for CYP21A2 genotyping (only for subjects who have not previously participated in Cohorts 1 or 2). Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. For Cohort 3, study drug (compound of Formula(I) 100 mg) will be administered at home on Days 1 to 13 at approximately 1900 hours with each subject's evening meal. For Cohort 4, study drug compound of Formula(I) 100 mg) will be administered at home on Days 2 to 14 at approximately 0700 hours with each subject's breakfast and on Days 1 to 13 at approximately 1900 hours with each subjects' evening meal. For both cohorts, the Day 14 evening dose will be administered at the study site. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 1 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center. Subjects will be admitted to the study center on Day 14 (last day of dosing). On Day 14, subjects will receive study drug in the study center at approximately 1900 hours with a standard (moderate fat/moderate calorie) evening meal. The subjects' usual morning dose of concurrent steroidal treatments will be administered after PK/PD samples are collected at approximately 1400 hours on Day 15. Subjects will be discharged from the study center the evening on Day 15 following completion of all study-related procedures.

[0486] For all cohorts, follow-up visits on Days 21, 28, and 35 will be conducted at the study center or the subject's home by a qualified home healthcare provider (based on the subject's preference). A final study visit will be conducted at the study site approximately 5 weeks after the last dose of study drug (on Day 49 or early termination). There will be a visit window of - 8 hours for Day 7, -8 hours/+3 days for Days 21, 28, and 35, and +7 days for the final study visit. Safety, tolerability, PK, and PD will be assessed at scheduled times throughout the study. The study design schematic is shown in FIG. 11.

*Dose **escalation procedure***

[0487] Cohort 1 will consist of approximately 8 to 10 subjects who will receive a daily dose of the compound of Formula (I) 50 mg at approximately 2200 hours for 14 days (subjects will receive study drug at the site on Days 1, 2, and 14, and self-administer study drug at home on Days 3 to 13). Following the completion of Day 15 assessments for all subjects in the Cohort 1, a medical monitor will review the accumulated safety and tolerability results to ensure there are no safety concerns with proceeding to the 100 mg dose (Cohorts 2 and 3), and to determine if a maximum tolerated dose (MTD) has been reached. If the MTD is reached, no dose escalation will occur. There will be an approximate 2-week period between Cohorts 1 and 2 to accommodate this safety review. A similar procedure will be used prior to proceeding to the 100 mg twice daily dose (Cohort 4).

[0488] If the medical monitor determines that it is safe to proceed to the compound of Formula (I) 100 mg, subjects in Cohort 2 will be administered the compound of Formula (I) 100 mg daily for 14 days. Dosing for Cohorts 3 and 4 may begin simultaneously with Cohort 2.

[0489] During the 14-day dosing period for any cohort, dosing may be postponed or halted if one or more subjects experience a severe or serious adverse event (AE), or if the type, frequency, or severity of AEs becomes unacceptable. If dosing is postponed, the medical monitor will review all available safety, tolerability, and PK data before allowing any further subjects to receive study drug.

Study Population

[0490] Approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21 -hydroxylase deficiency CAH, who meet all protocol eligibility criteria, will be enrolled. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects).

Duration** of **treatment

[0491] The expected duration of study participation for each subject is approximately 11 weeks, including up to approximately 3 weeks for screening, a 24-hour PD baseline period (approximately 7 days prior to the first day of dosing), 14 days of dosing, and a follow-up period of approximately 5 weeks. The total duration of the study will be an additional 8 to 11 weeks for subjects who reenroll.

Test product, dose, and mode** of **administration

[0492] The compound of Formula (I) will be supplied as capsules containing 50 mg of the compound of Formula (I) free base for oral administration (see, e.g., Reference 1 formulation as described in Example 9). Doses of the compound of Formula (I) are 50 mg and 100 mg, administered in oral capsule form. Each dose of study drug for Cohorts 1 and 2 is to be administered with a bottle of vanilla-flavored Ensure Plus® (~237 mL). Each dose of study drug for Cohort 3 is to be administered with each subject's evening meal at approximately 1900 hours. Each dose of study drug for Cohort 4 is to be administered with each subject's breakfast at approximately 1900 hours (i.e., a total daily dose of 200 mg).

Criteria for Evaluation

Cohorts 1 and 2

[0493] Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 1 to 2 and Days 14 to 15 at: 15 minutes pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose; Day 7 (at approximately 24 hours post-dose); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours post-dose); and at the final study visit (Day 49 or early termination).

Cohorts 3 and 4

[0494] Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 14 to 15 at the following times (for Cohort 4, all times are relative to evening dosing unless otherwise indicated): 15 minutes predose and at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 23, 24, and 27 hours postdose; Day 7 (at 24 hours postdose for Cohort 3 or at 12

hours post morning dose but prior to the evening dose for Cohort 4); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours postdose); and at the final study visit (Day 49 or early termination).

Pharmacokinetics

[0495] The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours ($AUC_{0\text{-}24}$)
- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)

[0496] Additional PK parameters for Day 14 only:

- Average plasma concentration at steady state (C_{avg})
- Percent fluctuation at steady state (% fluctuation)
- Accumulation index at steady state
- Apparent systemic clearance after oral administration (CL/F) (the compound of Formula (I) only)

Pharmacodynamics

[0497] Primary: Morning 17-OHP (serum; ng/dL) from the 0600, 0800, and 1000 hour samples (8-, 10-, and 12-hour post-dose samples from Cohorts 1 and 2 and 11-, 13-, and 15-hour postdose samples from Cohorts 3 and 4.

[0498] Secondary: 17-OHP at all other times, androstenedione (serum; ng/dL), testosterone (serum; ng/dL), cortisol (serum; μg/dL), and adrenocorticotropic hormone (plasma ACTH; pg/mL).

Safety

[0499] Safety and tolerability will be monitored throughout the study and will include the following assessments:

- Adverse events
- Clinical laboratory tests - clinical chemistry (including creatine kinase, myoglobin, total and conjugated bilirubin), hematology, coagulation (prothrombin time, aPTT, d-dimer, fibrinogen), and urinalysis (including quantitative myoglobin, casts and crystals)
- Vital signs
- Physical examinations (including musculoskeletal exam)
- 12-lead electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Brief Psychiatric Rating Scale (BPRS)

Statistical methods

[0500] Safety, PK, and PD variables will be summarized within each dose cohort (the compound of Formula (I) 50 mg and 100 mg) using descriptive statistics. Summaries of PD measures will include both observed values and changes from pre-dose.

Results

Pharmacokinetic results

[0501] Eight subjects (four female and four male) were enrolled in this study and completed Cohort 1. Age, sex, and BMI information for the study participants is shown in Table 28, below.

Table 28. Cohort 1 Subjects

Subject ID	Age (years)	Sex (Male/Female)	BMI (kg/m^2)
001	37	Female	24.9
002	25	Female	32.0
003	49	Male	37.2
004	36	Male	25.0
005	27	Female	25.5
006	19	Male	21.7
007	25	Male	27.5
008	31	Female	34.4

[0502] The subjects received a daily dose of the compound of Formula (I) at 50 mg at approximately 2200 hours (~10 p.m. or bedtime) for 14 days. Arithmetic mean values for ACTH (FIG. 12A) and 17-OHP (FIG. 12B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, Day 1, and Day 14. Both ACTH and 17OHP concentration profiles at day 1 and day 14 show clear reductions from the baseline mean profiles. Cohort 1 mean PK parameters of T_{max}, C_{max}, and AUC24 for the compound of Formula (I) are shown in Table 29 below. These PK parameters are consistent with observations from Phase 1 studies in healthy volunteers.

Table 29. Cohort 1 Mean PK parameters of T_{max}, C_{max}, and AUC_{24}

	Day 1			Day 14		
	T_{max}	C_{max}	AUC_{24}	T_{max}	C_{max}	AUC_{24}
Mean	**5.4**	**1305**	**10,292**	**4.4**	**1349**	**14,297**
CV%	30	25	24	32	15	24

[0503] Additional measurements of cohort 1 and cohort 2 mean PK parameters of T_{max}, C_{max}, and AUC_{24} for the compound of Formula (I) on Day 1 of dosing are shown in Table 30 below.

Table 30: Mean PK parameters of T_{max}, C_{max}, and AUC_{24} on Day 1 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure		
Day 1	**T_{max}* (h)**	**C_{max} (ng/ml)**	**AUC_{24} (h*ng/ml)**	**T_{max} (h)**	**C_{max} (ng/ml)**	**AUC_{24} (h*ng/ml)**
G.Mean	6	1,270	10,411	4	2,370	24,725
CV%	-	25	24	-	21	42
N	8	8	8	8	4	4
*Median						

[0504] Additional measurements of cohort 1, cohort 2 and cohort 3 mean PK parameters of T_{max}, C_{max}, and AUC24 for the compound of Formula (I) on Day 14 of dosing are shown in Table 31 below.

Table 31: Mean PK parameters of T_{max}, C_{max}, and AUC24 on Day 14 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure			Cohort 3 100 mg w/evening Meal		
Day 14	Tmax* (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)
G. Mean	4	1,335	14,070	4	3,379	35,416	3	3,650	34,706

(continued)

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure			Cohort 3 100 mg w/evening Meal		
Day 14	Tmax* (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)
CV%		15	24		31	7		2	15
N	8	8	8	6	6	6	8	8	8
*Median									

[0505] Arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, day 1, and day 14. The androstenedione concentration profile on Day 1 and Day 14 shows a clear reduction from the baseline mean profile.

