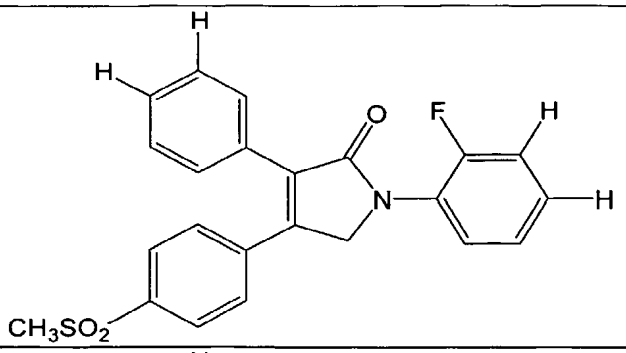
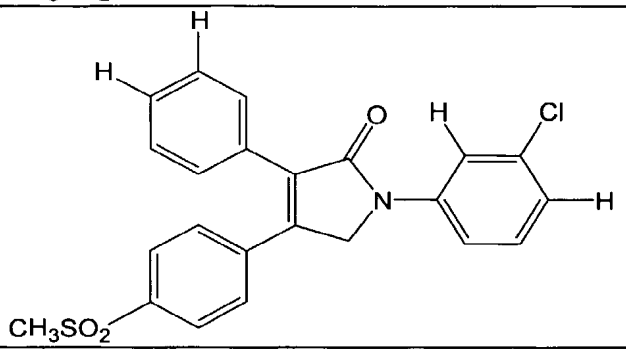
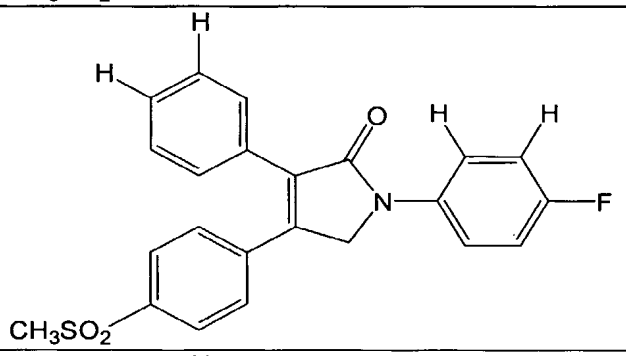
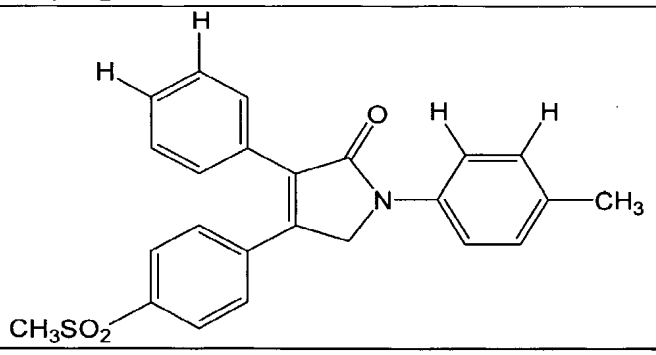
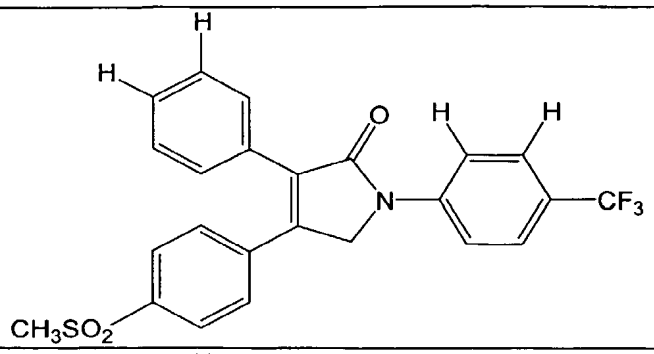
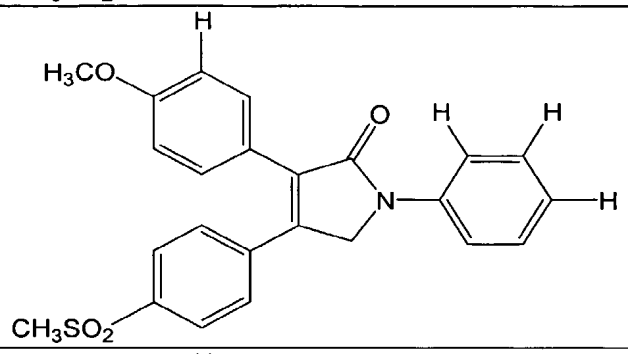
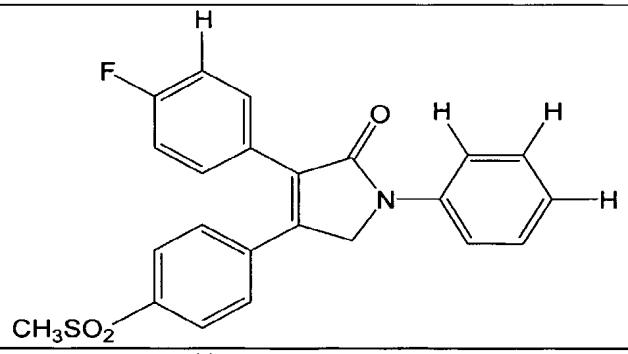
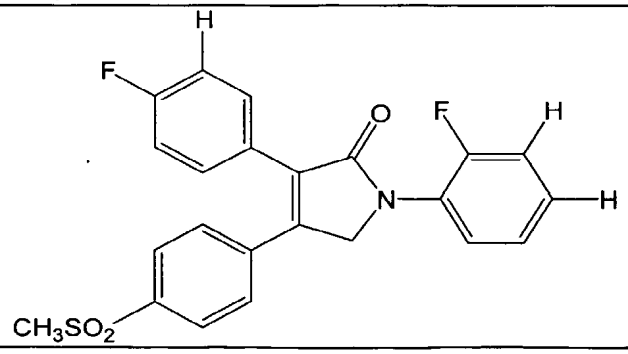
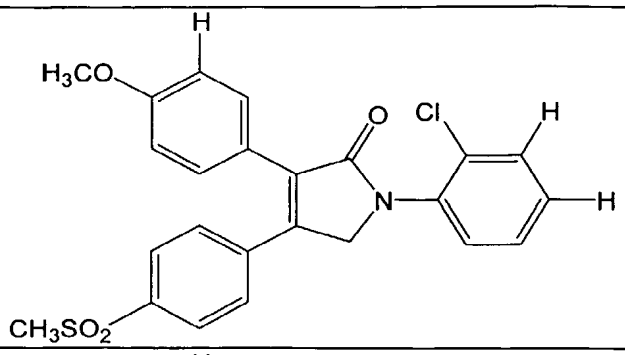
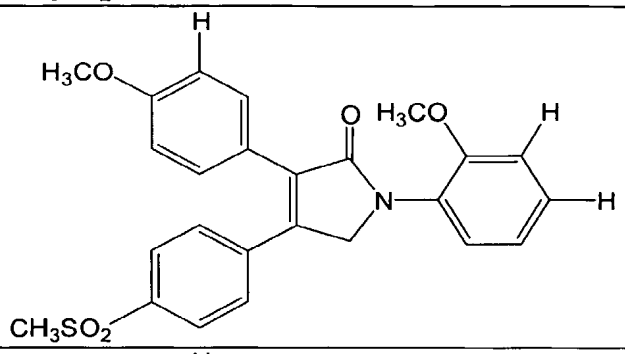
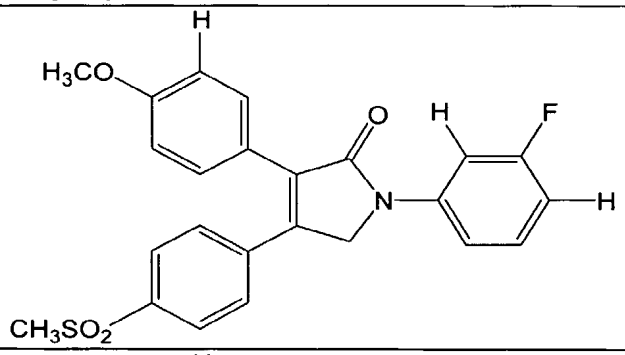
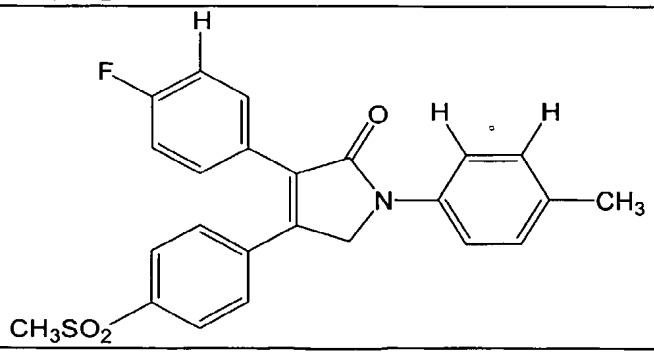
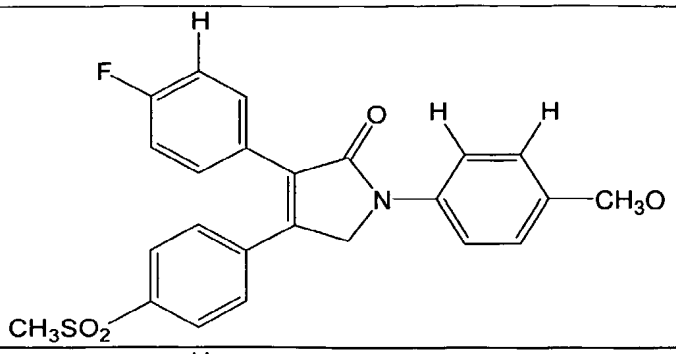
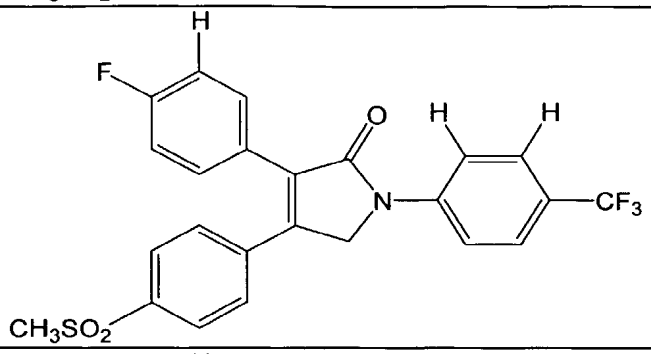
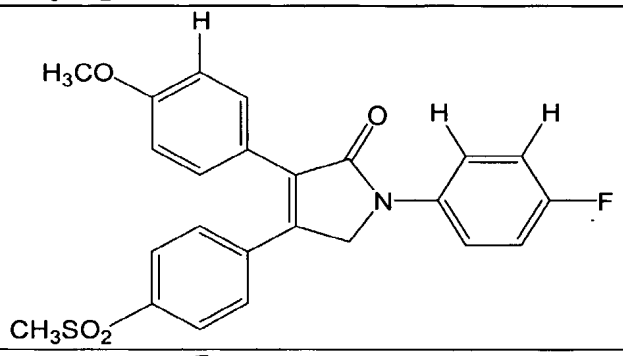
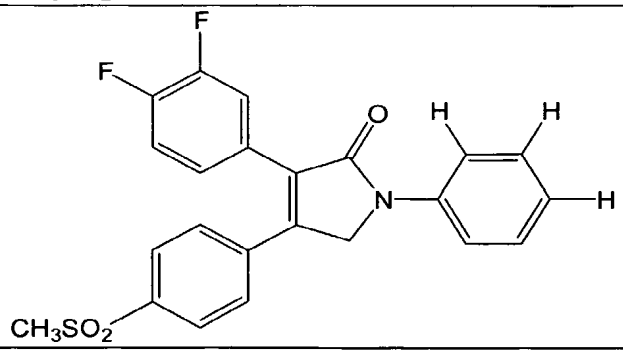
Compound Number	Structural Formula
B-237	
B-238	
B-239	
B-240	

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Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc. PGR2026-00061

Compound Number	Structural Formula
B-241	
B-242	
B-243	
B-244	

Compound Number	Structural Formula
B-245	
B-246	
B-247	
B-248	

Compound Number	Structural Formula
B-249	
B-250	
B-251	
B-252	

[0415] The cyclooxygenase-2 selective inhibitor employed in the present invention can exist in tautomeric, geometric or stereoisomeric forms. Generally speaking, suitable cyclooxygenase-2 selective inhibitors that are in tautomeric, geometric or stereoisomeric forms are those compounds that inhibit cyclooxygenase-2 activity by about 25%, more typically by about 50%, and even more typically, by about

75% or more when present at a concentration of 100 μM or less. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the invention. The terms "cis" and "trans", as used herein, denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans"). Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms. Furthermore, some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures or R and S forms for each stereocenter present.

[0416] The cyclooxygenase-2 selective inhibitors utilized in the present invention may be in the form of free bases or pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically-acceptable salts" are salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt may vary, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds for use in the present methods may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of use in the present methods include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for

example, the appropriate acid or base with the compound of any Formula set forth herein.

[0417] The cyclooxygenase-2 selective inhibitors of the present invention can be formulated into pharmaceutical compositions and administered by a number of different means that will deliver a therapeutically effective dose. Such compositions can be administered orally, parenterally, by inhalation spray, rectally, intradermally, transdermally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania (1975), and Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y. (1980).

[0418] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

[0419] Suppositories for rectal administration of the compounds discussed herein can be prepared by mixing the active agent with a suitable non-irritating excipient such as cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature, and which will therefore melt in the rectum and release the drug.

[0420] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds are

ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

[0421] For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

[0422] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0423] The amount of active ingredient that can be combined with the carrier materials to produce a single dosage of the cyclooxygenase-2 selective inhibitor will vary depending upon the patient and the particular mode of administration. In general, the pharmaceutical compositions may contain a cyclooxygenase-2 selective inhibitor in the range of about 0.1 to 2000 mg, more typically, in the range of about 0.5 to 500 mg and still more typically, between about 1 and 200 mg. A daily dose of about 0.01 to 100 mg/kg body weight, or more typically, between about 0.1 and about 50 mg/kg body weight and even more typically, from about 1 to 20 mg/kg body weight, may be

appropriate. The daily dose is generally administered in one to about four doses per day.

[0424] In one embodiment, when the cyclooxygenase-2 selective inhibitor comprises rofecoxib, it is typical that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more typically, from about 0.18 to about 0.4 mg/day·kg.

[0425] In still another embodiment, when the cyclooxygenase-2 selective inhibitor comprises etoricoxib, it is typical that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0426] Further, when the cyclooxygenase-2 selective inhibitor comprises celecoxib, it is typical that the amount used is within a range of from about 1 to about 20 mg/day·kg, even more typically, from about 1.4 to about 8.6 mg/day·kg, and yet more typically, from about 2 to about 3 mg/day·kg.

[0427] When the cyclooxygenase-2 selective inhibitor comprises valdecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0428] In a further embodiment, when the cyclooxygenase-2 selective inhibitor comprises parecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 1 to about 3 mg/day·kg.

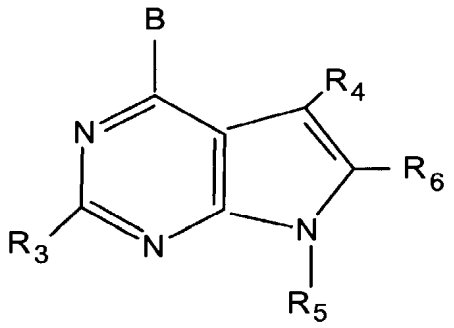
[0429] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

[0430] In addition to a cyclooxygenase-2 selective inhibitor, the combination therapy of the present invention comprises a corticotropin releasing factor antagonist. In one embodiment, the corticotropin releasing factor antagonist in this therapeutic combination is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695 (N-(2-chloro-4,6-dimethylphenyl)-1-[1-methoxymethyl-(2-

methoxyethyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine mesylate)), D-PheCRF 12-41, and N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine. In one embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of *α*-helical CRF 9-41, antalarmin, CP-154,526, and astressin. In another embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of *α*-helical CRF 9-41 and antalarmin. In yet another embodiment, the corticotropin releasing factor antagonist of this therapeutic combination is *α*-helical CRF 9-41.