[0506] When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of ACTH show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 14A). Arithmetic mean values across all three timepoints show >=50% reductions from baseline at Day 1 and Day 14 (FIG. 14B).

[0507] When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of 17-OHP show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 15A). Arithmetic mean values across all three timepoints show >=40% reductions from baseline at Day 1 and Day 14 (FIG 15B).

[0508] When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of androstenedione show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 16A). Arithmetic mean values across all three timepoints show >=30% reductions from baseline at Day 1 and Day 14 (FIG. 16B).

[0509] A summary of reduction in 17-OHP and androstenedione in cohort 1 is shown in Table 32. Further, the androstenedione levels of three subjects was normalized by the treatment for the three subjects with Subject ID Nos. 001, 002, and 006).

Table 32. Cohort 1 Summary of Reduction in 17-OHP and Androstenedione at each timepoint in the morning window (6 a.m. to 10 a.m.)

Subject ID	Sex/Age	Dosing Day	17-OHP % change from baseline			Androstenedione % change from baseline		
			6 AM	8 AM	10 AM	6 AM	8 AM	10 AM
001	F/37	D1 D14	-61.4 -90.3	14.7 -67.2	-24.1 -37.2	-42.0 -84.6	2.0 -58.6	-19.5 -55.1
002	F/25	D1 D14	-96.0 -37.7	-95.5 -58.6	45.4 -24.9	-68.0 -34.2	-66.7 -47.8	-21.7 -38.7
003	M/49	D1 D14	-11.8 -24.5	-46.6 -5.2	-34.0 -22.9	-13.4 -7.5	-47.1 -10.8	-22.7 -16.0
004	M/36	D1 D14	-13.7 -53.6	17.1 -46.8	10.1 -35.8	4.5 -13.8	15.9 -15.2	3.0 -21.2
005	F/27	D1 D14	-24.4 -78.8	-83.6 -95.1	-52.2 -86.3	-35.6 26.7	-50.3 -13.7	-33.5 -10.9
006	M/19	D1D14 D14	-5.1 -25.4	-1.1 -20.4	-97.8 -98.3	-10.0 -67.8	-18.5 -62.7	-78.9 -92.1
007	M/25	D1 D14	-50.0 14.9	-28.0 4.0	-27.4 -7.1	-24.8 -4.8	-30.0 -36.8	-15.8 -30.2
008	F/31	D1 D14	-64.5 -59.0	-80.7 -65.2	-92.8 -89.1	-12.2 74.5	7.0 99.4	-9.3 59.2

Table 33. Cohort 1 Summary of PK parameters of T_{max}, C_{max}, and AUC_{24} for each subject at days 1 and 14

Day 1	Day 1			Day 14		
Subject ID	T_{max} (h)	AUC_{24} C_{max} (ng/ml) (h*ng/ml)		T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)
001	6	1830	14,487	6	1570	20,863
002	6	1210	11,829	4	1610	15,494
003	6	1060	11,068	3	1310	15,599
004	4	1670	9,669	3	1160	10,180
005	8	961	9,266	6	1550	15,130
006	4	1030	6,574	3	1090	10,288
007	6	1550	8,239	6	1170	12,880
008	3	1130	11,209	4	1330	13,944
Mean	**5.4**	**1305**	**10,292**	**4.4**	**1349**	**14,297**
CV%	30	25	24	32	15	24
N	8	8	8	8	8	8

[0510] After 14 days of once-daily compound of Formula (I) administration, a majority of participants in Cohorts 1-3 showed reduced serum concentrations of adrenal androgens and precursors. Mean changes from baseline (±standard deviation) in Cohort 1 were as follows: 17-OHP, -2341.0±1535.0 ng/dL; androstenedione, -98.4±98.7 ng/dL; and ACTH, -157.0±194.9 pg/mL. Mean reductions were larger in Cohort 2 (17~OHP, -4406.0±5516.1; androstenedione, -362.8±354.0; ACTH, -180.9±155.2) and Cohort 3 (17-OHP, -4760.1±4018.2; androstenedione, -210.9±188.6; ACTH, -358.9±177.6), suggesting a possible dose response. FIGs. 17A-17C, 18A-18C, and 19A-19C depict results from Cohorts 1, 2, and 3, respectively.

Summary

[0511] The results from this ongoing Phase II open-label study demonstrated a reduction of at least 50 percent from baseline in 17-hydroxyprogesterone (17-OHP) and adrenocorticotropic hormone (ACTH) levels in more than 50 percent of CAH patients in cohort 1 treated with the compound of Formula (I) for 14 days (i.e., 6 of 8 patients in cohort 1 had a reduction of ≥50% from baseline levels of 17-OHP during at least one morning window timepoint, see, e.g., Table 32). Meaningful reductions were also observed in other biomarkers, including androstenedione (i.e., 4 of these patients also had a reduction of ≥50% from baseline levels of androstenedione during at least one morning window timepoint, see, e.g., Table 32). The greater reductions in biomarkers in cohorts 2 and 3, treated with double the dose of the compound of Formula (I) compared with cohort 1, suggest a possible dose response. Further, the compound of Formula (I) was well-tolerated with a relatively small number of mild adverse events (AEs) reported (e.g., headache, ovulation pain, fatigue, localized infection (toe), dizziness, nausea, URI, contusion with the most common being headache). No clinically significant findings from routine labs, vital signs, or electrocardiograms were found.

Example 9: Reference Formulation 1 of the compound of Formula (I)

[0512] Tables 34A and 34B show Reference formulation 1 of the compound of Formula (I) as used in the clinical studies described in Examples 6 and 8, above. An example manufacturing process is shown in FIG. 20. Another example manufacturing process is shown in FIG. 21.

Table 34A:

Component	Quality Standard	Function	50 mg Capsule	
			Weight mg/unit)	% (w/w)
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides Labrafac TM Lipophile WL1349)	NF	Oily Phase Vehicle	196.0	39.2
Propylene Glycol Dicaprylate/Dicaprate, (LabrafacTM PG)	NF	Emulsifying Agent	102.0	20.4
Lauroyl Polyoxyl-32 Glycerides (Gelucire® 44/14)	NF	Nonionic Surfactant & Solubilizing Agent	95.0	19.0
Vitamin E Polyethylene Glycol Succinate (Kolliphor® TPGS)	USP/NF	Solubilizing Agent	57.0	11.4
Total Emulsion Weight			**500.0**	**100.0**
Gelatin Capsule Shell. Size #00, Swedish Orange cap/body; (Coni-Snap®)	Non -Pharmacopoeial	Capsule Shell	--	
Gelatin Powder, 220 Bloom	USP	Capsule shell banding agent	--	--
Purified Water	USP	Capsule shell banding solvent	--	--

Table 34B:

Component	Quality Standard	Function	50 mg Capsule	
			Weight (mg/unit)	% (w/w)
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides (caprylic:capric acid 60: 40; Miglyol 812N)	Ph. Eur./NF	Vehicle	195.85	39.2
Propylene Glycol Dicaprylocaprate, (LabrafacTM PG)	Ph. Eur.	Vehicle	102.15	20.4
Lauroyl macrogolglycerides type 1500-Lauroyl polyoxylglycerides type 1500 (Gelucire® 44/14)	Ph. Eur./NF	Surfactant	95.0	19.0
Vitamin E Polyethylene Glycol Succinate, 260 mg/g d-alpha tocopherol (Vitamin E/TPGS 260)	NF	Surfactant	57.0	11.4
Total Emulsion Weight			**500.0**	**100.0**
Orange opaque hard capsule, size 0, composed of gelatin, titanium dioxide and red ferric oxide (Swedish Orange ®)	Non Pharmacopoeial	Capsule Shell	--	--
Ethanol (96%) and Purified Water	USP	Capsule shell banding solvent	--	--

Example 10: Study Evaluating Effect of Ensure Plus, Ensure Pudding, Milk and High Fat Meal on Reference Capsule

Study design

[0513] This is a Phase 1, open-label, randomized, four-period crossover study to evaluate the effect of food with different levels of fat and caloric content on the PK, safety, and tolerability of the compound of Formula (I) in healthy adult subjects.

[0514] A total of 16 healthy adult subjects (8 males and 8 females) will be randomly assigned to 1 of 4 treatment sequences (4 subjects per sequence [2 males and 2 females per sequence]; see Table 35 below). During each treatment period, subjects will receive a single dose of the compound of Formula (I) 100 mg administered with the appropriate meal, according to the randomization scheme. There will be a washout of at least 21 days between each dose.

Table 35:

Treatment Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
1	Reference meal	Test meal 1	Test meal 2	Test meal 3
2	Test meal 1	Test meal 3	Reference meal	Test meal 2
3	Test meal 2	Reference meal	Test meal 3	Test meal 1
4	Test meal 3	Test meal 2	Test meal 1	Reference meal
Reference meal: vanilla-flavored Ensure Plus® Test meal 1: Low fat, low caloric content meal 1 Test meal 2: Low fat, low caloric content meal 2 Test meal 3: standard high fat, high caloric content meal				

[0515] After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days before Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1 and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During each treatment period, subjects will fast overnight for at least 10 hours until the start of the assigned meal, according to the randomization scheme, and ingest the study drug at approximately 0800 hours. Subjects must complete the entire meal within the specified time period and should not consume any other food for 4 hours after dosing. For all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water provided with study drug dosing and planned meals.