[0431] In one embodiment, the corticotropin releasing factor antagonist is represented by Formula *(VI)*:



(VI)

[0432] wherein:

[0433] B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCR_1R_2R_{11}$, $-OCR_1R_2R_{11}$, $-SCR_1R2R_{11}$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$, $-CR_2R_{11}OR_1$, $-CR_2R_{11}SR_1$, or $-C(O)R_2$;

[0434] R_1 is hydrogen, or C_1-C_6 alkyl optionally substituted with from one to two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, $-O(C_1$-C_6 alkyl), $-ONH(C_1$-C_4 alkyl), $-ON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), amino, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), $-S(C_1$-C_6 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-NH(C_1$-C_4 alkyl), -COOH, $-O(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2$ (C_1-C_4 alkyl), $-SO_2$ NH(C_1-C_4 alkyl), $-SO_2$ (C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein each of the foregoing C_1-C_6 alkyl moieties in the definition of R_1 may contain one or two double or triple bonds;

[0435] R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl,

furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein one or two of the carbon atoms of any of said cycloalkyl moieties may optionally be replaced, independently, by O, S or -N-Z wherein Z is hydrogen, C_1-C_4 alkyl or C_1-C_4 alkanoyl, and wherein R_2 may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or by one substituent selected from hydroxy, bromo, iodo, C_1-C_6 alkoxy, -O(C_1-C_6 alkyl), -ON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl) (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -COOH, -O(C_1-C_4 alkyl), -NH(C1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2 (C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein each of the foregoing C_1-C_{12} alkyl and C_1-C_{10} alkylene moieties in the definition may optionally contain one to three double or triple bonds; or R_1 and R_2, taken together with the atom to which they are attached, may form a saturated 3- to 8-membered ring which, if it is a 5- to 8-membered ring, may optionally contain one to two double bonds, and wherein one or two of the carbon atoms of said 5- to 8- membered ring may optionally be replaced, independently, by O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl or benzyl;

[0436] R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), or -SO_2 (C_1-C_4 alkyl), wherein each of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the definition of R_3 may contain one double or triple bond and may optionally be substituted with from 1 to 3 substituents independently selected from the group consisting of hydroxy, C_1-C_3 alkoxy, fluoro, chloro or C_1-C_3 thioalkyl;

[0437] R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_2 alkyl), -SO_n (C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein each of the foregoing C_1-C_6 alkyl moieties in the definition of R_4 may optionally be substituted with one substituent selected from hydroxy, trifluoromethyl, amino, carboxy, amido, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano and nitro;

[0438] R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl,

benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolindinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or a 3- or 8-membered cycloalkyl or 9- or 12-membered bicycloalkyl ring, wherein one or two of the carbon atoms in said ring may optionally be replaced, independently, by O, S or -N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, and wherein each of the above R_5 groups may optionally be substituted with one or more substituents, preferably with two or three substituents, independently selected from fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and trifluoromethyl, or with one substituent selected from hydroxy, iodo, cyano, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -S(C_1-C_6 alkyl), -SO_2(C_1-C_6 alkyl), and wherein each of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the definition of R_5 may optionally be substituted with from one to two substituents independently selected from fluoro, chloro, hydroxy, C_1-C_4 alkoxy, amino, methylamino, dimethylamino and acetyl, and wherein each of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the definition of R_5 may optionally contain one double or triple bond; with the proviso that R_5 is not unsubstituted phenyl;

[0439] R_6 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_2 alkyl), -SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, and wherein each of the foregoing (C_1-C_6)alkyl moieties in the definition of R_6 may be optionally substituted with one substituent selected from hydroxy, trifluoromethyl, amino, carboxy, amido, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano and nitro;

[0440] R_7 is hydrogen, hydroxy, fluoro, chloro, -COO(C_1-C_2 alkyl), cyano, or -CO(C_1-C_2 alkyl); and

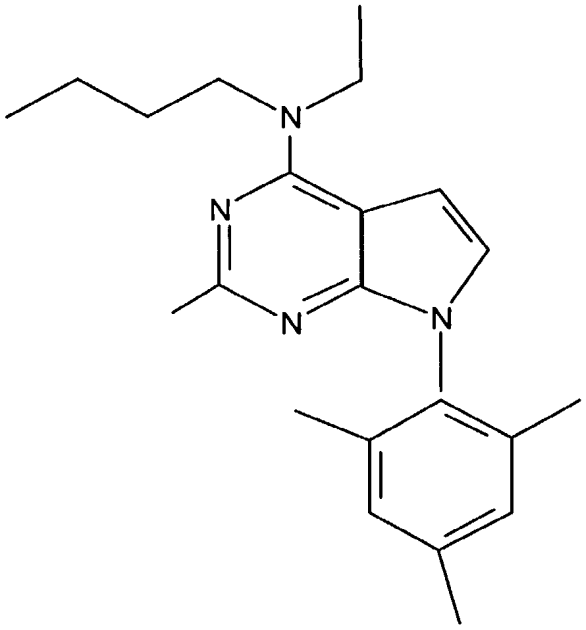
[0441] R_8 is hydrogen or C_1-C_4 alkyl;

[0442] with the proviso that:

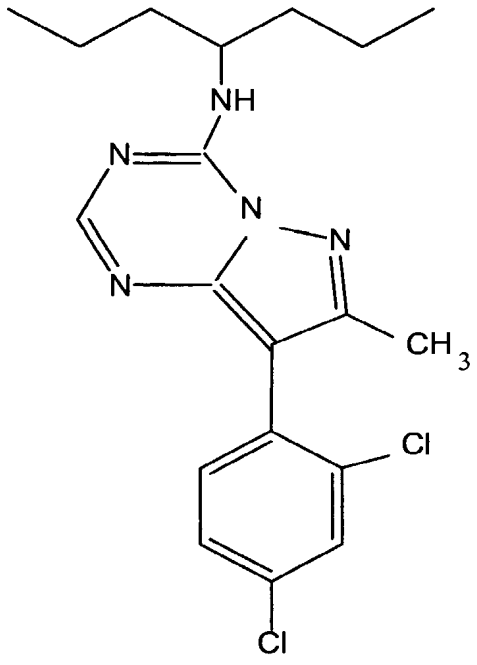
[0443] B is not a straight chain alkyl when R_5 is unsubstituted cycloalkyl, R_3 and R_4 are both hydrogen and R_6 is hydrogen or methyl; B is not NHR_2 wherein R_2 is benzyl or thienylmethyl; and B is not methylamino or hydroxyethylamino when R_5 is p-bromophenyl and R_3, R_4 and R_6 are methyl.

[0444] Suitable examples of compounds having formula VI are described in WO 94/13676, which is hereby incorporated by reference in its entirety.

[0445] In another embodiment, the corticotropin releasing factor antagonist is CP-154,526, having the formula:



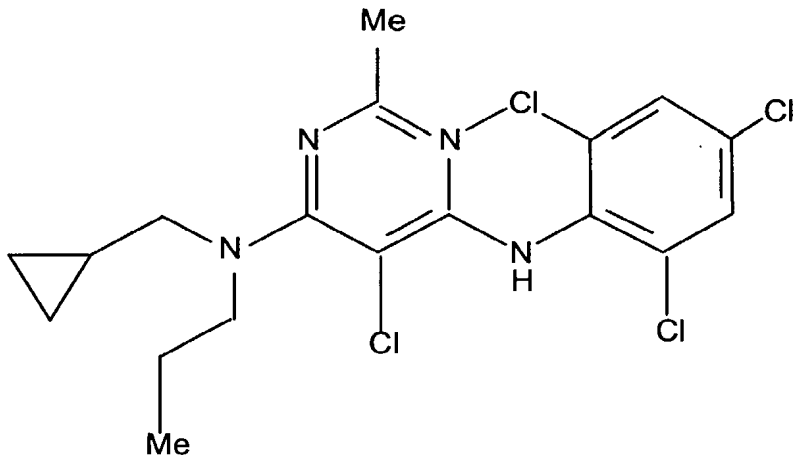
[0446] In yet another embodiment of the invention, the corticotropin releasing factor antagonist is DMP 696, having the formula:



[0447] In still another embodiment of the invention, the corticotropin releasing factor antagonist is α-helical CRF 9-41, having the sequence:

[0448] Asp-Leu-Thr-Phe-His-Leu-Arg-Glu-Met-Leu-Glu-Met-Ala-Lys-ala-Glu-Gln-Ala-Glu-Gln-Ala-Leu-Asn-Arg-Leu-Leu-Glu-Ala-NH2 (Sequence ID No.1).

[0449] In another embodiment of the invention, the corticotropin releasing factor antagonist is NBI 27914 hydrochloride, having the formula:



[0450] Generally speaking, the corticotropin releasing antagonist can be administered as a pharmaceutical composition with or without a carrier. The terms "pharmaceutically acceptable carrier" or "carrier" refer to any generally acceptable excipient or drug delivery composition that is relatively inert and non-toxic. Exemplary carriers include sterile water, salt solutions (such as Ringer's solution), alcohols, gelatin, talc, viscous paraffin, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, calcium carbonate, carbohydrates (such as lactose, sucrose, dextrose, mannose, albumin, starch), cellulose, silica gel, polyethylene glycol (PEG), dried skim milk, rice flour, magnesium stearate, and the like. Suitable formulations and additional carriers are described in Remington's Pharmaceutical Sciences, (17.sup.th Ed., Mack Pub. Co., Easton, Pa.). Such preparations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, preservatives and/or aromatic substances and the like which do not deleteriously react with the active compounds. Typical preservatives can include, potassium sorbate, sodium metabisulfite, methyl paraben, propyl paraben, thimerosal, etc. The compositions can also be combined

where desired with other active substances, e.g., enzyme inhibitors, to reduce metabolic degradation.

[0451] Moreover, the corticotropin releasing antagonist can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The method of administration can dictate how the composition will be formulated. For example, the composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, or magnesium carbonate.

[0452] In another embodiment, the corticotropin releasing antagonist can be administered intravenously, parenterally, intramuscularly, subcutaneously, orally, nasally, topically, by inhalation, by implant, by injection, or by suppository. For enteral or mucosal application (including via oral and nasal mucosa), particularly suitable are tablets, liquids, drops, suppositories or capsules. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Liposomes, microspheres, and microcapsules are available and can be used. Pulmonary administration can be accomplished, for example, using any of various delivery devices known in the art such as an inhaler. See. e.g. S. P. Newman (1984) in Aerosols and the Lung, Clarke and Davis (eds.), Butterworths, London, England, pp. 197-224; PCT Publication No. WO 92/16192; PCT Publication No. WO 91/08760. For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-polyoxypropylene block polymers, and the like.

[0453] The actual effective amounts of compound or drug can and will vary according to the specific composition being utilized, the mode of administration and the age, weight and condition of the subject. Dosages for a particular individual subject can be determined by one of ordinary skill in the art using conventional considerations.

[0454] By way of example, in one embodiment when the corticotropin releasing antagonist is α-helical CRF 9-41, the amount administered daily is typically from about 0.5 to about 3500 milligrams. In an alternative of this embodiment, the amount of α-helical CRF 9-41 administered daily is between about 1 and about 50 milligrams/kilogram of the subject's weight. In another alternative of this embodiment,

the amount of α-helical CRF 9-41 administered daily is between about 5 and about 20 milligrams/kilogram of the subject's weight.

[0455] By way of further example, in another embodiment the corticotropin releasing antagonist is antalarmin, and the amount administered daily is typically from about 50 to about 4000 miligrams. In an alternative of this embodiment, the amount of antalarmin administered daily is between about 1 and 50 milligrams/kilogram of the subject's weight. In another alternative of this embodiment, the amount of antalarmin administered daily is between about 5 and about 30 milligrams/kilogram of the subject's weight.

[0456] Moreover, the corticotropin releasing factor antagonist can be a combination of two or more different corticotropin releasing antagonists. The multiple antagonists can be administered separately or may be co-administered as a single composition and may be administered as discussed above.

[0457] By way of example, in another embodiment the corticotropin releasing antagonist is a combination of α-helical CRF 9-41 and antalarmin, and the amount of the combination antagonist administered daily is typically from about 0.1 to about 1000 μg. In an alternative of this embodiment, the amount of the combination antagonist administered daily is between about 1 and 50 milligrams/ kilogram of the subject's weight. In another alternative of this embodiment, the amount of the combination antagonist administered daily is between about 5 and about 25 milligrams/ kilogram of the subject's weight.

[0458] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

[0459] Generally speaking, when the composition is administered to treat an ischemic mediated condition, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered to the subject as soon as possible after the reduction in blood flow to the central nervous system in order to reduce the extent of ischemic damage. Typically, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered within about 10 days after the reduction of blood flow to the central nervous system and more typically, within 24 hours. In still another embodiment, the corticotropin releasing factor antagonist and

cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours after the reduction in blood flow to the central nervous system. In another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours after the reduction in blood flow to the central nervous system. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 3 to about 4 hours after the reduction in blood flow to the central nervous system. In yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours after the reduction in blood flow to the central nervous system.

[0460] Generally speaking, when the composition is administered to prevent an ischemic mediated condition, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered to the subject such that the antagonist has sufficient time to bind to the corticotropin releasing factor receptors and/or to exact its preventative effects. Typically, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered within about 24 hours before the reduction of blood flow to the central nervous system and more typically, within about 12 hours. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours before the reduction in blood flow to the central nervous system. In another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours before the reduction in blood flow to the central nervous system. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 3 to about 4 hours before the reduction in blood flow to the central nervous system. In yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours before the reduction in blood flow to the central nervous system. In still a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 1 hour before the reduction in blood flow to the central nervous system. In still yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 1/2 hour before the reduction in blood flow to the central nervous system.

[0461] Moreover, the timing of the administration of the cyclooxygenase-2 selective inhibitor in relation to the administration of the corticotropin releasing factor antagonist may also vary from subject to subject. In one embodiment, the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist may be administered substantially simultaneously, meaning that each agent may be administered to the subject at approximately the same time. For example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning on the same day as the beginning of the corticotropin releasing factor antagonist and extending to a period after the end of the corticotropin releasing factor antagonist. Alternatively, the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist may be administered sequentially, meaning that they are each administered at separate times during separate treatments. In one embodiment, for example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning prior to administration of the corticotropin releasing factor antagonist and ending after administration of the corticotropin releasing factor antagonist. Of course, it is also possible that the cyclooxygenase-2 selective inhibitor may be administered either more or less frequently than the corticotropin releasing factor antagonist. Moreover, it will be apparent to those skilled in the art that it is possible, and perhaps desirable, to combine various times and methods of administration in the practice of the present invention.

COMBINATION THERAPIES

[0462] Generally speaking, it is contemplated that the composition employed in the practice of the invention may include one or more of any of the cyclooxygenase-2 selective inhibitors detailed above in combination with one or more of any of the corticotropin releasing factor antagonists detailed above. By way of a non-limiting example, Table 4a details a number of suitable combinations that are useful in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4a.

TABLE 4a

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing Factor Antagonist
a compound having formula I	α-helical CRF 9-41
a compound having formula I	antalarmin
a compound having formula I	astressin
a compound having formula I	NBI 27914
a compound having formula I	R121919
a compound having formula I	R121920
a compound having formula I	antisauvagine-30
a compound having formula I	DMP-695
a compound having formula I	CP-154,526
a compound having formula II	α-helical CRF 9-41
a compound having formula II	antalarmin
a compound having formula II	astressin
a compound having formula II	NBI 27914
a compound having formula II	R121919
a compound having formula II	R121920
a compound having formula II	antisauvagine-30
a compound having formula II	DMP-695
a compound having formula II	CP-154,526
a compound having formula III	α-helical CRF 9-41
a compound having formula III	antalarmin
a compound having formula III	astressin
a compound having formula III	NBI 27914
a compound having formula III	R121919
a compound having formula III	R121920
a compound having formula III	antisauvagine-30
a compound having formula III	DMP-695
a compound having formula III	CP-154,526
a compound having formula IV	α-helical CRF 9-41
a compound having formula IV	antalarmin
a compound having formula IV	astressin
a compound having formula IV	NBI 27914
a compound having formula IV	R121919
a compound having formula IV	R121920
a compound having formula IV	antisauvagine-30
a compound having formula IV	DMP-695
a compound having formula IV	CP-154,526
a compound having formula V	α-helical CRF 9-41
a compound having formula V	antalarmin
a compound having formula V	astressin
a compound having formula V	NBI 27914
a compound having formula V	R121919
a compound having formula V	R121920
a compound having formula V	antisauvagine-30
a compound having formula V	DMP-695
a compound having formula V	CP-154,526

[0463] By way of further example, Table 4b details a number of suitable combinations that may be employed in the methods and compositions of the present invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4b.

TABLE 4b

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	*α*-helical CRF 9-41

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	antalarmin

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	astressin

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	NBI 27914

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	R121919

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	R121920

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	antisauvagine-30

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	DMP-695

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	CP-154,526

[0464] By way of yet further example, Table 4c details additional suitable combinations that may be employed in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4c.

TABLE 4c

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
Celecoxib	α-helical CRF 9-41
Celecoxib	antalarmin
Celecoxib	astressin
Celecoxib	NBI 27914
Celecoxib	R121919
Celecoxib	R121920
Celecoxib	antisauvagine-30
Celecoxib	DMP-695
Celecoxib	CP-154,526
Cimicoxib	α-helical CRF 9-41
Cimicoxib	antalarmin
Cimicoxib	astressin
Cimicoxib	NBI 27914
Cimicoxib	R121919
Cimicoxib	R121920
Cimicoxib	antisauvagine-30
Cimicoxib	DMP-695
Cimicoxib	CP-154,526
Deracoxib	α-helical CRF 9-41
Deracoxib	antalarmin
Deracoxib	astressin
Deracoxib	NBI 27914
Deracoxib	R121919
Deracoxib	R121920
Deracoxib	antisauvagine-30
Deracoxib	DMP-695
Deracoxib	CP-154,526
Valdecoxib	α-helical CRF 9-41
Valdecoxib	antalarmin
Valdecoxib	astressin
Valdecoxib	NBI 27914
Valdecoxib	R121919
Valdecoxib	R121920
Valdecoxib	antisauvagine-30
Valdecoxib	DMP-695
Valdecoxib	CP-154,526
Rofecoxib	α-helical CRF 9-41
Rofecoxib	antalarmin
Rofecoxib	astressin
Rofecoxib	NBI 27914
Rofecoxib	R121919
Rofecoxib	R121920
Rofecoxib	antisauvagine-30
Rofecoxib	DMP-695
Rofecoxib	CP-154,526
Etoricoxib	α-helical CRF 9-41

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
Etoricoxib	antalarmin
Etoricoxib	astressin
Etoricoxib	NBI 27914
Etoricoxib	R121919
Etoricoxib	R121920
Etoricoxib	antisauvagine-30
Etoricoxib	DMP-695
Etoricoxib	CP-154,526
Meloxicam	α-helical CRF 9-41
Meloxicam	antalarmin
Meloxicam	astressin
Meloxicam	NBI 27914
Meloxicam	R121919
Meloxicam	R121920
Meloxicam	antisauvagine-30
Meloxicam	DMP-695
Meloxicam	CP-154,526
Parecoxib	α-helical CRF 9-41
Parecoxib	antalarmin
Parecoxib	astressin
Parecoxib	NBI 27914
Parecoxib	R121919
Parecoxib	R121920
Parecoxib	antisauvagine-30
Parecoxib	DMP-695
Parecoxib	CP-154,526
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	α-helical CRF 9-41
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	antalarmin
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	astressin
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	NBI 27914
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	R121919
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	R121920
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	antisauvagine-30

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	DMP-695
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	CP-154,526
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	α-helical CRF 9-41
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	antalarmin
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	astressin
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	NBI 27914
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	R121919
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	R121920
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	antisauvagine-30
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	DMP-695
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	CP-154,526
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	α-helical CRF 9-41
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	antalarmin
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	astressin
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	NBI 27914
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	R121919

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	R121920
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	antisauvagine-30
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	DMP-695
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	CP-154,526
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	α-helical CRF 9-41
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	antalarmin
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	astressin
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	NBI 27914
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	R121919
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	R121920
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	antisauvagine-30
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	DMP-695
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	CP-154,526

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	α-helical CRF 9-41
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	antalarmin
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	astressin
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	NBI 27914
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	R121919
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	R121920
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	antisauvagine-30
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	DMP-695
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	CP-154,526
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	α-helical CRF 9-41
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	antalarmin
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	astressin
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	NBI 27914
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	R121919
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	R121920
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	antisauvagine-30

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	DMP-695
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	CP-154,526
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	α-helical CRF 9-41
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	antalarmin
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	astressin
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	NBI 27914
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	R121919
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	R121920
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	antisauvagine-30
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	DMP-695
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	CP-154,526
Lumiracoxib	α-helical CRF 9-41
Lumiracoxib	antalarmin
Lumiracoxib	astressin
Lumiracoxib	NBI 27914
Lumiracoxib	R121919
Lumiracoxib	R121920
Lumiracoxib	antisauvagine-30
Lumiracoxib	DMP-695
Lumiracoxib	CP-154,526

DIAGNOSIS OF A VASO-OCCLUSION

[0100] One aspect of the invention encompasses diagnosing a subject in need of treatment or prevention for a vaso-occlusive event. A number of suitable methods for diagnosing a vaso-occlusion may be used in the practice of the invention.