[0516] On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 100 mg. Blood samples will be collected for PK analysis over a period of 36 hours during the in-house stay. During each treatment period, subjects will remain in the clinic on the day of dosing and will be discharged on Day 2 after completing all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects will return for an outpatient visit to the clinic for PK blood sample collection and safety assessments. On Day 21 of treatment periods 1 to 3, subjects will arrive at the site and have Day 21 assessments completed and they will stay overnight at the site and begin Day 1 of the subsequent treatment period the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 4 (21 ± 2 days after treatment period 4 dosing) or upon early termination.

[0517] Blood samples for PK d/conducted at scheduled times throughout the study.

Study population

[0518] Sixteen healthy adult subjects (8 males and 8 females) between 18 and 55 years of age, inclusive, who meet all protocol eligibility criteria, will be enrolled.

Duration of treatment

[0519] The expected duration of study participation for each healthy adult subject will be approximately 16 weeks, including up to 28 days of screening, 4 days of dosing with at least 21 days between consecutive doses, and a final follow-up study visit 21 days (± 2 days) after receiving the last dose of study drug during treatment period 4.

Test product, dose, and mode of administration

[0520] The compound of Formula (I) will be supplied as capsules for oral administration (encapsulated, lipidic semi-solid formulation, e.g., Example 9). The compound of Formula (I) capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. During each treatment period, subjects will receive two 50 mg capsules (100 mg) of the study drug along with a meal and water as defined by the randomization scheme. The food, water, and study drug administration are as follows:

Reference meal: Two capsules of study drug will be administered approximately 5 minutes after the start of a liquid dietary supplement (i.e., Ensure Plus® [237 mL container]) and an additional 120 mL of water for study drug dosing.
Test meal 1: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 1 with 120 mL of water for study drug dosing.
Test meal 2: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 2 with 120 mL of water for study drug dosing.
Test meal 3: Two capsules of study drug will be administered approximately 30 minutes after the start of a high fat, high caloric meal with 120 mL of water for study drug dosing.

CRITERIA FOR EVALUATION

Pharmacokinetics

[0521] Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

[0522] The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)
- Molar AUC ratio of primary metabolite(s) to the parent drug compound of Formula (I). The following plasma PK parameters will be calculated only for the compound of Formula (I):
- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

Safety Assessments

[0523] Safety will be monitored throughout the study and will include the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

Statistical methods

[0524] Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by meal type (test meal/reference meal) using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test meal versus the reference meal for $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tlast}$, and C_{max} for the compound of Formula (I)

and metabolites.

[0525] Safety data will be summarized with descriptive statistics.

Results

Pharmacokinetic results

[0526] Pharmacokinetic results are shown in Table 36 below.

Table 36: Summary of Plasma Pharmacokinetic Parameters

		Compound of Formula (I) Plasma Concentration			
Parameter (units) Statistic	**Ensure Plus (Fed) (N=18)**	**Ensure Pudding (Fed) (N=18)**	**Whole Milk (Fed) (N=17)**	**High Fat Meal (Fed) (N=17)**	
$AUC_{0\text{-}tlast}$ (ng×hr/mL)					
Mean (SD)	36703 (17400)	34077 (11597)	35561 (15866)	55487 (23242)	
Geom CV(%)	58	39.7	44.6	41.9	
$AUC_{0\text{-}\infty}$ (ng×hr/mL)					
	Mean	45386 (19648)	40037 (9515)	46737 (17395)	63755 (19139)
	Geom CV(%)	43.3	23.8	38.8	31
C_{max} (ng/mL)					
	Mean (SD)	3090 (1070)	3038 (984)	2835 (1005)	4336 (1938)
	Geom CV(%)	39.7	34.9	34.5	53.6
t_{max} (hr)					
	Median (min, max)	5.0 (2.0, 10.0)	5.0 (4.0, 6.0)	5.0 (4.0, 7.0)	5.0 (4.0, 7.0)
T_{lag} (hr)					
	Mean (SD)	0.38 (0.46)	0.20 (0.25)	0.16 (0.31)	0.29 (0.37)
$t_{½}$ (hr)					
	Mean (SD)	361 (263)	373 (196)	373 (143)	326 (120)
	Geom CV(%)	61.1	48.6	37.1	33.8
CL/F (L/hr)					
	Mean (SD)	2.49 (0.956)	2.636 (0.659)	2.427 (0.975)	1.706 (0.526)
	Geom CV(%)	41.2	24.8	38.8	31.1
Vz/F (L)					
	Mean (SD)	1254 (906)	1414 (720)	1308 (627)	816 (378)
	Geom CV(%)	72.7	58.4	61.3	54.9

Example 11: Spray-dried Dispersion Granule Formulation of the Compound of Formula (I) (SDD-G)

[0527] Table 37 shows a granule formulation of the compound of Formula (I) using a SDD prepared according to Example 3, above. An example manufacturing process is shown in FIG. 22A and FIG. 22B.

Table 37:

Component	Quality Standard	Function	50 mg Sachet		Batch Weight (g)
			Weight (mg/ unit)	% (w/w)	
Example 3, SDD	In-house	Drug Substance	200.0	13.33	40
Calcium Silicate (ZEOPHARM 250)	NF	Glidant	10.0	0.67	2
Mannitol (Pearlitol 200SD)	NF / EP / JP	Filler	832.5	55.5	166.5
Microcrystalline Cellulose (Avicel PH-102)	NF / EP / JP	Filler	300.0	20.0	60
Croscarmellose Sodium (Ac-Di-Sol®) SD711	NF / EP / JP	Disintegrant	150.0	10.0	30
Sodium Stearyl Fumarate	NF / EP / JP	Lubricant	7.5	0.5	1.5
Total			1500	100.0	300

Example 12: Liquid Formulation 1 of the Compound of Formula (I)

[0528] Table 38 shows liquid formulation 1 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 23.

Table 38:

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.03
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.69
FONA orange flavor	NF	Flavor	1.0	0.1	0.41
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	94.58	358.87
Total			1 mL	100.0	380.6

Example 13: Liquid Formulation 2 of the Compound of Formula (I)

[0529] Table 39 shows liquid formulation 2 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 24.

Table 39:

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.17
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61

(continued)

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.68
LABRAFIL M 1944 CS	NF / EP	Surfactant	200.0	20	80.16
FONA orange flavor	NF	Flavor	1.0	0.1	0.40
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	74.58	278.68
Total			1 mL	100.0	380.7

Example 14: A Phase I, Open-Label Study to Evaluate the Pharmacokinetics, Relative Bioavailability, Effect of Food, Safety and Tolerability of Different Compound of Formula (I) Prototype Formulations in Healthy Adult Subjects.

Methodology

[0530] This is a single center, open-label, randomized, single dose 4-period crossover study in healthy adult subjects designed to investigate the pharmacokinetic (PK) and safety of up to 4 compound of Formula (I) liquid lipidic prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulations, 50 mg/mL), a compound of Formula (I) spray dried dispersion formulation (compound of Formula (I) Granule for Sprinkle, 25 - 50 mg) and compound of Formula (I), 50 mg Capsules (Reference). It is planned to enroll 36 subjects to be allocated as 3 cohorts of 12 subjects per cohort, with 6 sub-cohorts of 6 subjects per sub-cohort. In each of these 6 sub- cohorts, 6 subjects will be assigned to one of 3 sub-cohorts where a single oral dose of Investigational Medicinal Product (IMP) is administered in 4 dosing periods (Periods 1 to 4) in multiple fed or fasted states or to one of 3 sub-cohorts where a single oral dose of IMP is administered in 2 dosing periods (Periods 1 and 2) only in the fed state. Within each sub-cohort, subjects will also be randomized before administration of the first dose of IMP in Period 1 to one of the following treatment sequences (Table 40):

Table 40:

Sub-Cohort	Sequence	Number of Subjects	Total Number of Periods Dosed	Regimen			
				Period 1	Period 2	Period 3	Period 4
1A	ABEF	3	4	Regimen A	Regimen B	Regimen E	Regimen F
	BAEF	3	4	Regimen B	Regimen A	Regimen E	Regimen F
1B	AB	3	2	Regimen A	Regimen B	N/A	N/A
	BA	3	2	Regimen B	Regimen A	N/A	N/A
2A	ADEF	3	4	Regimen A	Regimen D	Regimen E	Regimen F
	DAEF	3	4	Regimen D	Regimen A	Regimen E	Regimen F
2B	AD	3	2	Regimen A	Regimen D	N/A	N/A
	DA	3	2	Regimen D	Regimen A	N/A	N/A

(continued)

Sub-Cohort	Sequence	Number of Subjects	Total Number of Periods Dosed	Regimen			
				Period 1	Period 2	Period 3	Period 4
3A	ACEF	3	4	Regimen A	Regimen C	Regimen E	Regimen F
	CAEF	3	4	Regimen C	Regimen A	Regimen E	Regimen F
3B	AC	3	2	Regimen A	Regimen C	N/A	N/A
	CA	3	2	Regimen C	Regimen A	N/A	N/A

[0531] At informed consent, subjects will agree either to participate in 2 study periods or 4 study periods. Once placed into a sub-cohort, the order in which subjects receive the study treatments will be randomized based on the schedule above.

[0532] Subjects will receive up to 4 regimens in up to 4 periods in an order according to the randomization schedule within each sub-cohort.

[0533] The effect of different prandial states on the PK of the compound of Formula (I) may be explored in Periods 3 and 4 by administering in the fasted state or after an alternative meal (e.g. high fat, standard or light breakfast, etc.).