In one such method, ultrasound may be employed. This method examines the blood flow in the major arteries and veins in the arms and legs with the use of ultrasound (high-frequency sound waves). In one embodiment, the test may combine Doppler® ultrasonography, which uses audio measurements to "hear" and measure the blood flow and duplex ultrasonography, which provides a visual image. In an alternative embodiment, the test may utilize multifrequency ultrasound or multifrequency transcranial Doppler® (MTCD) ultrasound.

Another method that may be employed encompasses injection of the subject with a compound that can be imaged. In one alternative of this embodiment, a small amount of radioactive material is injected into the subject and then standard techniques that rely on monitoring blood flow to detect a blockage, such as magnetic resonance direct thrombus imaging (MRDTI), may be utilized to image the vaso-occlusion. In an alternative embodiment, ThromboView® (commercially available from Agenix Limited) uses a clot-binding monoclonal antibody attached to a radiolabel. In addition to the methods identified herein, a number of other suitable methods known in the art for diagnosis of vaso-occlusive events may be utilized.

INDICATIONS TO BE TREATED

[0465] Typically, the composition comprising a therapeutically effective amount of a cyclooxygenase-2 selective inhibitor and a therapeutically effective amount of a corticotropin releasing factor antagonist may be employed to treat a number of ischemic mediated central nervous system disorders or injuries.

[0466] In some aspects, the invention provides a method to treat a central nervous system cell to prevent damage in response to a decrease in blood flow to the cell. Typically the severity of damage that may be prevented will depend in large part on the degree of reduction in blood flow to the cell and the duration of the reduction. By way of example, the normal amount of perfusion to brain gray matter in humans is about 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs when the flow of blood falls below approximately 8-10 mL/100 g of brain tissue/min, while at slightly higher levels (i.e. 20-35 mL/100 g of brain tissue/min) the tissue remains alive but not able to function. In one embodiment, apoptotic or necrotic cell death may be prevented. In still a further embodiment, ischemic-mediated damage, such as cytoxic edema or central nervous system tissue anoxemia, may be prevented. In each embodiment, the central nervous system cell may be a spinal cell or a brain cell.

[0467] Another aspect encompasses administrating the composition to a subject to treat a central nervous system ischemic condition. A number of central nervous system ischemic conditions may be treated by the composition of the invention. In one embodiment, the ischemic condition is a stroke that results in any type of ischemic central nervous system damage, such as apoptotic or necrotic cell death, cytoxic edema or central nervous system tissue anoxemia. The stroke may impact any area of the brain or be caused by any etiology commonly known to result in the occurrence of a stroke. In one alternative of this embodiment, the stroke is a brain stem stroke. Generally speaking, brain stem strokes strike the brain stem, which control involuntary life-support functions such as breathing, blood pressure, and heartbeat. In another alternative of this embodiment, the stroke is a cerebellar stroke. Typically, cerebellar strokes impact the cerebellum area of the brain, which controls balance and coordination. In still another embodiment, the stroke is an embolic stroke. In general terms, embolic strokes may impact any region of the brain and typically result from the blockage of an artery by a vaso-occlusion. In yet another alternative, the stroke may be a hemorrhagic stroke. Like embolic strokes, hemorrhagic stroke may impact any region of the brain, and typically result from a ruptured blood vessel characterized by a hemorrhage (bleeding) within or surrounding the brain. In a further embodiment, the stroke is a thrombotic stroke. Typically, thrombotic strokes result from the blockage of a blood vessel by accumulated deposits.

[0468] In another embodiment, the ischemic condition may result from a disorder that occurs in a part of the subject's body outside of the central nervous system, but yet still causes a reduction in blood flow to the central nervous system. These disorders may include, but are not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, a myocardial infarction, a transient ischemic attack, unstable angina, or sickle cell anemia. Moreover, the central nervous system ischemic condition may occur as result of the subject undergoing a surgical procedure. By way of example, the subject may be undergoing heart surgery, lung surgery, spinal surgery, brain surgery, vascular surgery, abdominal surgery, or organ transplantation surgery. The organ transplantation surgery may include heart, lung, pancreas or liver transplantation surgery. Moreover, the central nervous system ischemic condition may occur as a result of a trauma or injury to a part of the subject's body outside the central nervous system. By way of example, the trauma or injury may cause a degree of bleeding that significantly reduces the total volume of blood in the subject's body.

Because of this reduced total volume, the amount of blood flow to the central nervous system is concomitantly reduced. By way of further example, the trauma or injury may also result in the formation of a vaso-occlusion that restricts blood flow to the central nervous system.

[0469] Of course it is contemplated that the composition may be employed to treat the central nervous system ischemic condition irrespective of the cause of the condition. In one embodiment, the ischemic condition results from a vaso-occlusion. The vaso-occlusion may be any type of occlusion, but is typically a cerebral thrombosis or a cerebral embolism. In a further embodiment, the ischemic condition may result from a hemorrhage. The hemorrhage may be any type of hemorrhage, but is generally a cerebral hemorrhage or a subararachnoid hemorrhage. In still another embodiment, the ischemic condition may result from the narrowing of a vessel. Generally speaking, the vessel may narrow as a result of a vasoconstriction such as occurs during vasospasms, or due to arteriosclerosis. In yet another embodiment, the ischemic condition results from an injury to the brain or spinal cord.

[0470] In yet another aspect, the composition is administered to reduce infarct size of the ischemic core following a central nervous system ischemic condition. Moreover, the composition may also be beneficially administered to reduce the size of the ischemic penumbra or transitional zone following a central nervous system ischemic condition

[0471] In a further aspect, the invention provides treatment for subjects who are at risk of a vaso-occlusive event. These subjects may or may not have had a previous vaso-occlusive event. The invention embraces the treatment of subjects prior to a vaso-occlusive event, at a time of a vaso-occlusive event and following a vaso-occlusive event. Thus, as used herein, the "treatment" of a subject is intended to embrace both prophylactic and therapeutic treatment, and can be used either to limit or to eliminate altogether the symptoms or the occurrence of a vaso-occlusive event.

[0472] In addition to a cyclooxygenase-2 selective inhibitor and a corticotropin releasing factor antagonist, the composition of the invention may also include any agent that ameliorates the effect of a reduction in blood flow to the central nervous system. In one embodiment, the agent is an anticoagulant including thrombin inhibitors such as heparin and Factor Xa inhibitors such as warafin. In an additional embodiment, the agent is an anti-platelet inhibitor such as a GP IIb/IIIa inhibitor. In a further embodiment, the agent is selected from tissue plasminogen activator (t-PA), streptokinase, and

urokinase. Additional agents include but are not limited to, HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrizol; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); ß-adrenergic receptor blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

[0473] In a further aspect, the composition may be employed to reverse or lessen central nervous system cell damage following a traumatic brain or spinal cord injury. Traumatic brain or spinal cord injury may result from a wide variety of causes including, for example, blows to the head or back from objects; penetrating injuries from missiles, bullets, and shrapnel; falls; skull fractures with resulting penetration by bone pieces; and sudden acceleration or deceleration injuries. The composition of the invention may be beneficially utilized to treat the traumatic injury irrespective of its cause.

EXAMPLES

[0474] The following examples are intended to provide illustrations of the application of the present invention. The following examples are not intended to completely define or otherwise limit the scope of the invention.

EXAMPLE 1 - EVALUATION OF COX-1 AND COX-2 ACTIVITY *IN VITRO*

[0475] The COX-2 inhibitors suitable for use in this invention exhibit selective inhibition of COX-1 over COX-2, as measured by IC_{50} values when tested *in vitro* according to the following activity assays.

PREPARATION OF RECOMBINANT COX BACULOVIRUSES

[0476] Recombinant COX-1 and COX-2 are prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus

transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses are isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells ($2x10^8$) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer (10^7-10^8 pfu/mL) stocks of virus are prepared. For large scale production, SF9 insect cells are infected in 10 liter fermentors (0.5 x 106/mL) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet is homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80°C before being assayed for COX activity.

ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0477] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

FAST ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0478] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 µM phenol, 1 µM heme, 300 µM epinephrine) with the addition of 20 µl of 100 µM arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic

acid. Any reaction between the arachidonic acid and the enzyme is stopped after two minutes at 37°C by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. Indomethacin, a non-selective COX-2/COX-1 inhibitor, may be utilized as a positive control. The PGE_2 formed is typically measured by standard ELISA technology utilizing a PGE2 specific antibody, available from a number of commercial sources.

[0479] Each compound to be tested may be individually dissolved in 2 ml of dimethyl sulfoxide (DMSO) for bioassay testing to determine the COX-1 and COX-2 inhibitory effects of each particular compound. Potency is typically expressed by the IC_{50} value expressed as g compound/ml solvent resulting in a 50% inhibition of PGE2 production. Selective inhibition of COX-2 may be determined by the IC_{50} ratio of COX-1/COX-2.

[0480] By way of example, a primary screen may be performed in order to determine particular compounds that inhibit COX-2 at a concentration of 10 ug/ml. The compound may then be subjected to a confirmation assay to determine the extent of COX-2 inhibition at three different concentrations (e.g., 10 ug/ml, 3.3 ug/ml and 1.1 ug/ml). After this screen, compounds can then be tested for their ability to inhibit COX-1 at a concentration of 10 ug/ml. With this assay, the percentage of COX inhibition compared to control can be determined, with a higher percentage indicating a greater degree of COX inhibition. In addition, the IC_{50} value for COX-1 and COX-2 can also be determined for the tested compound. The selectivity for each compound may then be determined by the IC_{50} ratio of COX-1/COX-2, as set-forth above.

EXAMPLE 2

[0481] In the examples below, a combination therapy contains a corticotropin releasing factor antagonist with a vehicle and a COX-2 selective inhibitor. The efficacy of such combination therapy can be evaluated in comparison to a control treatment such as a placebo treatment, administration of a COX-2 inhibitor only, or administration of a corticotropin releasing factor antagonist only. By way of example, a combination therapy may contain α-helical CRF 9-41 and celecoxib, α-helical CRF 9-41 and valdecoxib, α-helical CRF 9-41 and rofecoxib, or α-helical CRF 9-41 and paracoxib. In addition, any of the above mentioned COX-2 selective inhibitors may be similarly combined with other CRF antagonists, both peptide and non-peptide, such as for example, the pyrrolopyrimidines disclosed in WO 94/13676, CP-154,526 (Schulz et. al.,

Proc. Natl. Acad. Sci. USA, Vol. 93 (1996) 10477-10482), [D-phe^{12},Nle^{21,38}]hCRF-(12-14) (Gulyas et al., *Proc. Natl. Acad. Sci. USA*, Vol 92 (1995) 10575-10579), D-phe CRF (12-14) (Lyons et al. (1991)), astressin (Gulyas et al., *Proc. Natl. Acad. Sci. USA*, Vol 92 (1995) 10575-10579), and antalarmin (Webster et al., *Endocrinology*, Vol. 137 (1996) 57475750), NBI 27914 (Chen et al., J Med. Chem. 39: 4358-4360 (1996)), R121919, R121920 (7-dipropylamino)-2,5-dimethyl-3-[2-(dimethylamino)-5-pyridyl] pyrazolo [1,5-a] pyrimidine) (Mackay et al. (2001)), and other CFR antagonists known in the art, including the monocyclic five membered and six membered ring antagonists, and antagonists from the fused bicyclic, fused tricyclic, polycyclic, and acyclic systems.

[0482] It should be noted that these are only several examples, and that any CFR antagonist in combination with any COX-2 inhibitor of the present invention may be tested as a combination therapy. The dosages of a CFR antagonist and COX-2 inhibitor in a particular therapeutic combination may be readily determined by a skilled artisan conducting the study. The length of the study treatment will vary on a particular study and can also be determined by one of ordinary skill in the art. The combination therapy may be administered for any time period necessary to treat the ischemic event. By way of example, the combination therapy may be administered for 12 weeks. The CFR antagonist and COX-2 inhibitor can be administered by any route as described herein, but are preferably administered orally or intravenously for human subjects.

[0483] The laboratory animal study can generally be performed as described in Strijbos, et al., (1994) *Brain Research*, 656: 405-408.

[0484] Briefly, the study can be performed on male, Sprague-Dawley rats ranging in size from 200 to 250 g. The rats are anesthetized with sodium pentobarbitone, and guide cannulae are implanted into the third ventricle of the brain. This is performed seven days prior to ischemia. At least four days later, the rats are subjected to a unilateral, permanent middle cerebral artery occlusion ("MCAo") under halothane anesthesia (2% in oxygen) by electrocoagulation according to a modification of the technique disclosed in Tamura et al. ((1981) *J. Cereb. Blood Flow Metab.*, 1: 53-60).Body temperature is maintained during surgery using a heated blanket.

[0485] Rats are then injected with either a vehicle (0.9% saline) or a corticotropin releasing hormone antagonist, such as, for example, α-helical CRF 9-41 (6.5 mmol; total volume 2 µl) both 30 minutes before and 10 minutes after the MCAo.

[0486] The brain tissue can then be examined histologically for the effects of combination therapy in comparison to the placebo. Neuronal damage is determined

histologically 24 hours after ischemia. 500 µm coronal brain slices are incubated with tetrazolium stain, a histological indicator of mitochondrial viability. Lesion size is then quantified by automated Seescan image analysis.

EXAMPLE 3

[0487] This laboratory animal study can generally be performed as described in Lyons, et al., (1991) *Brain Research*, 545: 339-342.

[0488] Male Winstar rats weighing 250-300 g are induced with 2.0% halothane, intubates, and ventilated with 1.0% halothane. PE-50 catheters are inserted into the femoral vein and artery, Core body temperature is monitored and maintained at 37.0± 0.5 °C. An intraventricular injection of α-helical CRF 9-41 is administered 0.80 mm posterior, 1.50 mm lateral to the bregma and 3.80 mm deep. Fifteen minutes after injection, transient forebrain ischemia is produced for a 10 minute period by the temporary occlusion of both common carotid arteries and phlebotomizing the rat to a MABP of 50 mm Hg. After 10 minutes of ischemia, previously withdrawn and heparinized blood was infused via the femoral venous catheter and cerebral blood flow is restored by removal of the carotid artery clips. Animals are then monitored under 1.0% halothane for a 1 hour period after reperfusion (restoration of carotid blood flow).

[0489] Seven groups of five animals each are studied. Three groups act as control groups: one normal control group, one ischemic control group, and one ischemic vehicle group. The remaining four groups receive α-helical CRF 9-41 in doses of 0.1, 1.0, 10.0, or 100.0 µg in 0.9 & BaCl, the volume of each injection being 5 µl. Arterial blood samples are taken and MABP is observed and recorded as follows: 10 minutes prior to injection of α-helical CRF 9-41; after 10 minutes of ischemia just prior to reperfusion; and 30 minutes following reperfusion.

[0490] Seven days post-op, each rat is anesthetized with 2.0% halothane and the brain fixed *in situ* with 40% formaldehyde/glacial acetic acid/methanol, 1:1:8 via transcardiac perfusion after briefly washing out the cephalic circulation with heparinized 0.9% NaCl for 45 seconds. The brains are then sectioned 7mm posterior to the rostral tip of the frontal lobes and 10µm paraffin sections are stained using hematoxylin and eosin. Hippocampal regions CA1-medial, CA1-lateral, CA3, and CA4 are examined bilaterally under light microscopy using an ocular grid with magnification X 400. Ten 100 X 100 µm area are analyzed in each hippocampal region. Neurons displaying a normal nucleus, cytoplasmic staining, and configuration are counted as living cells, as

opposed to pyknotic, hyperchromatic, and shrunken neurons that would be counted as dead cells.

[0491] The number of surviving neurons and dead neurons are compared to determine the efficacy of the combination therapy. Furthermore, the $PaCO_2$, PaO_2, pH_a, MABP, serum glucose, and core body temperatures among the rats representing the various control and experimental groups are compared to determine possible side effects of the therapy or the procedures used.

EXAMPLE 4

[0492] This laboratory animal study can generally be performed as described in Mackay et al., (2001) *J. Cerebral Blood Flow and Metabolism* 21:1208-1214.

[0493] Brain and plasma levels of R121920 are determined in a number of nonoccluded male Sprague–Dawley rats weighing 280 to 340 g. A skilled artisan can readily determine the appropriate number of animals to be used for a particular experiment. R121920 in a vehicle of water is administered to each of the rats as a single intravenous (IV) dose of 10 mg/kg. An equal number of the rats are killed at 2, 5, 15, 30, 60, 120, and 240 minutes subsequent to the administration of R121920. Brains are rapidly removed, flash frozen in liquid nitrogen, and stored at -70°C until analysis. 200 μL terminal blood samples are collected into tubes containing EDTA and are promptly centrifuged for 1.5 minutes at 10,000 g. The plasma is extracted, flash frozen in liquid nitrogen, and stored at –70°C until analysis. In order to quantify the concentration of R121920 in plasma, 150 μL acetonitrile is added to 50 μL plasma to precipitate protein, and the sample is centrifuged. The supernatant is collected and dried in a Speed Vac at room temperature. In order to prepare brain sample tissue, brain tissue is homogenized in 1 mL saline solution. Protein is precipitated by adding 3 vol acetonitrile to the sample solution. After reconstitution, all samples are analyzed in a reverse phase HPLC-UV system. The concentrations of R121920 in the samples is predicted from the linear regression of an external calibration curve of five spiked matrix standards.

[0494] All rats are initially anesthetized with a mixture of 5% halothane, 30% oxygen, and 70% nitrous oxide in an induction chamber and maintained thereafter with a nitrous oxide/oxygen mixture (70%:30%) containing 1.0% to 1.5% halothane administered through a face mask. Body temperature is monitored during the surgical

procedure by a rectal thermometer. The rats are maintained at a normothermic body temperature (37 °C ± 1°C) by use of a heating blanket controlled by the thermometer.

SUBTEMPORAL MIDDLE CEREBRAL ARTERY OCCLUSION MODEL

[0495] Permanent focal ischemia is induced in male Fischer 344 rats (240 to 280 g) through a subtemporal approach, as described in Tamara et al., (1981) *J. Cereb. Blood Flow Metab.* 1: 53-60. Briefly, the craniectomy is performed at the level where the MCA crosses the lateral olfactory tract. The dura is opened, and the artery is exposed and occluded by bipolar diathermy from its origin to the point where it crosses the inferior cerebral vein. All visible lenticulostriate branches are also occluded. The artery is transected to confirm complete occlusion and to prevent recanalization. The incision sites are closed, and the animals are allowed to recover from the anesthesia.

[0496] R121920 (10 mg/kg or 20 mg/kg) is administered as an initial bolus IV dose at the time of the onset of ischemia, followed by subsequent subcutaneous (SC) injections of R121920 (5 mg/kg or 10mg/kg, respectively) at hourly intervals thereafter for a period of 4 hours. Control rats are injected with a water vehicle (1 mL/kg) at the same time points.

[0497] The rats are killed 24 hours subsequent to MCA occlusion, the brains are removed, and 500 μm coronal sections are cut from the frontal pole on a vibratome. Brain sections are incubated in a 2% solution of triphenyl tetrazolium chloride at 37°C for 30 minutes to stain for viable tissue. Infarcted regions in the hemisphere, the cortex, and the striatum on each of the sections are delineated and transcribed onto scale diagrams and quantified by automated image analysis. The infarct volume for each of the brain regions is computed by summing the areas of damage from each section and multiplying them by the distance between the sections.

INTRALUMINAL SUTURE MIDDLE CEREBRAL ARTERY OCCLUSION MODEL.

[0498] The left middle cerebral artery (MCA) is permanently occluded in a number of male Sprague-Dawley rats weighing 280 to 340 g through a cervical carotid approach using the intraluminal suture technique in male as described in detail in Zea Longa et al., (1989) *Stroke* 20: 84-91. Briefly, the common carotid, the external carotid, and the internal carotid arteries are exposed via a midline cervical incision performed under an operating microscope. A 30-mm length of 3–0 monofilament nylon suture with tip heat-blunted and coated with poly-l-lysine solution (Belayev et al.,(1996) *Stroke* 27:

1616-1622) is advanced from the external carotid artery into the lumen of the internal carotid artery until mild resistance is felt (typically 19 to 20 mm depending upon the body weight of the rat), resulting in the occlusion of the origin of the MCA. After closure of the incision, the rats are allowed to recover from anesthesia.

[0499] R121920 (10 mg/kg) is administered as an IV injection at the time of MCA occlusion, followed by additional IV injections of R121920 (10 mg/kg) at 1, 2, 3 and 4 hours subsequent thereto. Control rats are injected with a water vehicle at the same time points. The period of neuroprotective effect of R121920 is examined by delaying induction of the dosing regimen to 0, 0.5, and 1 hour after occlusion of the MCA.

[0500] Twenty-four hours subsequent to MCA occlusion, the rats are killed and the brains are removed and frozen in isopentane at –40°C. Brains are cut into 20-μm serial coronal sections at 12 equidistant levels (1 mm apart, covering the entire forebrain), are fixed for 10 minutes in 4% paraformaldehyde, and are stained with hematoxylin and eosin. The sections, corresponding to 12 stereotactically predetermined coronal planes of the brain from anterior +12.7 mm to anterior +1.7 mm relative to the interaural line (Paxinos and Watson, *The rat brain in stereotaxic coordinates.* San Diego, CA: Academic Press), are examined using a light microscope. Areas of ischemic damage are delineated and transcribed onto scale diagrams of a normal forebrain at each of the 12 coronal planes. Infarcted areas are quantified using a computer-based image analysis system, and the total volumes of ischemic tissue for each brain are derived from integration of the areas of damage in the 12 planes and the known stereotactic coordinates of the planes. The volumes of the cerebral hemispheres ipsilateral and contralateral to the occluded MCA are determined from the stained histologic sections by assessment of the total surface area at the same coronal planes as used for assessing areas of ischemic damage. The difference between the two hemispheres provide a measure of brain swelling.

[0501] It should be noted that all of the above-mentioned procedures can be modified for a particular study, depending on factors such as a drug combination used, length of the study, subjects that are selected, etc. Such modifications can be designed by a skilled artisan without undue experimentation.

WHAT IS CLAIMED IS:

1. A method for treating a stroke, the method comprising:

(a) diagnosing a subject in need of treatment for a stroke; and

(b) administering to the subject a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a corticotropin releasing factor antagonist or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

3. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

4. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, parecoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

5. The method of claim 1 wherein the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

6. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist are administered substantially simultaneously.

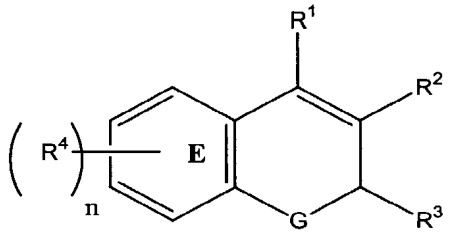
7. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist are administered sequentially.

8. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is administered to the subject in an amount of about 0.1 to about 20 mg/kg body weight per day.

9. The method of claim 1 wherein the corticotropin releasing factor antagonist is administered to the subject in an amount of about 1 to about 50 milligrams per kilogram of the subject's weight per day.

10. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula:



(I)

wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or NR^a;

R^a is alkyl;

R^1 is selected from the group consisting of H and aryl;

R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

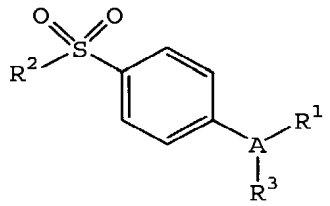
each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl,

heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of *α*-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

11. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof of the formula:



wherein:

A is selected from the group consisting of a partially unsaturated or unsaturated heterocyclyl ring and a partially unsaturated or unsaturated carbocyclic ring;

R^1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^2 is selected from the group consisting of methyl and amino; and

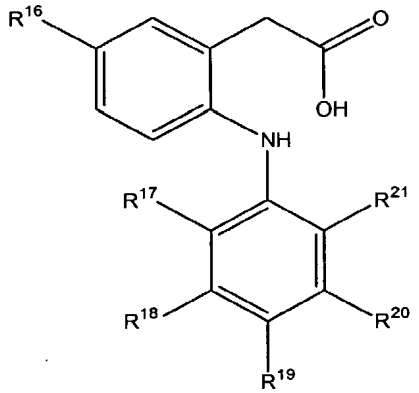
R^3 is selected from the group consisting of H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl,

alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,
N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of *α*-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

12. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula:



(III)

wherein:

R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided, however, that each of R^{17}, R^{18}, R^{20} and R^{21} is not fluoro when R^{16} is ethyl and R^{19} is H; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

13. A composition comprising a cyclooxygenase-2 selective inhibitor selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, parecoxib, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, and a corticotropin releasing factor antagonist selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

14. The composition of claim 13 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, and parecoxib, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, and the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

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<110> Pharmacia Corporation
Arneric, Stephen

<120> COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

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20 25

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
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Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Jennifer Vail
PATENT CENTER #	71529866	AUTHORIZED BY	Victoria Cheng
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

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FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	280.00	1	280.00
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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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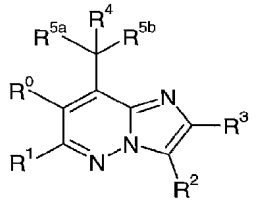
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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) Title: IMIDAZOPYRIDAZINE COMPOUNDS



(I)

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

WO 2006/102194 A1

IMIDAZOPYRIDAZINE COMPOUNDS

Field of the Invention

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

Background of the Invention

Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Natl. Acad. Sci* (*USA*) 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (1983); G. F. Koob, *Persp. Behav. Med.* 2:39 (1985); E. B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors [J. E. Blalock, *Physiological Reviews* 69:1 (1989); J. E. Morley, *Life Sci.* 41:527 (1987)].

There is evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis, as they relate to the dysfunction of CRF neurons in the central nervous system [for a review, see: E. B. De Souze, *Hosp. Practice* 23:59 (1988)]. Furthermore, CRF is known to have a broad extrahypothalmic distribution in the CNS, contributing therein to a wide spectrum of autonomic behavioral and physiological effects [see, e.g., Vale et al., 1983; Koob, 1985; and E. B. De Souze et al., 1985]. For example,

CRF concentrations are significantly increased in the cerebral spinal fluid of patients afflicted with affective disorder or major depression [C. B. Nemeroff et al., *Science* 226:1342 (1984); C. M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R. D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol. Psychiatry* 25:355 (1989)]. Moreover, excessive levels of CRF are known to produce anxiogenic effects in animal models [see, e.g., Britton et al., 1982; Berridge and Dunn, 1986 and 1987].
The density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C. B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (intravenously administered) observed in depressed patients [P.W. Gold et al., *Am. J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P. W. Gold et al., *New Engl. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R. M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is also preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of receptors in the brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF both in the conflict test [K. T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N. R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist Ro 15-1788, which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist FG 7142 enhanced the actions of CRF [K. T. Britton et al., *Psychopharmacology* 94:396 (1988)]. Preliminary studies using the putative CRF receptor antagonist α-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrates that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C. W. Berridge and A. J. Dunn, *Horm. Behav.* 21:393 (1987), Brain Research Reviews 15:71 (1990)].

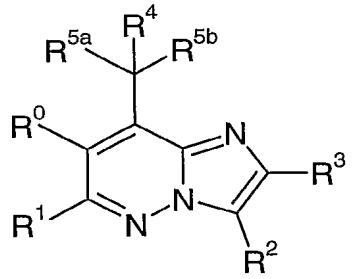
CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain [D. T. Chalmers et al., *TIPS* 17:166-72 (1996)] thereby suggesting potential functional diversity [S. C. Heinrichs et al., *Regul. Peptides* 71:15 (1997)]. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors [G. Liebsch et al., *Regul. Peptides* 59: 229-39 (1995); D. W. Schulz, *PNAS* 93: 10477-82 (1996)]. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors [Heinrichs et al., 1997]. A more discrete septal/hypothalmic distribution [D. T. Chalmers et al., *J. Neurosci.* 15(10): 6340-50 (1995)] and the availability of alternative endogenous ligands [J. Vaughan et al., *Nature* 378: 287-92 (1995)] suggest an altogether different functional role for the CRF2 receptor [Heinrichs et al., 1997]. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism (H. Tezval et al., *PNAS* 101(25): 9468-9473 (2004)]. In many cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF1 gene deletion [S. C. Heinrichs, *Trends in Pharmacological Sciences* 20(8):311-5 (1999)]. While CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well [C. Contoreggi et al., *Neuroendocrinology* 80(2):111-23 (2004)].

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

SUMMARY OF THE INVENTION

The compounds of the present invention include CRF1 receptor antagonists.

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



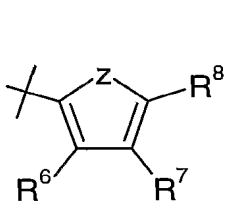
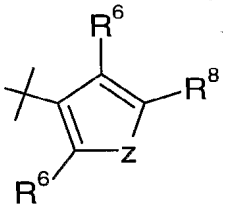
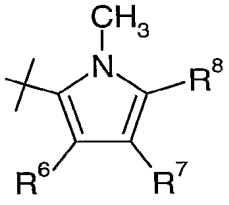
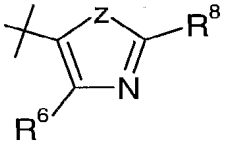
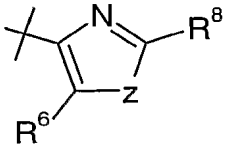
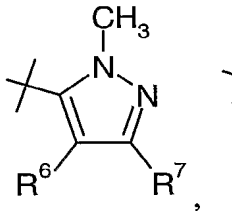
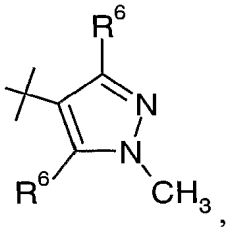
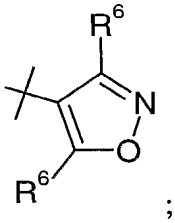
Formula I

wherein:

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

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

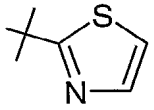
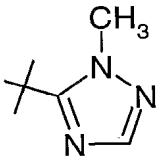
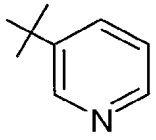
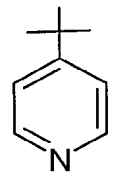
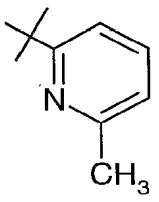
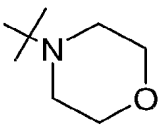
R^2 is selected from the group consisting of:


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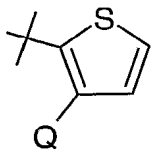
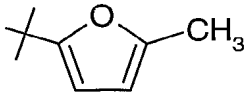
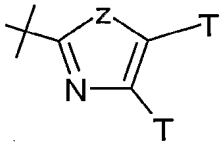
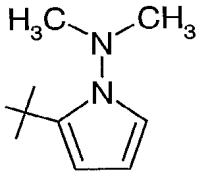
R^4 is hydrogen, halo, or hydroxy;

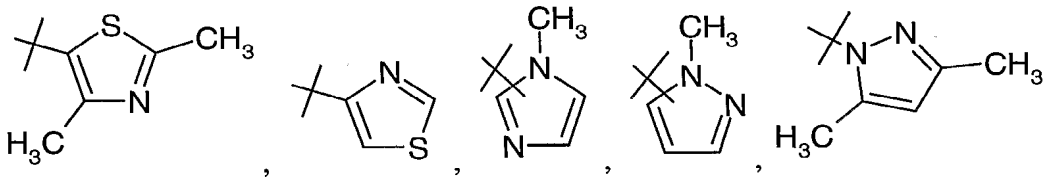
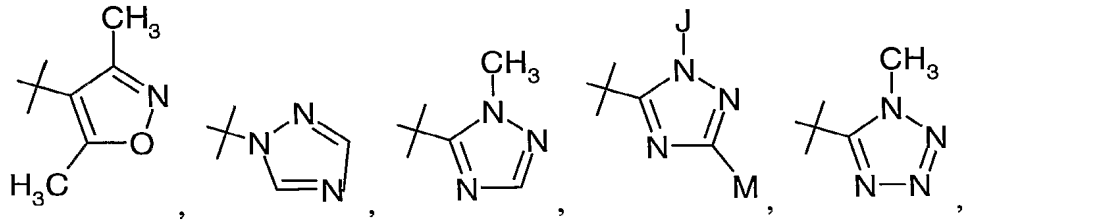
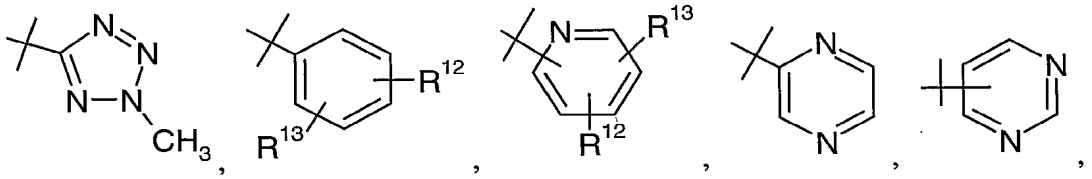
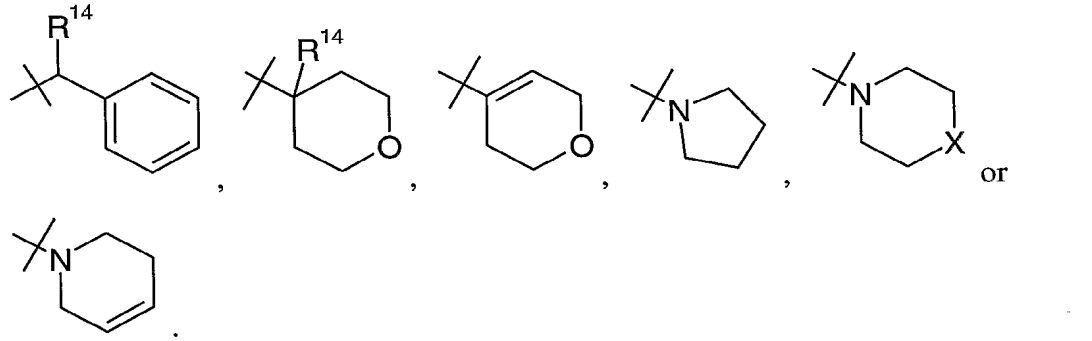
R^{5a} and R^{5b} are independently ethyl or n-propyl;

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

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

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


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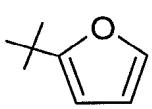
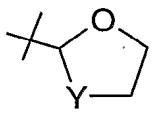
;

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

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

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

R^{14} is hydrogen or hydroxy;

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

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

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

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

Y is -CH_2- or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

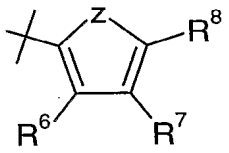
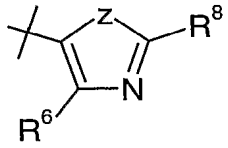
T is hydrogen or methyl;

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

M is methyl or halo;

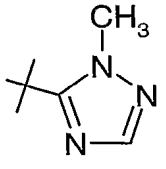
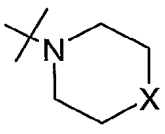
and pharmaceutically acceptable salts thereof.