[0534] The proposed regimens are presented in Table 41 below:

Table 41:

Regimen	Investigational Medicinal Product	Dose	Route of Administration	Prandial State
A	Compound of Formula (I), 50 mg Capsules (Reference)	50 mg	Oral	Fed (Ensure Plus)
B	Compound of Formula (I) Oral Solution, Prototype Formulation 1,50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
C	Compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
D	Compound of Formula (I) Granule for Sprinkle, 25 - 50 mg	50 mg	Oral	Fed (Ensure Plus)
E	Compound of Formula (I) Oral Solution, Prototype Formulation 1	100 mg	Oral	Fed (Ensure Plus)
F	Compound of Formula (I) Oral Solution, Granule for Sprinkle	50 mg	Oral	Fed (alternative meal)

Study Design:

[0535] Subjects will be screened for eligibility to participate in the study up to 28 days before the first dose of IMP in Period 1. Each study period will follow the same study design. Subjects will be admitted to the clinical unit on the evening prior to IMP administration (Day -1). For Periods 1 and 2 (Regimen A and one of either Regimens B, C or D), all subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement (Ensure Plus). For Periods 3 and 4 (Regimens E and F), subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement or an alternate prandial state (fasted or alternative meal). IMP administration will be performed on Day 1 with an appropriate interval between subjects based on logistical requirements (approximately 10 min). Meals will be standardized for each treatment regimen across periods.

[0536] Subjects will remain in the clinical unit until 36 h post-dose when they will be discharged. Subjects will return to the clinical unit at 168 h (7 days) and 336 h (14 days) postdose for a PK blood sample and safety assessments. The

minimum washout between IMP dosing occasions will be 14 days between Periods 1 and 2 and 21 days or more to accommodate interim data reviews between Periods 2 and 3 and between Periods 3 and 4.

[0537] There will be a follow-up phone call 18 to 24 days post-final visit to ensure the ongoing wellbeing of subjects.

[0538] Following the completion of Period 2 for all cohorts, there will be an interim data review during which the PK and safety data will be reviewed, plus any relevant emerging Chemistry, Manufacturing and Control (CMC) stability study information, to determine the formulation, dose level and prandial state in which to administer the IMP in Period 3 (Regimen E). There will be a similar interim review following completion of Period 3 (administration of Regimen E) to determine the formulation, dose level and prandial state in which to administer the IMP in Period 4 (Regimen F). The criteria for the interim decisions will be based on available compound of Formula (I) PK data: e.g., C_{max}, T_{max}, AUC(0-36), F_{rel} and safety data.

Number of Subjects Planned:

[0539] It is planned to enroll 36 healthy male and female (non-pregnant, non-lactating) subjects in 6 sub-cohorts of 6 subjects per sub-cohort. These sub-cohorts will be combined in sets of 2 to create 3 cohorts of n = 12 for Periods 1 and 2 to target data in 10 evaluable subjects in each cohort for the primary objectives per formulation variant. A total of 18 subjects, 6 from each of Sub-Cohorts 1A, 2A and 3A participating in Periods 1 and 2, will additionally participate in Periods 3 and 4 with a target of a minimum of 6 evaluable subjects. A subject will be considered evaluable for a particular regimen if they have received an IMP and has completed sufficient planned PK assessments up to 336 h (14 days) after dosing for that regimen to allow for the assessment of study endpoints. A subject will be considered evaluable for a particular comparison (e.g., food effect, relative bioavailability) if they have received both IMPs under comparison and have sufficient PK data up to 14 days after each regimen to allow for assessment of study endpoints.

[0540] Subjects withdrawn due to an IMP-related adverse event (AE) will not be replaced. Subjects who are withdrawn for other reasons may be replaced as required by agreement between the principal investigator (PI) and sponsor to ensure sufficient numbers of evaluable subjects at the end of each study period. Replacement subjects may be required to be dosed with specific formulations from the previous regimens in order to obtain the minimum number of evaluable subjects required for interim decisions and to obtain data in any other regimen that is required to fulfil the study objective comparisons, with the exception that any previously dosed IMP that has been considered sub-optimal will not be dosed. Up to 8 replacement subjects in total may be enrolled into the study. The maximum number of subjects that may be dosed is 44 in total.

[0541] If a subject withdraws from Sub-Cohort 1A, 2A or 3A after Period 2, it is acceptable to replace them with a subject from Sub-Cohort 1B, 2B or 3B provided the subject signs an updated consent form agreeing to participate in four treatment periods. At the discretion of the investigator, such a subject may not be required to undergo repeat screening procedures.

Duration of Study:

[0542] For subjects enrolled to receive single dose administration on 4 separate occasions in Periods 1 to 4 (Sub-Cohorts 1A, 2A and 3A), the estimated time from screening until the follow-up phone call is approximately 15 to 16 weeks.

[0543] For subjects enrolled to receive single dose administration on 2 separate occasions in Periods 1 to 2 only (Sub-Cohorts 1B, 2B and 3B), the estimated time from screening until the follow-up phone call is approximately 8 to 9 weeks.

Pharmacokinetic Assessments:

[0544] The plasma concentration data for a compound of Formula (I) will be analyzed for final reporting by Quotient Sciences and for interim reviews by Neurocrine Biosciences, Inc. (NBI), using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA). NBI will be responsible for PK analysis for interim review.

[0545] PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters (Table 42) where possible and appropriate:

Table 42:

T_{lag}	Time prior to the first measurable (nonzero) concentration
T_{max}	Time to maximum plasma concentration
C_{max}	Maximum plasma concentration
$AUC_{0\text{-tlast}}$	Area under the plasma concentration versus time curve (AUC) from 0 h to last measurable concentration

(continued)

$AUC_{0\text{-}inf}$	AUC from 0 h extrapolated to infinity
AUC_{extrap}	Percentage of $AUC_{0\text{-}inf}$ extrapolated beyond the last measurable concentration
Lambda-z	Slope of the apparent terminal phase
$T_{1/2}$	Apparent terminal half-life
CL/F[a]	Apparent systemic clearance after oral administration
Vd/F[a]	Apparent volume of distribution based on the area after a single oral administration
MRT	Mean residence time
MPR $AUC_{0\text{-}tlast}$	Metabolite to parent ratio based on $AUC_{0\text{-}tlast}$
MPR $AUC_{0\text{-}inf}$	Metabolite to parent ratio based on $AUC_{0\text{-}inf}$

Taste Assessments:

[0546] Taste will be assessed for each IMP formulation and vehicle (e.g., Ensure Plus, soft food) using a questionnaire designed for this purpose and adapted for this specific study as required.

[0547] The questionnaire will ask subjects to rate the acceptability of smell, sweetness, bitterness, flavor, mouth feel, and aftertaste on a 6-point scale, and overall experience on a 5-point scale for each IMP formulation independently of any previous formulations.

Statistical Methodology:

[0548] Descriptive summaries for all safety data, PK assessments and taste questionnaire data will be provided. No hypothesis testing will be performed for the safety or taste questionnaire data.

Periods 1 and 2 - for Each Cohort Separately

Relative Bioavailability

[0549] Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability (Frel) using a mixed effects model with terms for regimen, period and sequence as fixed effects and subject within sequence as a random effect. Ratios of geometric means (GMRs) and 90% confidence interval (CI) for the relevant comparison of interest, i.e., between each of the prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL, e.g., Example 12; compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL, e.g., Example 13; and compound of Formula (I) Granule for Sprinkle, 25 - 50 mg, e.g. Example 11 [Regimens B, C and D, respectively]) and compound of Formula (I), 50 mg Capsules, e.g., Example 9 (Reference; Regimen A) will be presented.

All Periods (Periods 1 to 4)

Food Effect

[0550] Statistical modelling will be performed on the compound of Formula (I) PK parameters AUC(0-tlast), AUC(0-inf) and Cmax to assess for the effects of food, if relevant. The natural log-transformed PK parameters will be analyzed for bioavailability using a mixed effects model with terms for prandial state (and meal type if applicable) as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparisons of interest will be presented where the ratio is defined as fasted/fed or test meal/reference meal (if applicable).

Relative Bioavailability

[0551] Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability using a mixed effects model with terms for regimen as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparison of interest i.e., between each of the prototype formulations (Regimens E and F, IMPs to be determined by interim reviews

following completion of Periods 2 and 3) and compound of Formula (I), 50 mg Capsules (Reference; Regimen A) will be presented.