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

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

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

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

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

Another embodiment of the present invention is a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

Yet another embodiment of the present invention is a compound of Formula I, for use as a medicament.

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

DETAILED DESCRIPTION OF THE INVENTION

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

"Alkoxy" means an alkyl-O- group, wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, and *n*-butoxy.

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

"Alkenyl" means an unsaturated aliphatic hydrocarbon group, which may be straight or branched, having 2 to 4 carbon atoms in the chain.

"Cycloalkyl" means a monocyclic group, having 3 to 5 carbon atoms.

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

"Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulphamates, malonates, salicylates, propionates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinateslaurylsulphonate salts, and the like. See, for example S.M. Berge, et al.,

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

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

"Therapeutically effective amount" or "effective amount" means the amount of the compound of formula I of the present invention or pharmaceutical composition containing a compound of formula I of the present invention that will elicit the biological or medical response of or desired therapeutic effect on a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The terms "treatment," "treat," "treating," and the like, are meant to include both slowing or reversing the progression of a disorder. These terms also include alleviating, ameliorating, attenuating, eliminating, or reducing one or more symptoms of a disorder or condition, even if the disorder or condition is not actually eliminated and even if progression of the disorder or condition is not itself slowed or reversed. The term "treatment" and like terms also include preventive (e.g., prophylactic) and palliative treatment. Prevention of the disease is manifested by a prolonging or delaying of the onset of the symptoms of the disease.

The symbol "——" in a molecular structure indicates the position of attachment for that particular substituent.

When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1, R^2, etc., are to be chosen in conformity with well- known principles of chemical structure connectivity.

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

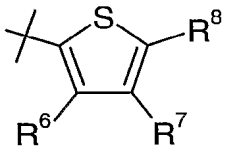
The present invention contemplates specific classes of compounds of Formula I. The following paragraphs describe such specific classes:

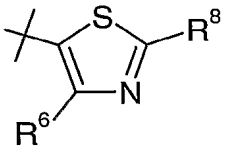
(a) R^0 is hydrogen;

(b) R^1 is methyl;

(c) R^3 is methyl;

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

(e) R^2 is  ;

(f) R^2 is  ;

(g) R^4 is hydrogen;

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

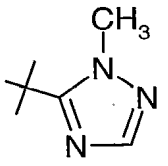
(i) R^{5b} is ethyl;

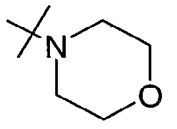
(j) R^{5a} and R^{5b} are ethyl;

(k) R^6 is halo;

(l) R^6 is methyl;

(m) R^7 is hydrogen;

(n) R^8 is  ;

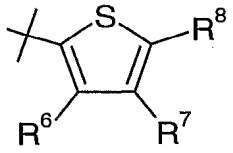
(o) R^8 is  .

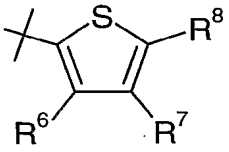
While all the compounds of Formula I are useful CRF1 receptor antagonists, the following paragraphs describe further specific classes:

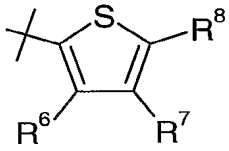
(a) Each of R^1 and R^3 is methyl and each of R^{5a} and R^{5b} is ethyl;

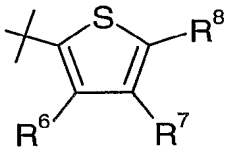
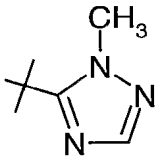
(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 is hydrogen;

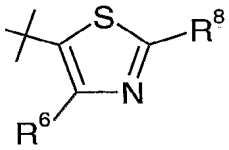
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen;

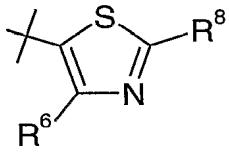
(d) R^2 is  and R^7 is hydrogen;

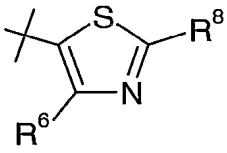
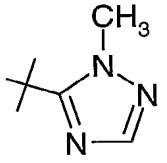
(e) R^2 is  , R^7 is hydrogen, and R^6 is halo;

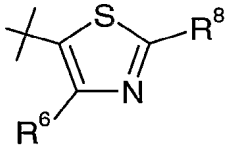
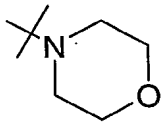
(f) R^2 is  , R^7 is hydrogen, and R^6 is methyl;

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

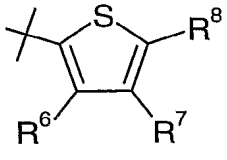
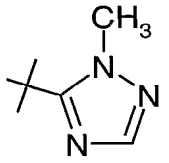
(h) R^2 is  and R^6 is halo;

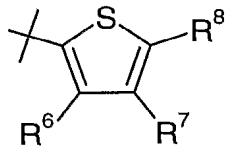
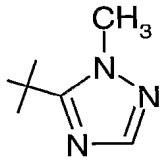
(i) R^2 is  and R^6 is methyl;

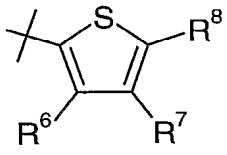
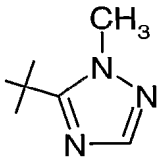
(j) R^2 is  , R^6 is halo or methyl, and R^8 is  ;

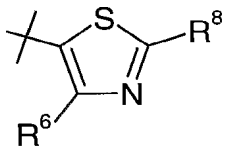
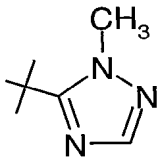
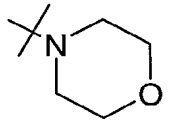
(k) R^2 is  , R^6 is halo or methyl, and R^8 is  .

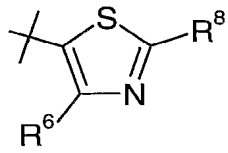
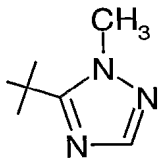
The following paragraphs describe even more specific classes of CRF1 receptor antagonists of the invention:

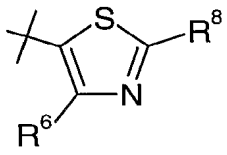
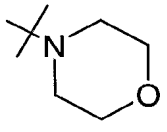
(a) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo or methyl, and R^8 is  ;

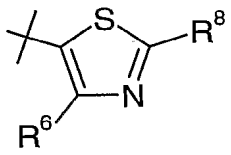
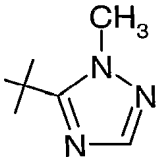
(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo, and R^8 is  ;

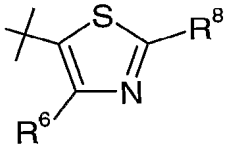
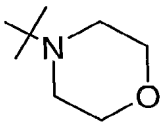
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is methyl, and R^8 is  ;

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

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

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

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

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

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

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

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

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

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

Dosage forms suitable for administration generally contain from about 1 mg to about 300 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of formula I are antagonists at the CRF1 receptor and are useful in the treatment of anxiety disorders, depression, major depressive disorder, and stress related disorders. Anxiety disorders are a group of diseases, recognized in the art, that includes phobic disorders, anxiety states, post-traumatic stress disorder and atypical anxiety disorders [The Merck Manual of Diagnosis and Therapy, 16 th edition (1992)]. Emotional stress is often a precipitating factor in anxiety disorders, and such disorders generally respond to medications that lower response to stress. The compounds are also useful in smoking cessation programs. The method of treatment involves administration to a mammal (e.g. a human) an effective amount of a compound of the invention. In particular, therapeutically effective amounts of the compounds of this invention are amounts effective to antagonize, or lower, levels of corticotropin releasing factor (CRF) in a mammal (e.g. a human), thereby alleviating in the mammal's conditions characterized by abnormally high levels of CRF expression.

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

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

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

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

Compounds of Formula I, or a pharmaceutically acceptable salt thereof, are useful for treating various disorders and conditions in a mammal (e.g. human) including social anxiety disorder; panic disorder; obsessive-compulsive disorder; major depressive disorder; anxiety with co-morbid depressive illness; affective disorder; anxiety; depression; irritable bowel syndrome; post-traumatic stress disorder; supranuclear palsy; immune suppression; gastrointestinal disease; anorexia nervosa, bulimia, or other feeding disorder; drug or alcohol withdrawal symptoms; substance abuse disorder (e.g., nicotine, cocaine, ethanol, opiates, or other drugs); inflammatory disorder; fertility problems; disorders the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF; a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; sleep disorders induced by stress; stress- related illnesses; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; chronic fatigue syndrome; stress- induced headache; headache; cancer; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, senile

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

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

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

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

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

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

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

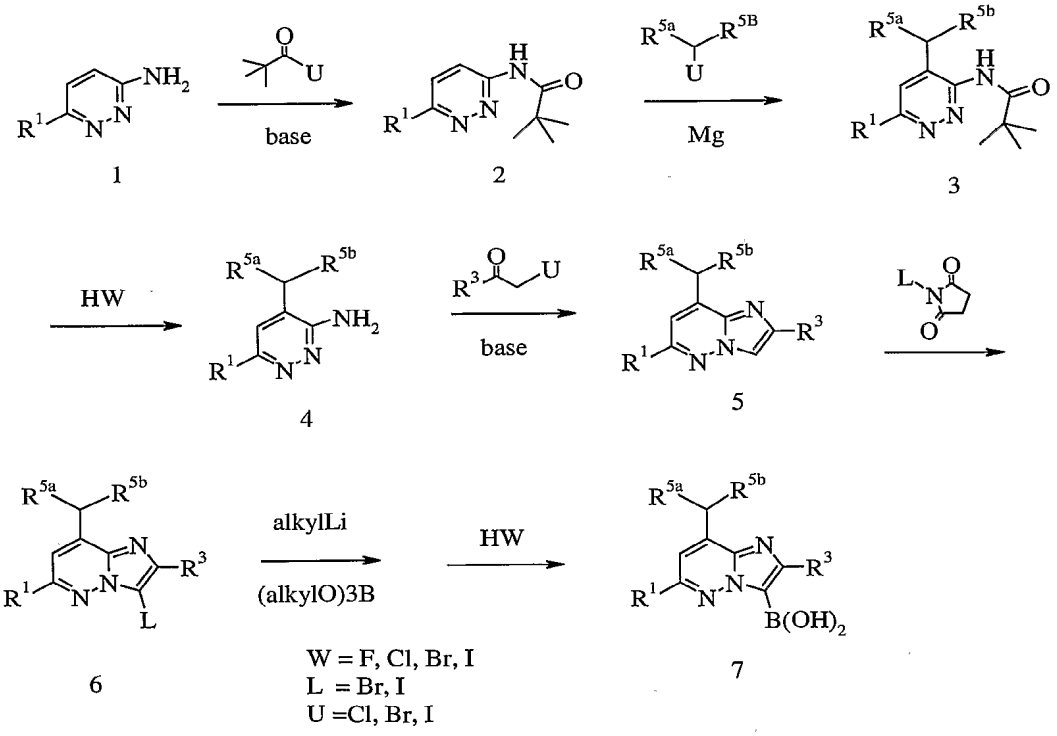
also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

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

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

Scheme I

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



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

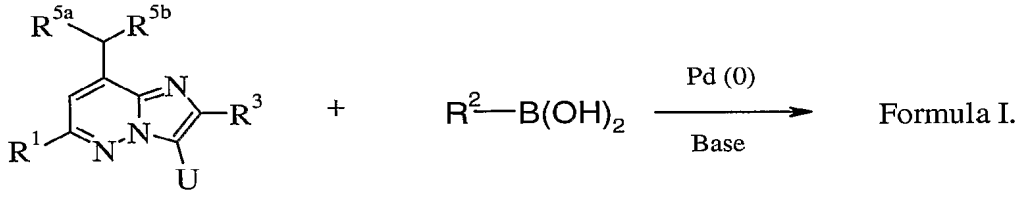
In Scheme I, a substituted 3-amino-pyridazine 1 is acylated with pivaloyl halide and a base, e.g., triethylamine in a polar aprotic solvent, e.g., methylene chloride at from

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

Scheme II

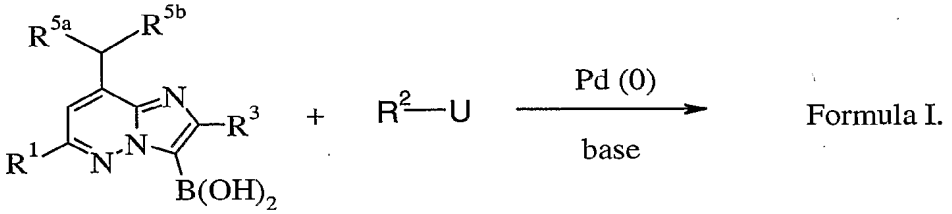
Synthesis of Compounds of Formula I by transition metal catalysis.

Equation 1.



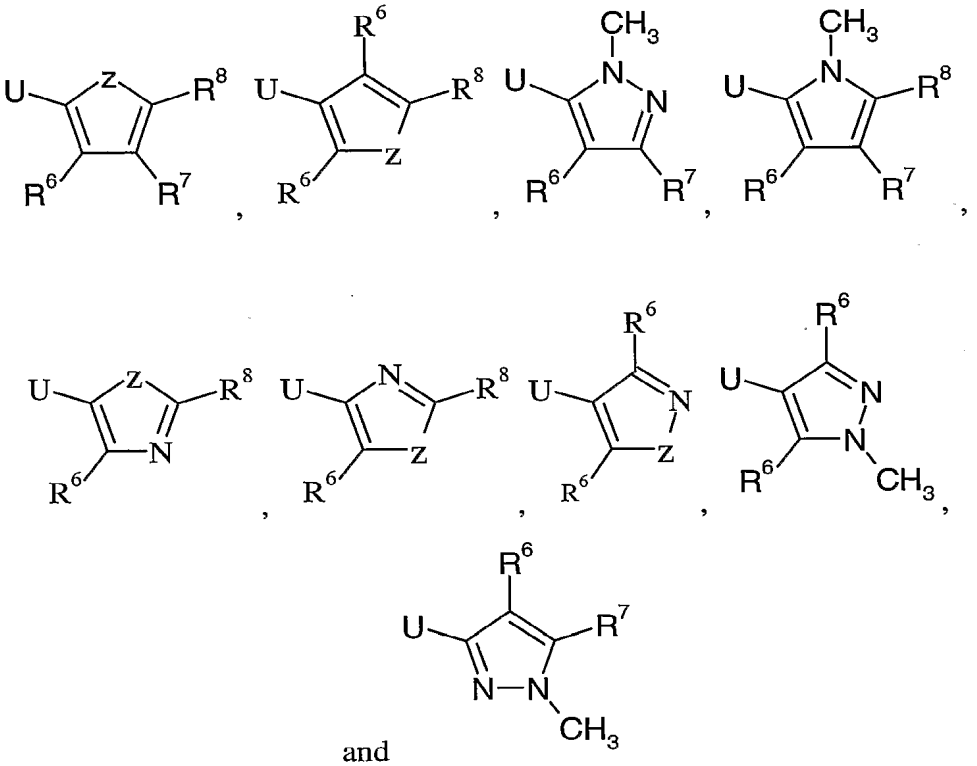
6 8

Equation 2.



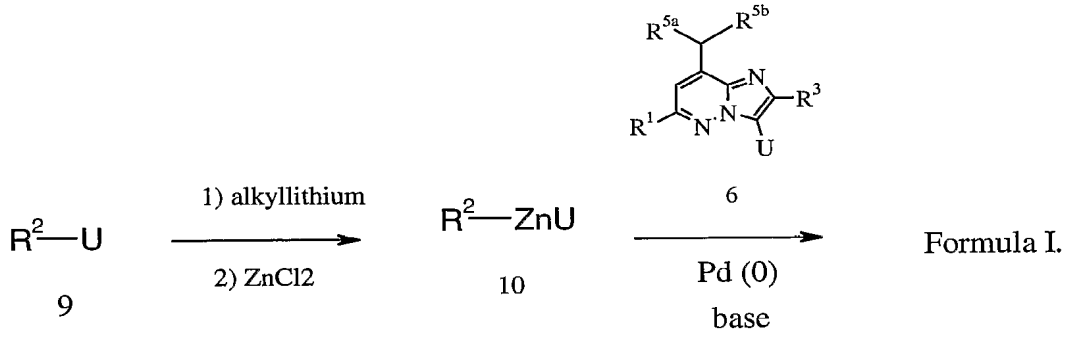
7 9

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

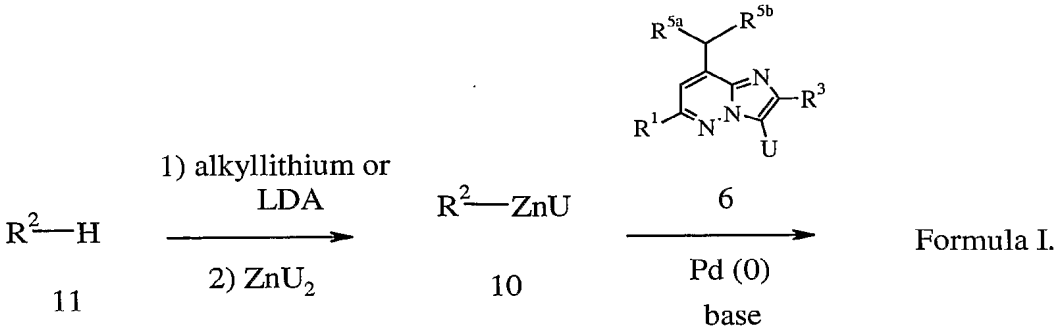


and

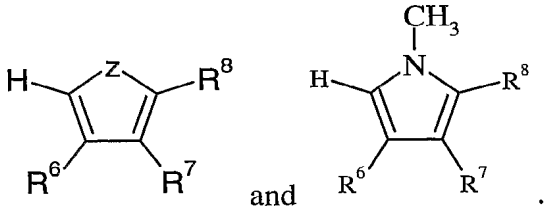
Equation 3.



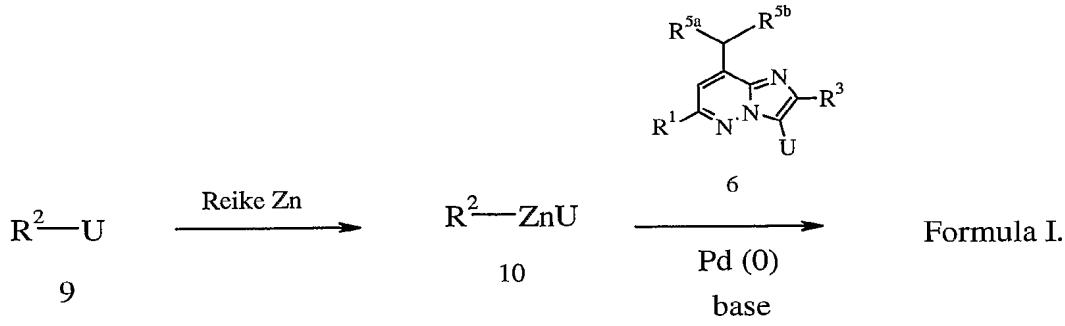
Equation 4.



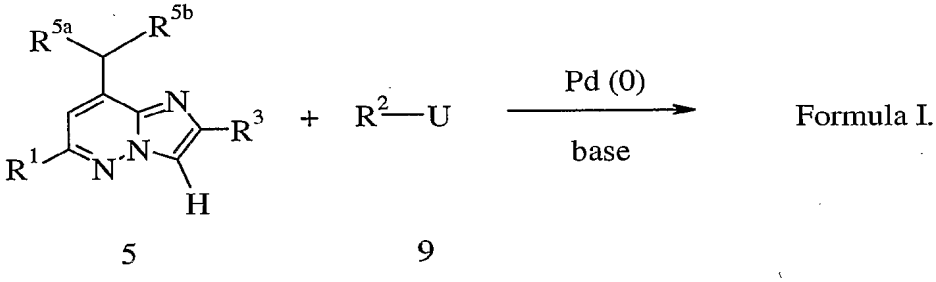
Where R^2-H is selected from the group consisting of:



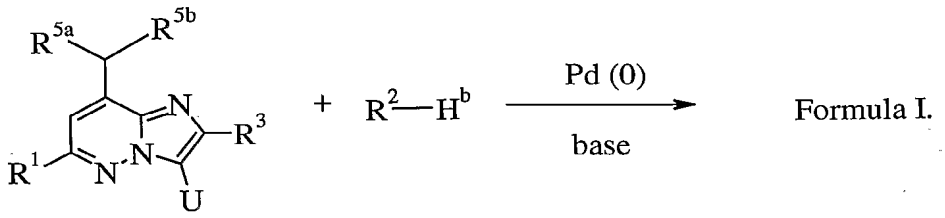
Equation 5.



Equation 6.

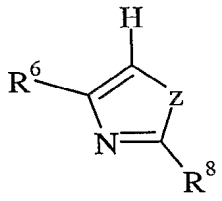


Equation 7.



6 12

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



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

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

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

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

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

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

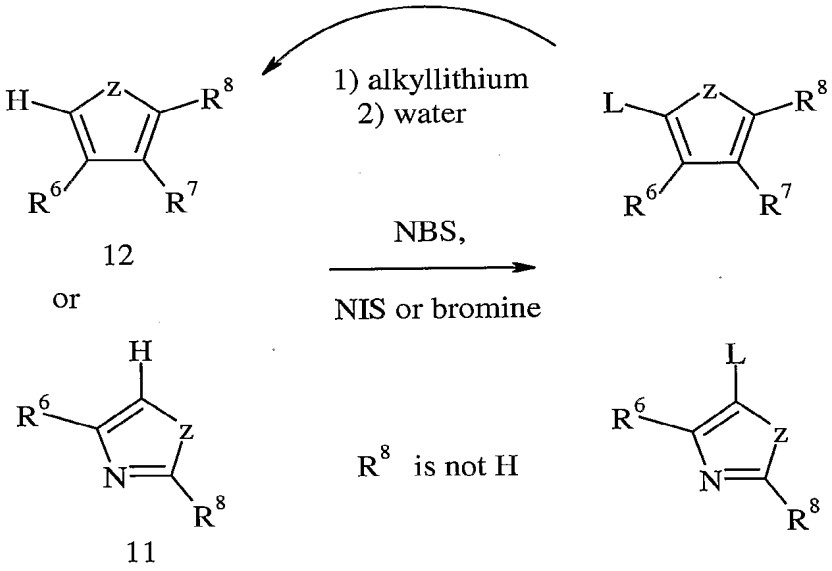
Furthermore from equation 5, it may be advantageous or convenient to use Reike Zn in THF to directly convert a 5-membered ring heterocyclic halide 9 to an organozinc reagent 10 for coupling with a halide 6.

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

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

Scheme III

Synthesis of Substituted 5 Membered Heterocyclic Halides



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

Several 5 membered heterocyclic rings and/or their bromides and/or iodides useful as starting materials for the synthesis of compounds of Formula I are commercially available or may be prepared by methods well know to the skilled artisan. From Scheme III, they may also be prepared by halogenation, e.g., with bromine, NBS or NIS. Furthermore, some of the intermediates 11 and 12 may be prepared by lithium halogen exchange followed by water quench.

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

Abbreviations

TBDMSCl or TBDMSiCl – tert-butyl-dimethylsilyl chloride

MS (ES) – Electrospray Mass spectrum

THF – tetrahydrofuran

DMSO – Dimethylsulfoxide

DMF – Dimethylformamide

DCM, CH2Cl2 – dichloromethane

Dioxane – 1,4-dioxane

N2 – nitrogen gas

NIS – N-iodosuccinimide

NBS – N-bromosuccinimide

MeOH - methanol

EtOH – 95% ethanol

RBF, RB – round bottom flask

RBSN – round bottom single neck flask

SiO2 – silica gel

EtOAc, AcOEt – ethylacetate

GFF - glass microfiber filter

HPLC – high pressure liquid chromatography on silica gel

ISCO – ISCO brand low pressure liquid chromatography on silica gel

AcCl – acetyl chloride

LDA – lithium diisopropylamine

KOAc – Potassium Acetate

TBABr – Tetrabutyl ammonium bromide

NMP – N-Methylpyrrolidinone

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

Pd_2dba_3 – Tris(dibenzylideneacetone)dipalladium

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

Tetrakis – tetrakis-(triphenylphosphine)-palladium

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

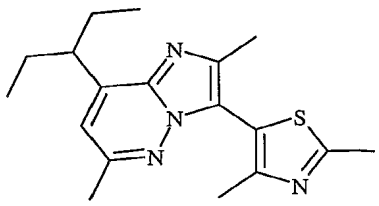
r.t., RT – room temperature

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following examples are provided to describe the invention in further detail. They are intended to illustrate and not to limit the invention in any way whatsoever. Examples 1-255 provide exemplary compounds and illustrate the preparation thereof. Examples A-D illustrate various biological assays that can be used for determining the biological properties of the compounds of the inventions. Those skilled in the art will promptly recognize appropriate variations from the procedures described in the examples.

Example 1.

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



A. 6-Methyl-pyridizin-3-ylamine.

3-Chloro-6-methylpyridazine (25.0g, 0.229 moles) is dissolve in 250 mL of NH_4OH and heated to 170 °C in a sealed container for 24 hours. The solvents are evaporated. The residue is triturated in methylene chloride, and a solid is filtered. This trituration procedure is repeated with the filtrate four times. The filtered solids are combined and dried in a vacuum oven overnight to obtain the title compound as an off-white solid 4.32 g (0.040 moles, 20%). ^{1}H-NMR (dmso-d6): δ 7.1 (d, J = 8.9 Hz, 1H); 6.67 (d, J = 8.9 Hz, 1H); 6.04 (s, br, 2H); 2.33 (s, 3H) ppm. ES+ = 110 (100%, M + 1).

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

Method 1: To a dry flask is added 7.12 g (0.065 mole) of 6-methyl-pyridizin-3-ylamine in 170 ml dry methylene chloride. Next, 14.5 ml of triethylamine is added and the reaction is cooled to 0 °C. Pivaloyl chloride (2.7 ml, 1.2 eq) is carefully added, and the reaction mixture is stir 10 minutes, removed from the bath, and stirred 4 hours more. Dichloromethane (200 mL) is added, and the reaction mixture is washed 3 times with saturated aqueous sodium bicarbonate, then brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to an oil. The crude product is purified via silica gel chromatography using a hexane:ethyl acetate gradient giving the title compound as a white solid weighing 1.51 g (7.8 mmoles, 42.7%). ^{1}H-NMR (DMSO-d_6), δ 10.39 (s, 1H); 8.11 (d, J = 9.30 Hz, 1H); 7.51 (d, J = 9.29 Hz, 1H); 2.54 (s, 3H); 1.23 (s, 9H) ppm. ES^+ = 194 (M+1).

Method 2: To a dry pressure tube is added 200 mg (1.56 mol) of 3-chloro-5-methylpyridazine, 190 mg (1.87 mmol) of trimethylacetamide, 14.6 mg (0.023 mmol) of rac-2,2'-bis(diphenylphosphine)-1,1'-binaphthyl , tris(dibenzylideneacetone)-dipalladium (0) , 762.4 mg (2.34 mmol) of cesium carbonate and 1.5 ml dry tetrahydrofuran. The pressure tube is purged with nitrogen and sealed. The reaction is heated to 100 °C overnight. The reaction is then cooled, diluted with dichloromethane, and filtered through celite. Solvents are evaporated and the crude product is purified via silica gel chromatography using a ethyl acetate:hexane gradient to obtain 91 mg (0.47 mmol, 30%) as a white solid.

C. N-[4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide.

Activated magnesium powder (19.2 g, 0.792 moles) is added to a dry 3 L flask fitted with a condensor and a drop funnel. The entire apparatus is heated with a gun dry under vacuum and allowed to cool. Enough ether is added to cover the magnesium. 3-Bromopentane (100 g, 0.662 mmol) is added to the addition funnel in 175 ml of diethyl ether. A 1/3 of the bromopentane solution is added to the magnesium and the reaction mixture is stirred under nitrogen until bubbling occurs. Then, the rest is dripped in at such a rate that the bubbling continues gently. The reaction is stirred for 30 minutes after bubbling ceases. Next, 2,2-dimethyl-*N*-(6-methyl-pyridazine-3-yl)-propionamide (21.3 g, 0.110 mmol) dissolved in 225 ml of dry THF is added dropwise. The reaction mixture is stirred for 1 hour. Saturated sodium tartrate (1 L) is carefully added, and the reaction is stirred for 30 minutes. The reaction mixture is transferred to a larger flask, 2 L of ethyl acetate is added, and the reaction is stirred 1 hour more. The layers are separate and the aqueous layer is extracted several times with ethyl acetate. The organic extracts are combined, and the solvents are evaporated. The residue is taken up in 600 mL of dichloromethane, and iodine (28 g, 0.110 mol) is added. The reaction is stirred for 2 hours. The organic layer is washed once with aqueous solution of sodium sulfite and then with water. The organic layer is dried over sodium sulfate, filtered, and evaporated to red oil. The crude product is purified via silica gel chromatography using a hexanes:ethyl acetate gradient. The product fractions are combined and evaporated. The residue is triturated in ethyl acetate and a light tan solid is filtered to obtain 12.0 g (45.6 mmol, 41 %) of the title compound. ^{1}H-NMR (DMSO-d_6), δ 9.88 (s, 1H); 7.59 (s, 1H); 2.60 (s, 3H); 2.39-2.42 (m, 1H); 1.21-1.37 (m, 2H); 1.38-1.43(m, 2H); 1.23(s, 9H); 0.71 (t, J = 7.49 Hz, 6H) ppm. MS/ES$^+$ = 264.

D. 4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine.

N-[4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide (12.0 g, 45 mmol) is dissolved in 60 mL of concentrated hydrochloric acid. The reaction mixture is heated to 95 °C in a sealed flask for 2 hours. The reaction is worked up by pouring over ice and extracting with ethyl acetate three times. The organic layer is discarded, and the pH of the aqueous layer is adjusted using 2 N sodium hydroxide. The basic solution is extracted with ethyl acetate five times. The organic extracts are

combined, dried over magnesium sulfate, filtered, and evaporated to obtain 6.68 g (37 mmol, 81%) of the title compound as a brownish oil. ^{1}H-NMR (DMSO-d_6), δ 6.95 (s, 1H); 5.89 (s, br, 2H); 2.52-2.56 (m, 1H); 2.34 (s, 3H); 1.44-1.58 (m, 4H); 0.72 (t, J = 7.04 Hz, 6H) ppm. MS/ES$^+$ = 180 (100%, M+1).

E. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine (850 mg, 4.74 mmol), chloroacetone (0.415 ml, 5.22 mL) and 20 mL of ethanol are heated in the microwave at 110 °C for 35 minutes. Sodium bicarbonate (1.2 g, 14.2 mmol) is added, and the reaction mixture is heated in an oil bath at 100 °C overnight. The solvent is evaporate and the residue is taken up in ethyl acetate and washed three times with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a brown oil. The crude product is purified via silica gel chromatography using a hexane:ethyl acetate gradient. The title compound is an oil weighing 3.69 g (17.0 mmol, 84%). ^{1}H-NMR (DMSO-d_6), δ 7.34 (s, 1H); 6.84 (s, 1H); 2.85-3.10 (m, 1H); 2.43 (s, 3H); 2.32 (s, 3H); 1.70-1.80 (m, 4H); 0.712 (t, J = 7.49 Hz, 6H) ppm. MS/ES$^+$ = 219 (100%, M+2).

F. 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (5.1 g, 0.023 moles) and 50 mL of dry acetonitrile are added to a nitrogen purged flask and are cooled to 0 °C. *NIS* (5.54 g,0.025 moles) in 90 mL of dry acetonitrile is added. The bath is allowed to come to room temperature, and the reaction to stir overnight. The solvents are evaporated. The residue is taken up in ethyl acetate, washed two times with 50% aqueous solution of sodium thiosulfate and with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a residue again. The crude product is triturated in a small amount of acetonitrile, and a solid is filter off. The trituration is repeated several times to obtain the title compound as a light tan solid weighing 7.29 g (0.021 moles, 91%). ^{1}H-NMR (DMSO-d_6), δ 6.96 (s, 1H); 3.0-3.3 (m, 1H); 2.51 (s, 3H); 2.35 (s, 3H); 1.71-1.80 (m, 4H); 0.71 (t, J = 7.48 hz, 6H) ppm. MS/ES$^+$ = 344 (100%, M+1).

G. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine-3-yl boronic acid.

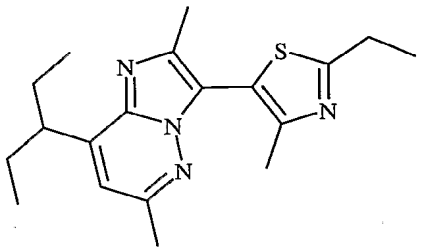
In an oven dried nitrogen purged 3 neck 50mL round bottom flask, 1.00g (2.91 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine in 60mL of dry THF is cooled to -78°C. 4.12mL (7.00mmol) of 1.7 M tert-butyllithium in hexanes is added and reaction is stirred at -78 °C for 1 hour. 0.818mL (7.30mmol) of trimethyl borate is added and reaction is followed by MS and TLC (1:1 Hexane:EA) Indication of product is observed by mass spectrum. The reaction is allowed to stir for an additional hour, quenched with 1 N hydrochloric acid, and diluted with ethyl acetate. The organic layer is separated, and the aqueous layer is extracted three times with 100 mL of ethyl acetate. The extracts are combined, dried over $MgSO_4$, filtered, and concentrated. The reaction residue is triturated in hexanes and a solid is filter off. MS, ES^+ = 262.2 (M+1).

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

To a microwave pressure tube is added 0.340g (1.30mmol) of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine-3-yl boronic acid, 0.100g (0.521mmol) of 5-bromo-2,4-dimethylthiazole, 0.361g (0.313mmol) of Pd(PPh3)4, 0.650mL (1.30mmol) of 2 M aqueous Na2CO3, and 2mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 40min. Reaction is checked by MS which indicates product present. The reaction mixture is partitioned between 75mL of ethyl acetate and 75mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.100g of the product, 58% yield. MS, ES+ = 329.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.974 (s, 1H); 3.085-3.052 (m, 1H); 2.665 (s, 3H); 2.438 (s, 3H); 2.290 (s, 3H); 2.147 (s, 3H); 1.849-1.727 (m, 4H); 0.776-0.738 (m, 6H) ppm.

Example 2.

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



A. 5-Bromo-2-ethyl-4-methylthiazole.

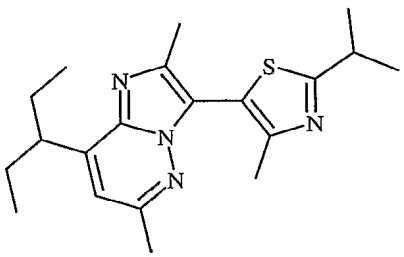
In an oven dried, N_2 purged, 50 mL round bottom flask, 1.00 g (7.86 mmol) of 2-ethyl-4-methylthiazole is reacted with 0.487 mL (9.43 mmol) of bromine in 7mL of acetic acid at room temperature. Reaction is checked by MS after 2 hours. The reaction mixture is partitioned between 50 mL H_2O and 25 mL of CH_2Cl_2. The layers are separated and the aqueous is extracted 3X25mL of CH_2Cl_2. The organics are combined and washed 1X25mL 1N $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated under vacuum to give 1.38g of the title compound, 85% yield. MS, ES+ = 206.0 (M+1); ^{1}H-NMR (DMSO-d6) = 2.940-2.810 (m, 2H); 2.253-2.251 (m, 3H); 1.225-1.222 (m, 3H) ppm.