Results

[0552] Preliminary PK data is summarized in Table 43 below:

Table 43: Preliminary Data from Periods 1 and 2

	A- Reference	B-Oral Solution 1	C-Oral Solution 2	D- SDD Granule
N	35	12	12	12
Tmax * (h)	5 (2,6)	6 (5,7)	5 (5,7)	5 (5,7)
Cmax (ng/ml)	1361 (33)	790 (31)	1082 (46)	1075 (35)
AUC36 (h*ng/ml)	9452 (30)	5556 (34)	7582 (37)	6691 (41)
*Geometric Mean /CV% for AUC and Cmax; Median for Tmax				

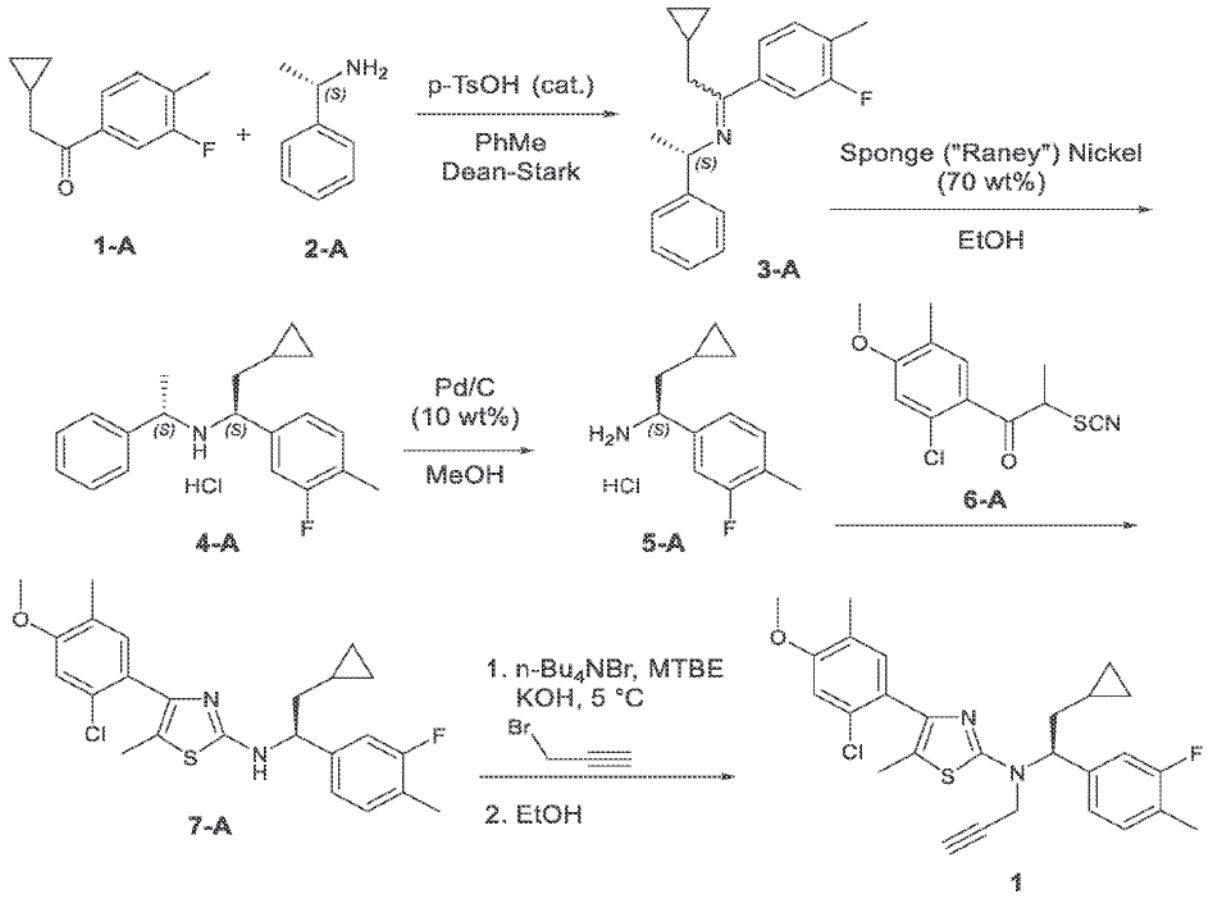
Example 15. Compound of Formula (I) Crystalline Free Base Form I

Example 15A

Scheme 1: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), Form I)

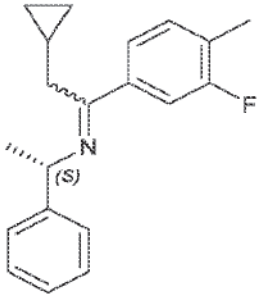
[0553]

Scheme 1



Step 1: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-(1-phenylethyl)ethan-1-imine (Compound 3-A)

[0554]



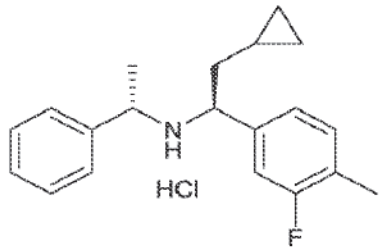
Compound 3-A

[0555] A mixture of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (1-A, 150.7 kg, 1 eq., as a 27.6% w/w solution in toluene, Example 15C), (*S*)-(-)-1-Phenylethylamine (2-A, 112.9 kg, 1.19 eq.), and *p*-toluenesulfonic acid (7.4 kg, 0.05 eq.) is refluxed at 110 - 120 °C for 23 - 25 h in a reactor set up in a Dean-Stark configuration. The solvent is then removed at 125 - 135 °C under atmospheric pressure until distillation halts and a portion of toluene (275 kg, 2.24 w/w) is added to afford a suspension. The suspension is refluxed at 110 - 120 °C for 23 - 25 h. The mixture is cooled to

22 °C and washed twice with aqueous NH_4Cl (10%, 301.2 kg, 0.72 eq.) and once with aqueous $NaHCO_3$ (5%, 301.2 kg, 0.23 eq., check pH 8 - 9). The solvent is removed at 125 - 135 °C and atmospheric pressure to a target volume of 256 L, the mixture is filtered over celite, the cake is washed with toluene (25 kg). The resulting mixture containing compound 3-A is used directly in the next step without isolation. The yield is determined by correcting for the LOD and GC-FID purity of the sample (208.4 kg, 90.0% corrected, 0.89% Compound 2-A). EI-MS: 294.1 $[M-H]^+$, 190.1 $[M-C_6H_5CH(CH_3)]^+$, 105.1 $[C_6H_5CH(CH_3)]^+$.

Step 2: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-((*S*)-1-phenylethyl)ethan-1-amine hydrochloride (Compound 4-A)

[0556]



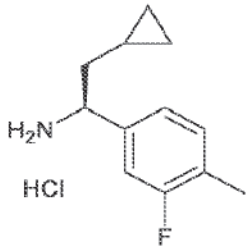
Compound 4-A

[0557] Sponge nickel catalyst (144 kg, 0.70 w/w, shipped as a 50% w/w suspension in water) is added to a hydrogenation reactor, equipped with a dip tube capable of removing material from the top of the mass inside, minimizing the amount of water introduced. The supernatant is discarded, ethanol (329.3 kg, 1.58 w/w, anhydrous) is added, the suspension is stirred and then allowed to settle. This process is repeated four more times and the Karl Fisher (KF) of the supernatant is checked (≤ 1% H_2O w/w). Compound 3-A (208.4 kg, 1 eq., as a 62.6% solution in toluene) is added to the mixture in the hydrogenation reactor and ethanol (387.6 kg, 1.86 w/w) is used to rinse the addition flask into the hydrogenation reactor. The hydrogenation reactor is pressurized/depressurized twice with nitrogen (2 bar) and twice with hydrogen (5 bar) then pressurized with hydrogen (9.8 - 10.2 bar) and heated to 33 - 37 °C and stirred for 17 - 19 h. The system is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed with three times with ethanol (493.8 kg, 2.37 w/w). HCl (concentrated, 83.4 kg, 1.07 eq.) is added and the mixture stirred 25 - 35 min at 20

[0558] - 24 °C. The mixture is concentrated by distillation at 78 - 80 °C and atmospheric pressure to remove water with a distillate target volume of 1167 L (5.6 L/kg, Compound 3-A) and the KF of the solution is checked (≤ 1.5% H_2O w/w). The mixture is stirred at 48 - 52 °C for 55 - 65 min, then 68 - 72 °C for 55 - 65 min, then cooled to 20 - 24 °C at a rate of 12 °C/h and stirred for 25 - 35 min, then cooled to 0 - 4 °C at a rate of 10 °C/h and stirred for 55 - 65 min. The suspension is filtered, the cake is washed twice with precooled ethanol (329.2 kg, 1.58 w/w, 0 °C), and the collected solid is dried at 40 °C to afford compound 4-A (156.5 kg, 66.4% uncorrected). ^1H NMR (400 MHz, DMSO-*d*6) δ ppm -0.33 - -0.06 (m, 2 H) 0.11 - 0.31 (m, 3 H) 1.57 (d, *J*=6.57 Hz, 3 H) 1.95 (br t, *J*=7.07 Hz, 2 H) 2.26 (d, *J*=1.26 Hz, 3 H) 3.68 (br d, *J*=7.83 Hz, 1 H) 3.92 (br t, *J*=6.44 Hz, 1H) 6.98 (dd, *J*=7.71, 1.14 Hz, 1H) 7.28 - 7.36 (m, 2 H) 7.37 - 7.50 (m, 5 H). ESI-MS: 298.2 m/z $[M+H]^+$.