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

Using a procedure similar to Example 1H, 5-bromo-2-ethyl-4-methylthiazole produces the title product in 27% yield. MS, ES+ = 343.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.975 (s, 1H); 3.090-3.056 (m, 1H); 3.025-2.968 (m, 2H); 2.439 (s, 3H); 2.291 (s, 3H); 2.155 (s, 3H); 1.835-1.744 (m, 4H); 1.338-1.300 (m, 3H); 0.776-0.740 (m, 6H) ppm.

Example 3.

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



A. 5-Bromo-2-isopropyl-4-methylthiazole.

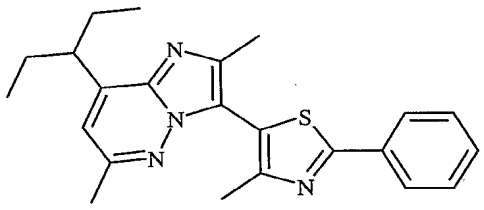
Using a procedure similar to Example 2A, 2-isopropyl-4-methylthiazole produces the title product in 90% yield. MS, ES+ = 220.0 (M+1); ^{1}H-NMR (DMSO-d6) = 3.210-3.175 (m, 1H); 2.257 (s, 3H); 1.264-1.248 (d, 6H) ppm.

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

Using a procedure similar to Example 1H, 5-bromo-2-isopropyl-4-methylthiazole produces the title product in 29% yield. MS, ES+ = 357.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.990 (s, 1H); 3.120-3.050 (m, 1H); 2.442 (s, 3H); 2.294 (s, 3H); 2.158 (s, 3H); 1.810-1.750 (m, 4H); 1.362-1.344 (d, 6H); 0.777-0.741 (m, 6H) ppm.

Example 4.

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



A. 5-Bromo-4-methy-2-phenylthiazole.

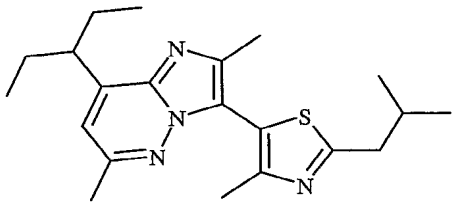
Using a procedure similar to Example 2A, 4-methyl-2-phenylthiazole produces the title product in 90% yield. MS, ES+ = 256.0 (M+1); ^{1}H-NMR (DMSO-d6) = 7.900-7.867 (m, 2H); 7.538-7.512 (m, 3H); 2.407 (s, 3H) ppm.

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

Using a procedure similar to Example 1H, 5-bromo-4-methyl-2-phenylthiazole produces the title product in 24% yield. MS, ES+ = 391.3 (M+1); ^{1}H-NMR (DMSO-d6) = 8.005-7.995 (m, 2H); 7.538-7.534 (m, 3H); 7.010 (s, 1H); 3.185-3.095 (m, 1H); 2.496 (s, 3H); 2.394 (s, 3H); 2.316 (s, 3H); 1.895-1.785 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 5.

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



A. 5-Bromo-4-methy-2-(2-methyl)propylthiazole.

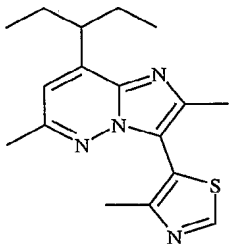
Using a procedure similar to Example 2A, 4-methyl-2-(2-methyl)propylthiazole produces the title product in 96% yield. MS, ES+ = 234.1 (M+1); ^{1}H-NMR (DMSO-d6) = 2.744 (m, 2H); 2.259 (s, 3H); 1.895-2.000 (m, 1H); 0.905-0.888 (m, 6H) ppm.

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

Using a procedure similar to Example 1H, 5-bromo-4-methyl-2-(2-methyl)propylthiazole produces the title product in 7% yield. MS, ES+ = 371.3 (M+1); ^{1}H-NMR (DMSO-d6) = 7.013 (s, 1H); 3.109 (m, 1H); 2.892-2.875 (d, 2H); 2.517 (s, 3H); 2.513 (s, 3H); 2.476 (s, 3H); 2.107-2.073 (m, 1H); 1.868-1.780 (m, 4H); 1.018-1.002 (d, 6H); 0.813-0.775 (m, 6H) ppm.

Example 6.

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

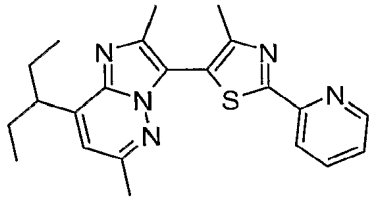


3.00 g of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (8.74 mmol), 4.32 g of 4-methyl-2*H*-thiazole (43.6 mmol), 453 mg of triphenylphosphine (1.73 mmol) and 5.85 g of cesium carbonate (18.0 mmol) are placed into the sealed tube with

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

Example 7.

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



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

In an oven dried, N2 purged, 15mL round bottom flask, 0.028 g (0.089 mmol) of 8-(1-ethyl-propyl)-3-[4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. in 1.5mL of dry CH_2Cl_2 is cooled to 0 C. 0.019 g (0.107 mmol) of NBS is added and reaction is stirred overnight allowing bath to come to room temperature. Reaction mixture is directly purified by chromatography using hexane/ethyl acetate as solvent system. The product containing fractions are combined to obtain 0.012 g, 34% yield. MS, ES+ = 395.1 (M+1); ^{1}H-NMR (DMSO-d6) = 7.070 (s, 1H); 3.10 (m, 1H); 2.49 (s, 3H); 2.36 (s, 3H); 2.25 (s, 3H); 1.85-1.78 (m, 4H); 0.81-0.77 (m, 6H) ppm.

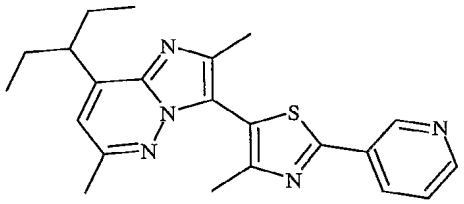
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-2-yl-thiazol-5-yl)-imidazo[1,2-*b*]pyridazine.

A mixture of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-*b*]pyridazine (380 mg, 0.96 mmol), 2-pyridinezinc bromide (0.5 M in THF, 2.1 mL, 4 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) and THF (3 mL) is heated at 80 °C for 18 hours. Ethyl acetate (20 mL) is added. The organic layer is separated, dried over

magnesium sulfate, filtered, and the solvent removed in vacuo. Purification is performed via silica gel chromatography using a 3:1 mixture of hexanes and ethyl acetate as eluent to produce the title compound 325 mg (86%). ^{1}H-NMR ($CDCl_3$), δ 9.55 (m,1H); 8.10 (m, 1H); 7.73 (m,1H); 7.26 (m,1H); 6.58 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. MS/ES$^+$ = 391 (100%, M+1).

Example 8.

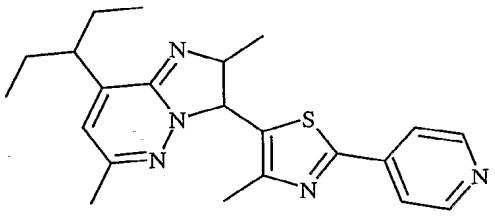
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 0.070 g (0.178 mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 0.066g (0.534 mmol) of pyridine-3-boronic acid, 0.103 g (0.089 mmol) of Pd(PPh3)4, 0.267mL (0.534 mmol) of 2 M aqueous Na2CO3, and 1mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 60 min. The reaction mixture is partitioned between 25mL of ethyl acetate and 25 mL of water. The layers are separated and the aqueous is extracted 3X 25 mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/Ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.045 g of the product, 64% yield. MS, ES+ = 392.2 (M+1); ^{1}HNMR (DMSO-d6) δ 9.18 (s, 1H); 8.65 (m, 1H); 8.34 (d, 1H); 7.60 (m, 1H); 7.06 (s, 1H); 3.06 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.34 (s, 3H); 1.87-1.82 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 9.

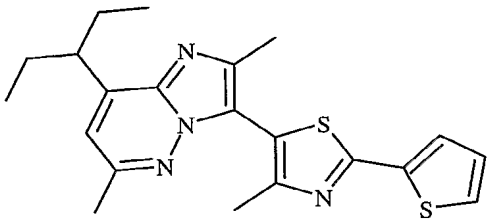
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, pyridine-4-boronic acid produces the title compound in 10% yield. MS, ES+ = 392.3 (M+1); ^{1}HNMR (DMSO-d6) = 8.79 (s, 2H); 7.80 (m, 2H); 7.07 (s, 1H); 3.12 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.36 (s, 3H); 1.90-1.80 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 10.

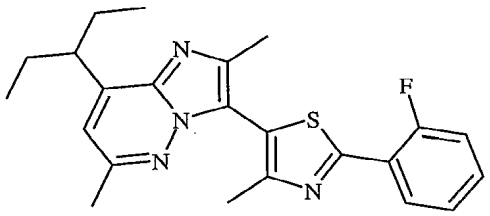
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(thiophene-2-yl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, thiophene-2-boronic acid produces the title compound in 89% yield. MS, ES+ = 397.1 (M+1); ^{1} H-NMR (DMSO-d6) = 7.81-7.79 (d, 1H); 7.78-7.77 (d, 1H); 7.21-7.20 (m, 1H); 7.05 (s, 1H); 3.19-3.15 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.27 (s, 3H); 1.85-1.83 (m, 4H); 0.82-0.79 (m, 6H) ppm.

Example 11.

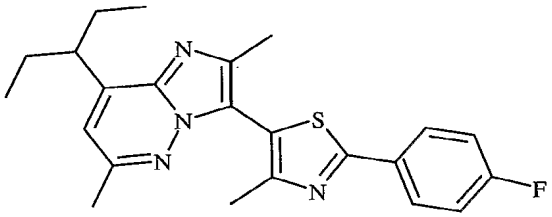
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2-fluorophenyl boronic acid produces the title compound in 82% yield. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.32-8.28 (m, 1H); 7.60-7.58 (m, 1H); 7.57-7.41 (m, 2H); 7.05 (s, 1H); 3.13-3.12 (m, 1H); 2.49 (s, 3H); 2.40 (s, 3H); 2.35 (s, 3H); 1.91-1.780 (m, 4H); 0.87-0.79 (m, 6H) ppm.

Example 12.

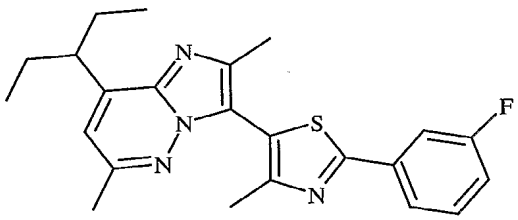
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluorophenyl boronic acid produces the title compound in 63% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.06-8.03 (m, 2H); 7.408-7.36 (m, 2H); 7.05 (s, 1H); 3.14-3.11 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.31 (s, 3H); 1.90-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 13.

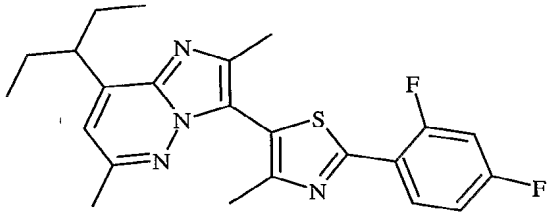
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3-fluorophenyl boronic acid produces the title compound in 77% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 7.84-7.78 (m, 2H); 7.64-7.57 (m, 2H); 7.41-7.36 (m, 1H); 7.06 (s, 1H); 3.15-3.111 (m, 1H); 2.45 (s, 3H); 2.40(s, 3H); 2.32 (s, 3H); 1.91-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 14

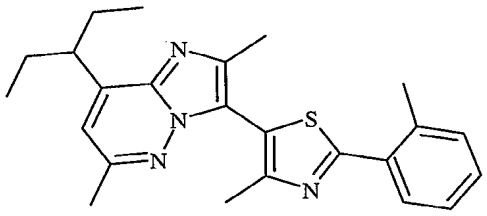
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2,4-difluorophenyl boronic acid produces the title compound in 76% yield. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.370-8.310 (m, 1H); 7.586-7.540 (m, 1H); 7.36-7.32 (m, 1H); 7.054 (s, 1H); 3.14-3.13 (m, 1H); 2.492 (s, 3H); 2.391 (s, 3H); 2.345 (s, 3H); 1.906-1.797 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 15.

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

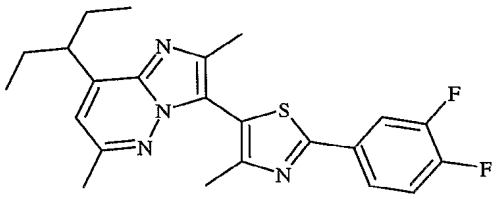


Using a procedure similar to Example 8, o-tolyl boronic acid produces the title compound in 87% yield where the crude mixture is purified by silica gel chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 405.2 (M+1); ^{1}H-

NMR (DMSO-d6) = 7.857-7.838 (d, 1H); 7.429-7.419 (d, 2H); 7.393-7.352 (m, 1H); 7.049 (s, 1H); 3.145-3.114 (m, 1H); 2.647 (s, 3H); 2.502 (s, 3H); 2.406 (s, 3H); 2.337 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 16.

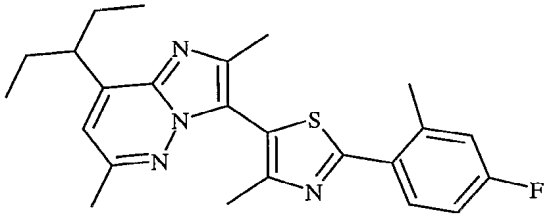
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3,4-difluorophenyl boronic acid produces the title compound in 74% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.07-8.02 (m, 1H); 7.849 (s, 1H); 7.66-7.59 (m, 1H); 7.062 (s, 1H); 3.12-3.11 (m, 1H); 2.498 (s, 3H); 2.392 (s, 3H); 2.319 (s, 3H) 1.905-1.779 (m, 4H); 0.826-0.790 (m, 6H) ppm.

Example 17.

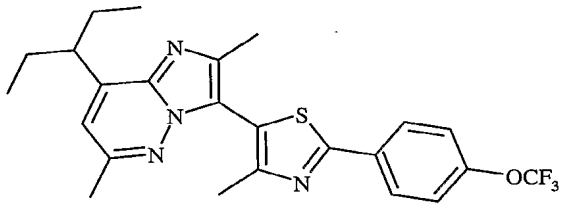
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluoro-2-methylphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluoro-2-methylphenyl boronic acid produces the title compound 0.040g (37% yield). MS, ES+ = 423.2 (M+1); ^{1}H-NMR (DMSO-d6) = 7.918-7.882 (m, 1H); 7.323-7.241 (d, 1H); 7.234-7.192 (m, 1H); 7.049 (s, 1H); 3.142-3.111 (m, 1H); 2.650 (s, 3H); 2.499 (s, 3H); 2.401 (s, 3H); 2.330 (s, 3H); 1.905-1.779 (m, 4H); 0.969-0.788 (m, 6H) ppm.

Example 18.

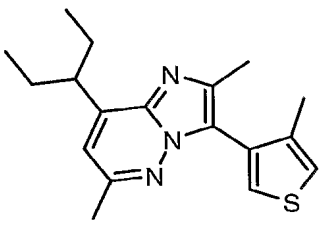
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-trifluoromethoxyphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 0.100g (0.254mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 0.157g (0.762mmol) of 4-(trifluoromethoxy)benzene boronic acid, 0.147g (0.127mmol) of Pd(PPh3)4, 0.381mL (0.762mmol) of 2 M aqueous sodium carbonate, and 2mL Ethanol. The reaction mixture is heated in the microwave at 160°C for up to 1 hour. The reaction mixture is partitioned between 50 mL of ethyl acetate and 50 mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. The product containing fractions are combined to obtain 0.085g of the product, 70% yield. MS, ES+ = 475.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.134-8.112 (d, 2H); 7.553-7.532 (d, 2H); 7.059 (s, 1H); 3.142-3.113 (m, 1H); 2.500 (s, 3H); 2.399 (s, 3H); 2.330 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 19.

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



A. 4,4,5,5-Tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane.

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

B. 4-Methyl 3-thiophene boronic acid.

A solution of 4,4,5,5-tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (3.69 g, 16.47 mmol) in acetone (30 mL) is treated with H_2O (30 mL), followed by $NaIO_4$ (7.05 g, 32.95 mmol). The resulting mixture is stirred at rt overnight. The organic solvent is removed in vacuo. The residue is diluted with H_2O (50 mL), extracted with EtOAc ((2 x 100 mL). The organic extracts are combined, dried with Na_2SO_4, filtered and concentrated. Purification of the crude material by chromatography gives the title compound (0.82 g, 5.78 mmol, 35%). ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H), 2.64-2.66 (m, 2H), 7.00-7.02 (m, 1H), 8.27 (d, J = 3.0 Hz, 1H). ES-MS (m/z): calcd for $C_5H_7BO_2S$ $(M-H)^-$: 141.0; found: 141.1.

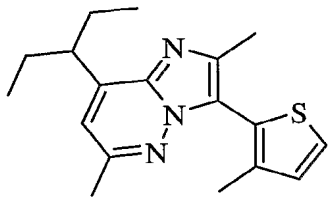
C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

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

6H), 1.75-1.90 (m, 4H), 2.13 (d, J = 0.8 Hz, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.30-3.39 (m, 1H), 6.64 (s, 1H), 7.08-7.11 (m, 1H), 7.34 (d, J = 3.1 Hz, 1H). ES-MS (m/z): calcd for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.5; found: 314.2.

Example 20.