Step 3: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-amine hydrochloride (Compound 5-A)

[0559]

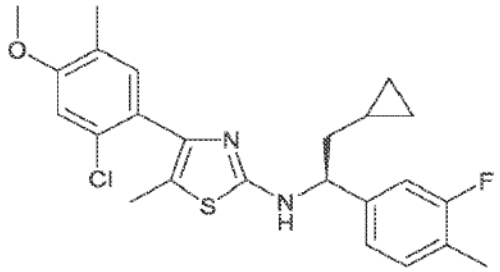


Compound 5-A

[0560] Compound 4-A (156.5 kg, 1.00 eq.) and Pd/C (7.8 kg, 10% Pd basis) are added to an inerted hydrogenation reactor. The reactor is then pressurized/depressurized twice with nitrogen (2 bar) and then methanol (494.5 kg, 3.16 w/w) is added. The reactor is depressurized/pressurized three times with nitrogen (2 bar) then three times with hydrogen (5 bar), pressurized with hydrogen (9.8 - 10.2 bar), heated to 58 - 62 °C and stirred for 7 - 9 h. The reaction mixture is cooled to 20 - 24 °C. The reactor is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed three times with methanol (492.9 kg, 3.15 w/w). The solution is concentrated at 63 - 67°C and atmospheric pressure to a distillate target volume of 1408 L (9.0 L/kg Compound 4-A). *n*-Heptane (1173.8 kg, 7.5 w/w) is added and the mixture is refluxed at 65 - 80 °C and atmospheric pressure in Dean-Stark configuration to remove methanol. The suspension is cooled to 31 - 35 °C and filtered, the cake washed with n-heptane (147.1 kg, 0.94 w/w), and the solid dried at 40 °C (101.0 kg, 93.8% uncorrected, 99.2% ee). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.12 - 0.14 (m, 2 H) 0.26 - 0.42 (m, 2 H) 0.44 - 0.55 (m, 1 H) 1.70 - 1.83 (m, 2 H) 2.23 (d, *J*=1.52 Hz, 3 H) 4.24 (t, *J*=7.33 Hz, 1 H) 7.22 - 7.29 (m, 1 H) 7.29 - 7.36 (m, 1 H) 7.40 (dd, *J*=10.99, 1.39 Hz, 1 H). ESI-MS: 194.2 $[M+H]^+$, 177.0 $[M-NH_2]^+$.

Step 4: Preparation of (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyt-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (Compound 7-A)

[0561]



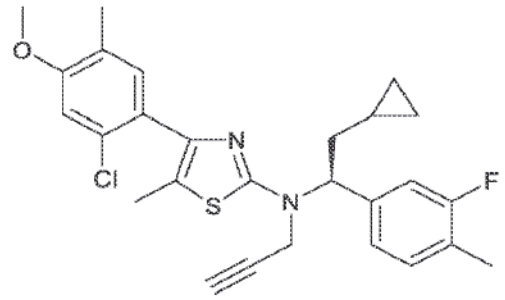
Compound 7-A

[0562] A mixture of n-heptane (146 kg), water (142 kg), Compound 5-A (57.4 kg), and aqueous sodium hydroxide (30% w/w, 41.0 kg) was stirred together. The layers were partitioned, and the aqueous layer removed. The organic layer was washed with water (170 kg) and the layers partitioned. The organic layer was set aside using n-heptane (40 kg) to rinse and n-heptane (145 kg) and 1-(2-chloro-4-methoxy-5-methylphenyl)-2-thiocyanatopropan-1-one (6-A, 66.1 kg) were added to the reactor and heated to 85 °C. The previously set aside organic layer containing the free base of Compound 5-A was added at 84 - 85 °C to the reactor and rinsed with n-heptane (20 kg). The resulting mixture was stirred for 2 h at 83 °C. Subsequently, the solvent was switched to methanol by four put-and-take additions/vacuum distillations of methanol (180 kg) at 55 °C with the target volume being 287 L remaining in the reactor. The suspension was cooled to 5 °C and water (570 kg) was added over 4 h at 5 - 10 °C, with the first 60 kg added very slowly. The suspension was aged 2 h at °C and then isolated by filtration and washed with a mixture of methanol/water (91/115 kg) and then a mixture of methanol/water (134/57 kg). The yellow solid was dried at 25 °C and 1 mbar for 17 h then 40 °C and 1 mbar for 22 h to afford Compound 7-A (97.4 kg, 87.5% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.01 - 0.14 (m, 2 H) 0.29 - 0.42 (m, 2 H) 0.61 - 0.73 (m, 1 H) 1.47 (dt, *J*=13.83, 6.85 Hz, 1 H) 1.76 (dt, *J*=13.89, 7.20 Hz, 1 H) 2.00 (s, 3 H) 2.11 (s, 3 H) 2.19 (d, *J*=1.01 Hz, 3 H) 3.82 (s, 3 H) 4.54 (q, *J*=7.58 Hz, 1 H) 7.00 (s, 1 H) 7.06 (d, *J*=0.76 Hz,

1H) 7.08 - 7.14 (m, 2 H) 7.18 - 7.23 (m, 1 H) 7.89 (d, *J*=8.08 Hz, 1 H). ESI-MS: 445.3 m/z $[M+H]^+$.

Step 5: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I))

[0563]



Compound of Formula (I)

[0564] A mixture of MTBE (279 kg), tetra-n-butylammonium bromide (10.5 kg), and Compound 7-A (95.4 kg) were heated at 60 °C external temperature for 30 min and then cooled to 0 °C. Aqueous potassium hydroxide (52.4% w/w, 364 kg) and propargyl bromide (39.4 kg as an 80% w/w solution in toluene, 1.19 eq.) were added at 0 - 5 °C and the biphasic mixture aged 14.5 h at 4 - 6 °C with vigorous stirring. Subsequently, water (191 kg) was added and the aqueous layer was discharged. The organic layer was washed twice with water (382 kg) and once with aqueous acetic acid (5.26% w/w, 190 kg) at 20 °C. The mixture is polish filtered, rinsed with ethanol (11 kg) and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol (300 kg) at 25 - 30 °C for the first cycle and then 35 - 40 °C with the target volume of each cycle being 250 L remaining in the reactor. Ethanol (164 kg) was added and the mixture heated at 60 °C external for 0.5 h before it was cooled to 25 °C in 1 h and seeded with authentic compound of Formula (I) (0.340 kg) which may be prepared as described below in Example 15B. The suspension was aged for 5 h, cooled to 0 °C in 2 h, aged 12 h, filtered, and washed twice with ethanol (24 kg each) precooled to 0 °C. The white solid was dried at 40 °C and 1 mbar for 19 h to yield 80.15 kg of the compound of Formula (I), Form I (77.2% yield). ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.14 (qt, *J*=8.59, 4.42 Hz, 2 H) 0.29 - 0.48 (m, 2 H) 0.61 - 0.82 (m, 1 H) 1.89 (dt, *J*=14.08, 6.98 Hz, 1 H), 2.07 (br d, *J*=7.83 Hz, 1 H) 2.10 (s, 3 H) 2.14 (s, 3 H) 2.20 (d, *J*=1.01 Hz, 3 H) 3.11 (t, *J*=2.27 Hz, 1 H) 3.83 (s, 3 H) 3.94 - 4.22 (m, 2 H) 5.26 (t, *J*=7.58 Hz, 1 H) 7.05 (s, 1 H) 7.10 ~ 7.36 (m, 4 H). ESI-MS: 483.2 m/z $[M+H]^+$.

[0565] The crystallinity of the crystalline free base Compound of Formula (I), Form I was confirmed by XRPD (Figure 25, Table 44) and further supported by DSC (Figure 26), indicating the crystalline compound having an onset of melt at about 84.4 °C (71.9 J/g). TGA of the crystalline free base exhibited about 0.6% of weight loss due to solvent/H_2O.

Table 44. XRPD Peak Data for the Compound of Formula (I) Crystalline Free Base Form I

2-Theta (°)	Height (cps)
5.901(15)	1221(101)
10.367(11)	1280(103)
11.762(13)	1377(107)
12.582(11)	1591(115)
13.802(2)	7326(247)
14.1541(16)	20179(410)
15.173(14)	449(61)
15.854(7)	2906(156)
16.746(5)	5113(206)
18.366(7)	1171(99)

(continued)

2-Theta (°)	Height (cps)
19.586(2)	27789(481)
20.100(4)	10759(299)
20.794(4)	5441(213)
21.730(5)	7125(244)
22.239(7)	10370(294)
23.056(11)	3482(170)
23.714(7)	2300(138)
24.115(7)	8402(265)
25.666(4)	26173(467)
26.296(6)	1505(112)
26.752(4)	9919(288)
27.264(7)	1016(92)
27.874(7)	2092(132)
28.623(3)	10560(297)
29.546(6)	5811(220)
30.025(3)	2248(137)
30.737(10)	1333(105)
31.017(19)	1406(108)
31.588(10)	2292(138)
31.809(8)	2212(136)
32.126(13)	593(70)
33.200(16)	839(84)
	996(158)
33.914(13)	1156(98)
34.276(16)	1008(92
34.564(12)	1056(94
35.397(18)	816(82)
36.073(10)	1928(127)
36.67(3)	562(68)
37.347(9)	1553(114)
37.776(12)	1573(114)
39.070(7)	1890(125)
39.743(15)	1042(93)
40.643(9)	2808(153)
41.106(8)	1107(96)
41.984(11)	2686(150)
42.376(16)	986(91)
42.901(16)	492(64)

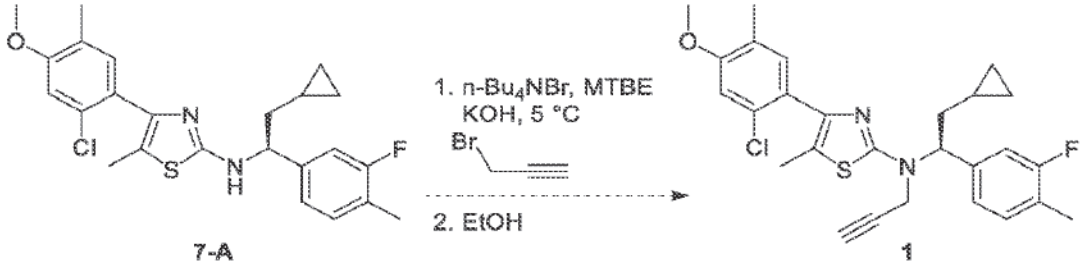
(continued)

2-Theta (°)	Height (cps)
43.543(10)	4744(199)
44.419(16)	2810(153)

Example 15B

Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropy1-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), seed batch)

[0566]



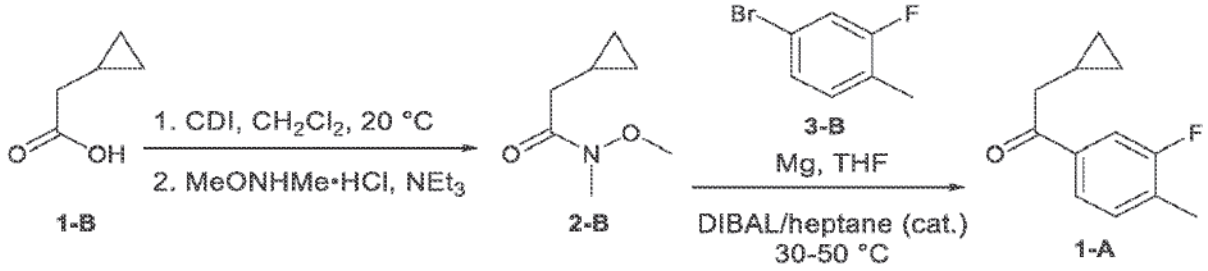
[0567] A mixture of MTBE, *tetra*-n-butylammonium bromide, and Compound 7-A cooled to 0 °C is treated with aqueous potassium hydroxide and propargyl bromide maintaining the temperature at 0 - 5 °C. The resulting biphasic mixture is aged 23 h at 4 - 6 °C. Subsequently, water and MTBE are added and the aqueous layer is discharged. The organic layer is washed twice with water and once with aqueous acetic acid at 20 °C. Ethanol is added and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol at 35 - 40 °C with a target volume of each cycle remaining in the vessel, except for the third cycle where the mixture is concentrated to dryness. Ethanol is added to the vessel and the mixture heated at 60 °C external for 0.5 h before it is cooled to 20 °C in 1 h and aged 18 h affording a suspension. The suspension is cooled to 0 °C, aged 6 h, filtered, and washed twice with ethanol pre-cooled to 0 °C to afford a solid. The solid is dried at 40 °C under vacuum to afford the compound of Formula (I).

Example 15C

Scheme 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)

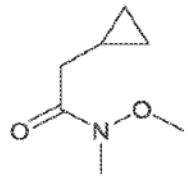
[0568]

Scheme 2



Step 1: Preparation of 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (Compound 2-B)

[0569]

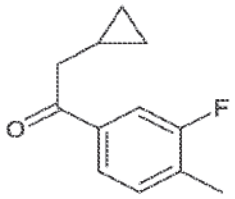


Compound 2-B

[0570] A suspension of 1,1'-Carbonyldiimidazole (152.6 kg, 1.01 eq.) in DCM (682 kg, 513 L, 7.3 w/w relative to 2-cyclopropylacetic acid) was treated with a solution of 2-cyclopropylacetic acid (1-B, 93.6 kg, 1 eq.) in DCM (248 kg, 186 L, 2.65 w/w) over at least 1 h, keeping the temperature ≤ 25 °C and compensating for significant effervescence. The resulting mixture is stirred for 15 min at 22 °C and then *N,O*-dimethylhydroxylamine•HCl (93.3 kg, 1.03 eq.) is added in portions, keeping the temperature ≤30 °C. Subsequently, triethylamine (46.4 kg, 0.49 eq.) is added to the stirring mixture at 20 - 25 °C. The resulting mixture is stirred at 22 °C at least 1 h. The mixture is washed once with $KHSO_4$ solution (0.24 M, 357.1 kg, 0.09 eq.), once with $KHSO_4$ solution (0.40 M, 365.4 kg, 0.15 eq.), once with $KHSO_4$ solution (0.80 M, 384.5 kg, 0.30 eq.), and once with $NaHCO_3$ solution (0.60 M, 393.1 kg, 0.24 eq.). Residual DCM is removed by three put-and-takes of THF (166.6 kg, 1.78 w/w) and vacuum distillation (50 - 60 °C, to minimum volume/until distillation stops). THF (333.2 kg. 3.56 w/w) is added and the yield is determined by correcting for the LOD and GC-FID purity of the sample (131.5 kg, 98.2% corrected). ^{1}H-NMR (400 MHz, DMSO-d6) δ: - 0.01 - 0.03 (m, 2H) 0.32 - 0.36 (m, 2H) 0.81 - 0.90 (br m, 1H) 2.18 (d, *J*=6.80 Hz, 2H) 2.97 (s, 3 H) 3.53 (s, 3H). ESI-MS: 144.0 $[M+H]^+$.

Step 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)

[0571]



Compound 1-A

[0572] Mg (turnings, 28.6 kg, 1.37 eq.) are suspended in THF (244.7 kg, 2.0 w/w) and DIBAL-H (1 M in n-heptane, 18.9 kg, 0.03 eq.) is added dropwise at 30 °C, The resulting mixture is stirred at 30 °C for at least 10 min and then 4-bromo-2-fluoro-1-methylbenzene (3-B, neat, 21.1 kg, 0.13 eq.) is added over at least 30 min at 30 - 50 °C. Subsequently, the mixture is treated with a solution of 4-bromo-2-fluoro-1-methylbenzene (3-B, 191.6 kg, 1.18 eq.) in THF (414.5 kg, 3.37 w/w) at 30 - 50 °C over 3 h or less. The mixture is stirred at 30 °C for at least 1 h. Subsequently, the mixture is treated with 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (2-B, 123.0 kg, 1 eq., 25.9% w/w solution in THF) over at least 1 h at 15 - 25 °C. The resulting mixture is stirred at 20 - 25 °C for at least 1 h. The stirring mixture is then treated with aqueous HCl (3 M, 10.3% w/w, 668.9 kg, 2.24 eq.) at 10 - 25 °C and the resulting mixture is stirred at least 2 h (check pH 3.0 - 3.5). The layers are separated, and the aqueous layer is combined with heptane (290.3 kg, 2.36 w/w). The layers are separated, and the organic layer is washed once with $NaHCO_3$ solution (0.63 M, 211.6 kg, 0.15 eq.) and once with NaCl solution (2.57 M, 213.0 kg, 0.55 eq.). The residual solvents are removed by vacuum distillation at 58 - 62 °C until distillation stops and then one put-and-take of toluene (275.5 kg, 2.24 w/w) at 107 - 117 °C until distillation stops. Toluene (275.5 kg, 2.24 w/w) is added and the yield is determined by correcting for the LOD and GC-FID purity of the sample (150.7 kg, 91.3% corrected). ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.07 - 0.21 (m, 2 H) 0.40 - 0.54 (m, 2 H) 1.02 (ttt, *J*=8.16, 8.16, 6.68, 6.68, 4.86, 4.86 Hz, 1 H) 2.30 (d, *J*=1.77 Hz, 3 H) 2.91 (d, *J*=6.57 Hz, 2 H) 7.44 (t, *J*=7.83 Hz, 1 H) 7.57 - 7.78 (m, 2 H). ESI-MS: 193.1 $[M+H]^+$.

Example 16: Compound of Formula (I) Crystalline Tosylate Salt Form 1

[0573] Approximately 20 mg of the Compound of Formula (I) was weighed into a vial. Using a positive displacement

pipette, 250 μL of solvent (IPA) was added to the vial along with a stir bar. The vial was placed in an aluminum block on a Reacti-Therm mixer and heated to 60 °C for ~1 hour. A molar equivalent of para-toluenesulfonic acid was added to the vial (20 μL of a 2M solution in water) and allowed to stir. The sample was slow cooled back to room temperature along with mild Nitrogen gas for evaporation. Precipitate was collected, left to dry overnight, and then analyzed by XRPD, DSC, and TGA.

[0574] The crystallinity of the crystalline tosylate form 1 was confirmed by XRPD (Figure 27, Table 45) and further supported by DSC (Figure 28), indicating the crystalline compound having an onset of melt at about 156 °C (22.2 J/g). TGA of the crystalline compound is provided in Figure 28, and exhibited about 0.5% of weight loss due to solvent/H_2O.

Table 45. XRPD Peak Data for the Compound of Formula (I) Crystalline Tosylate Form 1

2-Theta (°)	Height (cps)
8.112(9)	957(89)
9.124(2)	12296(320)
9.471(2)	4519(194)
10.525(3)	8507(266)
11.316(3)	10211(292)
13.182(5)	6158(227)
13.494(6)	1598(115)
14.249(9)	2197(135)
15.208(9)	1746(121)
15.711(7)	1437(109)
16.252(5)	5723(218)
16.692(3)	3848(179)
17.540(4)	1578(115)
19.031(6)	6774(238)
19.265(4)	6491(233)
19.499(10)	3152(162)
20.401(3)	8581(267)
20.656(4)	3040(159)
21.142(3)	11498(310)
21.703(6)	4979(204)
21.870(11)	5331(211)
22.277(5)	3701(176)
22.769(3)	10159(291)
23.297(3)	14954(353)
23.532(4)	3597(173)
23.810(3)	9590(283)
24.73(2)	2325(139)
25.47(4)	1704(119)
26.087(5)	2413(142)
26.71(3)	422(59)
27.210(6)	1648(117)
27.593(5)	2825(153)

(continued)

2-Theta (°)	Height (cps)
28.472(4)	6417(231)
29.51(3)	1423(109)
29.98(3)	849(84)
30.63(6)	1262(103)
30.77(3)	1121(97)
31.577(3)	5563(215)
32.74(4)	874(85)
33.73(4)	1111(96)
34.415(13)	2054(131)
34.799(11)	706(77)
35.139(15)	1320(105)
35.682(16)	1028(93)
38.39(4)	751(79)
39.743(17)	1790(122)
40.219(16)	762(80)
41.23(3)	925(88)
43.16(3)	1540(113)
44.288(12)	1142(98)

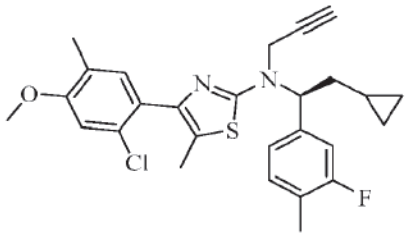
OTHER EMBODIMENTS

[0575] It is to be understood that the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

[0576] The following numbered paragraphs set out preferred features and preferred combinations of features of the present invention:

1. A pharmaceutical composition comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

2. The pharmaceutical composition of paragraph 1, comprising about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

3. The pharmaceutical composition of paragraph 1, comprising about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

4. The pharmaceutical composition of paragraph 1, comprising about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

5. The pharmaceutical composition of any one of paragraphs 1-4, comprising an oily phase vehicle.

6. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 1 wt% to about 50 wt% of the oily phase vehicle.

7. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 20 wt% to about 50 wt% of the oily phase vehicle.

8. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 35 wt% to about 45 wt% of the oily phase vehicle.

9. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 39 wt% of the oily phase vehicle.

10. The pharmaceutical composition of any one of paragraphs 1-9, wherein the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

11. The pharmaceutical composition of any one of paragraphs 1-10, wherein the oily phase vehicle is medium-chain triglycerides.

12. The pharmaceutical composition of any one of paragraphs 10-11, wherein the medium-chain triglycerides are Labrafac TM Lipophile WL1349.

13. The pharmaceutical composition of any one of paragraphs 10-11, wherein the medium-chain triglycerides are Miglyol 812N.

14. The pharmaceutical composition of any one of paragraphs 1-13, comprising an emulsifying agent.

15. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 5 wt% to about 50 wt% of the emulsifying agent.

16. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 10 wt% to about 30 wt% of the emulsifying agent.

17. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 15 wt% to about 25 wt% of the emulsifying agent.

18. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 20 wt% of the emulsifying agent.

19. The pharmaceutical composition of any one of paragraphs 1-18, wherein the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

20. The pharmaceutical composition of any one of paragraphs 1-19, wherein the emulsifying agent is propylene glycol dicaprylate/dicaprate.

21. The pharmaceutical composition of any one of paragraphs 19-20, wherein the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

22. The pharmaceutical composition of any one of paragraphs 1-21, comprising a nonionic surfactant.

23. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 5 wt% to about 50 wt% of the nonionic surfactant.

24. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 10 wt% to about 30 wt% of the nonionic surfactant.

25. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 15 wt% to about 25 wt% of the nonionic surfactant.

26. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 19 wt% of the nonionic surfactant.

27. The pharmaceutical composition of any one of paragraphs 1-26, wherein the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides.

28. The pharmaceutical composition of any one of paragraphs 1-27, wherein the nonionic surfactant is lauroyl polyoxyl-32 glycerides.

29. The pharmaceutical composition of any one of paragraphs 27-28, wherein the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

30. The pharmaceutical composition of any one of paragraphs 1-29, comprising a solubilizing agent.

31. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 1 wt% to about 50 wt% of the solubilizing agent.

32. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 1 wt% to about 20 wt% of the solubilizing agent.

33. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 5 wt% to about 15 wt% of the solubilizing agent.

34. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 11 wt% of the solubilizing agent.

35. The pharmaceutical composition of any one of paragraphs 1-34, wherein the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer.

36. The pharmaceutical composition of any one of paragraphs 1-35, wherein the solubilizing agent is vitamin E polyethylene glycol succinate.

37. The pharmaceutical composition of any one of paragraphs 35-36, wherein the vitamin E polyethylene glycol succinate is Kolliphor® TPGS.

38. The pharmaceutical composition of any one of paragraphs 35-36, wherein the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

39. The pharmaceutical composition of paragraph 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) an oily phase vehicle;
(c) an emulsifying agent;
(d) a nonionic surfactant; and
(e) a solubilizing agent.

40. The pharmaceutical composition of paragraph 1, comprising:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 35 wt% to about 45 wt% of an oily phase vehicle;
(c) about 15 wt% to about 25 wt% of an emulsifying agent;
(d) about 15 wt% to about 25 wt% of a nonionic surfactant; and
(e) about 5 wt% to about 15 wt% of a solubilizing agent.

41. The pharmaceutical composition of paragraph 1, comprising:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 39 wt% of an oily phase vehicle;
(c) about 20 wt% of an emulsifying agent;
(d) about 19 wt% of a nonionic surfactant; and
(e) about 11 wt% of a solubilizing agent.

42. The pharmaceutical composition of paragraph 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) a medium-chain triglycerides component;
(c) a propylene glycol dicaprylate/dicaprate component;
(d) a lauroyl polyoxyl-32 glycerides component; and
(e) a vitamin E polyethylene glycol succinate component.

43. The pharmaceutical composition of paragraph 1, comprising:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) about 35 wt% to about 45 wt% of medium-chain triglycerides;
(c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;
(d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and
(e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

44. The pharmaceutical composition of paragraph 1, comprising:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) about 39 wt% of medium-chain triglycerides;
(c) about 20 wt% of propylene glycol dicaprylate/dicaprate;
(d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and
(e) about 11 wt% of vitamin E polyethylene glycol succinate.

45. The pharmaceutical composition of any one of paragraphs 1-44, wherein the compound of Formula (I), or pharmaceutically acceptable salt thereof, is in crystalline form.

46. The pharmaceutical composition of any one of paragraphs 1-45, comprising the compound of Formula (I) as a free base.

47. The pharmaceutical composition of paragraph 45, wherein the crystalline form comprises Form I of the compound of Formula (I).

48. The pharmaceutical composition of any one of paragraphs 1-47, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to

about 200 mg, based on the weight of the free base.

49. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg, based on the weight of the free base.

50. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg, based on the weight of the free base.

51. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg, based on the weight of the free base.

52. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg, based on the weight of the free base.

53. The pharmaceutical composition of any one of paragraphs 1-52, that is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

54. The pharmaceutical composition of any one of paragraphs 48-53, wherein the pharmaceutical composition is in tablet form.

55. The pharmaceutical composition of any one of paragraphs 48-53, wherein the pharmaceutical composition is in capsule form.

56. The pharmaceutical composition of any one of paragraphs 48-55, wherein the dosage form is coated.

57. A method for preparing the pharmaceutical composition of any one of paragraphs 1-56, comprising:

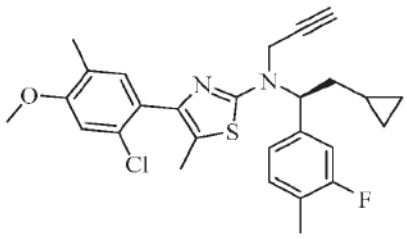
(a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;
(b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

58. The method of paragraph 57, further comprising:

(d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and
(e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

59. A pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;
(b) one or more of a sweetener, an anti-oxidant, and a flavor; and
(c) a liquid vehicle.

60. The pharmaceutical composition of paragraph 59, comprising about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

61. The pharmaceutical composition of paragraph 59, comprising about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

62. The pharmaceutical composition of paragraph 59, comprising about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

63. The pharmaceutical composition of any one of paragraphs 59-62, comprising a sweetener.

64. The pharmaceutical composition of any one of paragraphs 59-63, comprising about 0.01 w/v% to about 1.5 w/v% of the sweetener.

65. The pharmaceutical composition of any one of paragraphs 59-63, comprising about 0.1 w/v% to about 0.5 w/v% of the sweetener.

66. The pharmaceutical composition of any one of paragraphs 59-63, comprising about 0.15 w/v% of the sweetener.

67. The pharmaceutical composition of any one of paragraphs 59-66, wherein the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and avantame.

68. The pharmaceutical composition of any one of paragraphs 59-67, wherein the sweetener is saccharin.

69. The pharmaceutical composition of any one of paragraphs 59-68, comprising an anti-oxidant.

70. The pharmaceutical composition of any one of paragraphs 59-69, comprising about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant.

71. The pharmaceutical composition of any one of paragraphs 59-69, comprising about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant.

72. The pharmaceutical composition of any one of paragraphs 59-69, comprising about 0.17 w/v% of the anti-oxidant.

73. The pharmaceutical composition of any one of paragraphs 59-72, wherein the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid.

74. The pharmaceutical composition of any one of paragraphs 59-73, wherein the anti-oxidant is butylated hydroxytoluene.

75. The pharmaceutical composition of any one of paragraphs 59-74, comprising a flavor.

76. The pharmaceutical composition of any one of paragraphs 59-75, comprising about 0.01 w/v% to about 0.5 w/v% of the flavor.

77. The pharmaceutical composition of any one of paragraphs 59-75, comprising about 0.05 w/v% to about 0.2 w/v% of the flavor.

78. The pharmaceutical composition of any one of paragraphs 59-75, comprising about 0.10 w/v% of the flavor.

79. The pharmaceutical composition of any one of paragraphs 59-78, wherein the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor.

80. The pharmaceutical composition of any one of paragraphs 59-79, wherein the flavor is FONA orange flavor.

81. The pharmaceutical composition of any one of paragraphs 59-80, comprising about 50 w/v% to about 99.9 w/v%