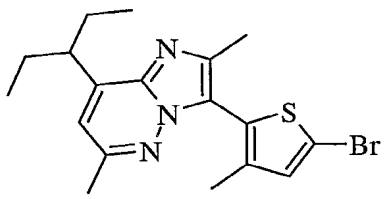
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To mixture of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (12.0 g, 34.96 mmol) and $PdCl_2$(dppf) (1.28 g, 1.75 mmol) is added a 0.5 M solution of 3-methyl-2-thienylzinc bromide in THF (100 mL, 50.0 mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (500 mL), washed with 10% citric acid (500 mL), water (400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (10%-20% EtOAc/hexane gradient) furnish the title compound (8.83 g, 28.17 mmol, 81%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.78-1.95 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.33-3.43 (m, 1H), 6.69 (s, 1H), 7.06 (d, J = 4.9 Hz, 1H), 7.46 (d, J = 4.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.6; found: 314.2.

Example 21.

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

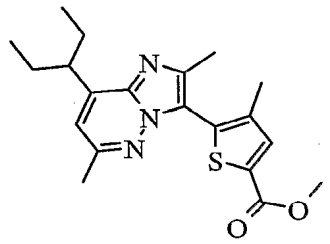


To a solution of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (8.83 g, 28.17 mmol) and CH_2Cl_2 (90 mL) is added NBS (5.26

g, 29.58 mmol). The solution is stirred at ambient temperature for 2 hours. The solution is washed with water (3 X 75 mL), dried over MgSO4, filtered and concentrated to furnish the title compound (10.5 g, 26.76 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.3 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.68 (s, 1H), 6.98 (d, J = 4.9 Hz, 1H) ppm. LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.6; found: 392.1, 394.1.

Example 22.

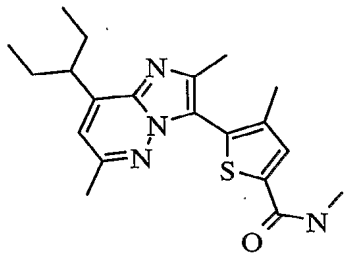
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methyl ester.



A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.00 g, 2.66 mmol) in CH_3OH (12 mL), DMSO (18 mL), Et_3N (2.0 mL) with $Pd(OAc)_2$ (0.12 g, 0.538 mmol), dppf (0.937 g, 1.69 mmol) is reacted at CO atmosphere (100 psi) at 80 °C for 24 h. The reaction mixture is diluted with EtOAc (200 mL), washed with 0.1 M HCl (2 x 50 mL), brine (50 mL); dried with Na_2SO_4; filtered through silica gel and eluted with excess EtOAc. Purification of the crude material by chromatography gives the title compound (0.79 g, 2.12 mmol, 80%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.7 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.32-3.42 (m, 1H), 3.91 (s, 3H), 6.72 (s, 1H), 7.73 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{25}N_3O_2S$ $(M+H)^+$: 372.5; found: 372.2.

Example 23.

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



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

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

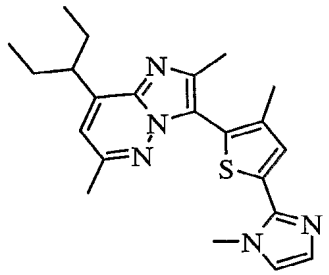
B. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methylamide.

5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (0.17 g, 0.47 mmol) is reacted with 2.0 M oxalyl chloride in CH_2Cl_2 (3.0 mL) at rt for 1h. The excess reagent and solvent are removed in vacuo. The residue is dissolved in CH_2Cl_2 (3mL), cooled to 0 °C and treated with 2.0 M methyl amine in THF (3 mL). The reaction is stirred at 0 °C for 10 min and rt for 30min. It is diluted with EtOAc (50 mL), washed with H_2O (15 mL0, 0.1 M NaOH (2 x 30 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the crude material by chromatography to give the title compound (0.91g, 0.25 mmol, 53%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 6H), 1.75-1.91 (m, 4H), 2.14 (s, 3H), 2.47 (s, 3H), 2.52 (s, 3H), 3.02

(d, J = 4.8 Hz, 3H), 3.28-3.36 (m, 1H), 5.90-6.01 (m, 1H), 6.69 (s, 1H), 7.43 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{26}N_4OS$ $(M+H)^+$: 371.5; found: 371.2.

Example 24.

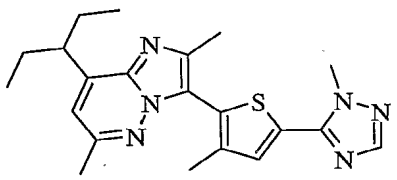
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-imidazol-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo-[*1,2-b*]pyridazine (0.98 g, 2.51 mmol) and 1-methyl-*1H*-imidazole (0.2 mL), $Pd(OAc)_2$ (34 mg, 0.15 mmol), PPh_3 (79 mg, 0.299 mmol), Cs_2CO_3 (1.95 g, 6.0 mmol) in DMF (50 mL) is stirred under N_2 at 130-140°C overnight. The reaction mixture is cooled, diluted with EtOAc (300 mL), washed with H_2O (3 x 100 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the resulting crude material by chromatography yields the title compound (0.51 g, 1.29 mmol, 51%). ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 6H), 1.77-1.92 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.54 (s, 3H), 3.30-3.40 (m, 1H), 3.81 (s, 3H), 6.69 (s, 1H), 7.02 (s, 1H), 7.24 (s, 1H), 7.52 (s, 1H). ES-MS (m/z): calcd for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.6; found: 394.3.

Example 25.

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

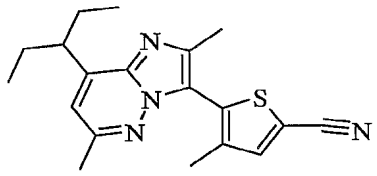


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.15 mL, 2.04 mmol) and THF (3 mL) is added a 1.34 M solution of n-Bu-Li in hexanes (1.60 mL, 2.14 mmol) over 20

minutes, then stirred at –78 °C for 1.5 hours. A 0.5 M solution of $ZnCl_2$ in THF (4.28 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.019 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution heated at 65 °C overnight diluted with CH_2Cl_2 (30 mL). The organic layer is washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (20%-60% EtOAc/hexane gradient). The residue is dissolved in Et_2O, treated with Darco®-60 for 15 minutes, dried with Na_2SO_4, and filtered to furnish the title compound (0.24 g, 0.61 mmol, 60%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.20 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.37 (m, 1H), 4.14 (s, 3H), 6.69 (s, 1H), 7.45 (s, 1H), 7.87 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.6; found: 395.2.

Example 26.

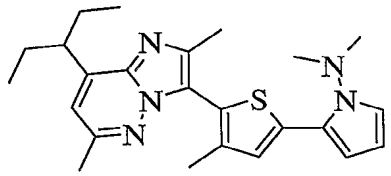
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile.



A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.28 mmol), DMF (5 mL), and $Zn(CN)_2$ (0.090 g, 0.76 mmol) is degassed with nitrogen for 15 minutes. $Pd(PPh_3)_4$ (0.74 g, 0.064 mmol) and the solution heated at 100 °C overnight. The solution is diluted with EtOAc (50 mL), washed with 2 M NH_4OH (2 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15% - 20% EtOAc/hexane gradient) furnish the title compound (0.39 g, 1.15 mmol, 91%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.15 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 3.26-3.34 (m, 1H), 6.72 (s, 1H), 7.53 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{22}N_4S$ $(M+H)^+$: 339.6; found: 339.2.

Example 27.

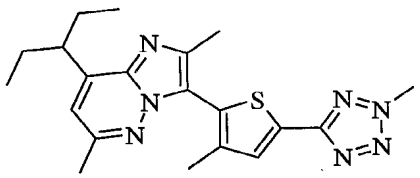
Preparation of (2-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyrrol-1-yl)-dimethyl-amine.



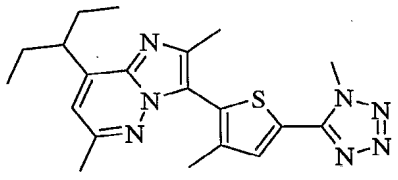
To a 0 °C solution 1-(dimethylamino)-pyrrole (0.24 mL, 2.04 mmol) and THF (4 mL) is added 1.24 M *n*-BuLi (1.73 mL, 2.14 mmol). The solution is warmed to ambient temperature and stirred for two hours. 0.5 M $ZnCl_2$ (4.28 mL, 2.14 mmol) is added and the solution is stirred for one hour. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution is heated at 65 °C overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -20% EtOAc gradient) furnish the title compound (0.41 g, 0.97 mmol, 95%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.11 (s, 3H), 2.51 (s, 6H), 2.83 (s, 6H), 3.29-3.39 (m, 1H), 6.18-6.21 (m, 1H), 6.35 (dd, J = 4.0, 1.8 Hz, 1H), 6.65 (s, 1H), 6.98 (dd, J = 4.0, 1.8 Hz, 1H), 7.25 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{31}N_5S$ $(M+H)^+$: 422.2; found: 422.4.

Example 28 and 29.

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



Ex 28.



Ex. 29.

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

To a solution of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile (0.25 g, 0.74 mmol) and DMF (2.5 mL) is added Et_3N•HCl (0.31 g, 2.22 mmol) and NaN_3 (0.14 g, 2.20 mmol). The solution is heated at 100 °C overnight. The solution is diluted with water (20 mL) and extracted with EtOAc (3 X 15 mL), the combined organic layers are washed with 0.1 M HCl (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is recrystalized from acetonitrile furnish the title compound (0.14 g, 0.37 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.81 (t, J = 7.5 Hz, 6H), 1.66-1.87 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.26-3.35 (m, 1H), 6.83 (s, 1H), 7.84 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{23}N_7S$ $(M+H)^+$: 382.6; found: 382.2.

B. 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2,5-dihydro-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[1,2 b]pyridazine.

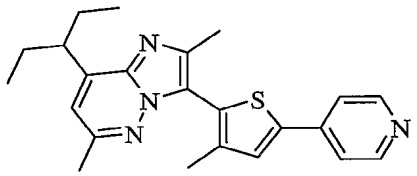
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.14 g, 0.35 mmol) and THF (3 mL) is added Et_3N (0.1 mL, 0.71 mmol) and MeI (0.024 mL, 0.39 mmol). The solution is stirred overnight, diluted with EtOAc (20 mL), washed with water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

Ex. 28: ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.92 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.38 (m, 1H), 4.38 (s, 3H), 6.68 (s, 1H), 7.71 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 396.3.

Ex. 29: ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.73-1.94 (m, 4H), 2.23 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.37 (m, 1H), 4.30 (s, 3H), 6.62 (s, 1H), 7.63 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 396.3.

Example 30.

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



A. 3-(5-Boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a -78 °C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.20 g, 3.06 mmol) and THF (10 mL) is added 1.30 M *n*-Bu-Li (2.47 mL, 3.21 mmol) drop wise. The solution is stirred at –78 °C for one hour. $B(OMe)_3$ (0.38 mL, 3.65 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hours. 1 M HCl is added and the solution stirred for 10 minutes extracted with CH_2Cl_2 (2 X 30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.47 g, 1.32 mmol, 43%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.71-1.98 (m, 4H), 2.02 (s, 3H), 2.64 (s, 3H), 2.69 (s, 3H), 3.64-3.83 (m, 1H), 7.06 (d, J = 5.3 Hz, 1H), 7.54 (d, J = 5.3 Hz, 1H), 7.20 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{24}BN_3O_2S$ $(M+H)^+$: 358.4; found: 358.2.

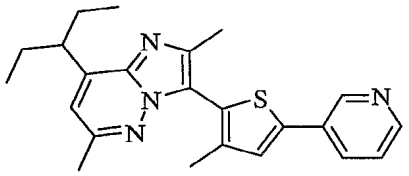
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

A solution of 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.70 mmol), 4-bromopyridine hydrochloride (0.16 g, 0.84 mmol), and 2 M Na_2CO_3 (0.87 mL, 1.75 mmol) and *n*-PrOH (2.5 mL) is degassed with nitrogen for 10 minutes. $Pd(PPh_3)_4$ (0.040 g, 0.035 mmol) is added and the solution heated at 85 °C overnight. The solution is diluted with CH_2Cl_2 (40 mL), washed with 10% Na_2CO_3 (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.41 mmol, 59%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.52 (s,

3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.43 (s, 1H), 7.52 (d, J = 5.5 Hz, 2H), 8.62 (d, J = 5.5 Hz, 2H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2 found: 391.2.

Example 31.

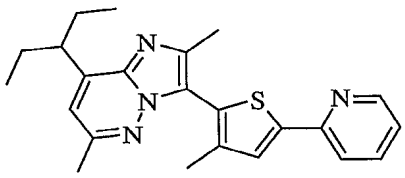
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-3-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol), and THF (5 mL) is added 1.34 M *n*-Bu-Li (1.0 mL, 1.34 mmol). The solution is stirred for at -78 °C for 30 minutes and 0.5 M $ZnCl_2$ in THF (2.7 mL, 1.34 mmol) is added and the solution warmed to ambient temperature. After 30 minutes 3-bromopyridine (0.15 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with CH_2Cl_2 (40 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) concentrated and re-dissolved in Et_2O. The solution is treated with Darco®-60 for 15 minutes, dried over Na_2SO_4, and filtered thru celite® furnish the title compound (0.26 g, 0.67 mmol, 52%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.26-7.32 (m, 2H), 7.86 (dt, J = 7.9, 1.8 Hz, 1H), 850 (d, J = 3.2 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 32.

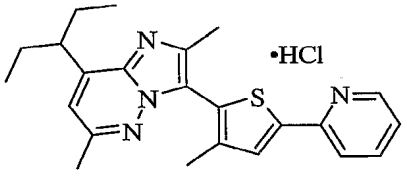
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a mixture of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide in THF (5.1 mL, 2.55 mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with 10% citric acid (50 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.45 g, 1.15 mmol, 89%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.52 (s, 6H), 3.30-3.39 (m, 1H), 6.67 (s, 1H), 7.12-7.16 (m, 1H), 7.53 (s, 1H), 7.63-7.71 (m, 2H), 8.57 (dt, J = 1.3, 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 33.

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

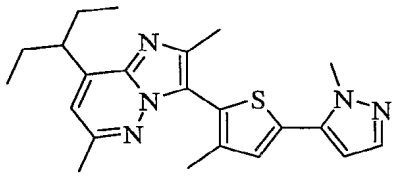


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.15 g, 38 mmol) and MeOH (2 mL) is added AcCl (0.028 mL, 0.39 mmol). After one hour the solution is concentrated and the residue recrystalized from EtOAc/ hexane furnish the title compound (0.11 g, 0.26 mmol, 69%). ^{1}H NMR ($CDCl_3$), δ 0.97 (t, J = 7.4 Hz, 6H), 1.75-2.03 (m, 4H), 2.17 (s, 3H), 2.66 (s, 3H), 2.77 (s, 3H), 3.86-3.98 (m, 1H), 7.17 (s, 1H), 7.21-7.30 (m, 2H), 7.62 (bs, 1H), 7.67-

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

Example 34.

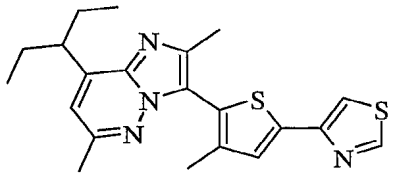
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-*2H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 1-methylpyrazole (0.17 g, 2.04 mmol), 1.56 M *n*-Bu-Li (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.35 g, 0.89 mmol, 88%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 4.05 (s, 3H), 6.42 (d, J = 1.8 Hz, 1H), 6.68 (s, 1H), 7.08 (s, 1H), 7.46 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.7; found: 394.2.

Example 35.

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

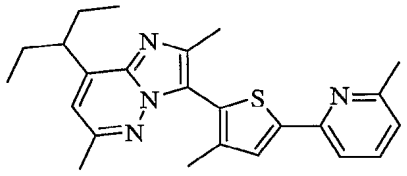


Using a procedure similar to Example 31, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40 g, 1.02 mmol), 1.34 M *n*-Bu-Li (0.8 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-thiazole (0.20 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16g, 0.40 mmol, 40%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.70-1.96 (m, 4H), 2.17 (s, 3H), 2.64 (s, 3H), 2.66 (s, 3H), 3.38-3.48 (m, 1H), 7.16 (d, J = 1.8

Hz, 1H), 7.44 (s, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 397.2.

Example 36.

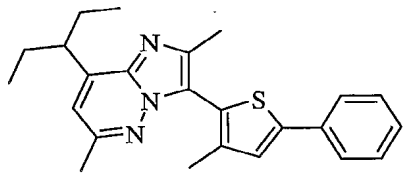
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.53 mmol) and $PdCl_2$(dppf) (0.056 g, 0.076 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (6.0 mL, 3.06 mmol) furnish the title compound (0.29 g, 0.72 mmol, 47%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 2.58 (s, 3H), 3.31-3.40 (m, 1H), 6.67 (s, 1H), 7.00 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 8.56 (t, J = 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.7; found: 405.2.

Example 37.

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

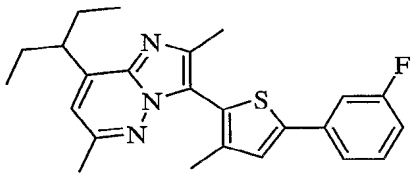


Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.05 g, 0.069 mmol) and 0.5 M solution of phenylzinc iodide in THF (5.5 mL, 2.76 mmol) furnish the title compound (0.25 g, 0.64 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.52 (s, 3H), 2.53 (s,

3H), 3.31-3.41 (m, 1H), 6.68 (s, 1H), 7.26 (s, 1H), 7.27-30 (m, 1H), 7.35-7.41 (m, 2H), 7.61-7.66 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.3; found: 390.3.

Example 38.

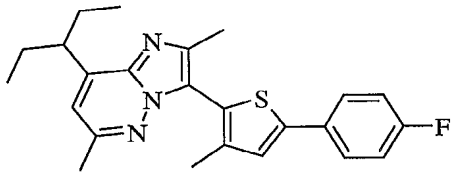
Preparation of 8-(1-ethyl-propyl)-3-[5-(3-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.063 mmol) and 0.5 M solution of 3-flourophenylzinc iodide in THF (5.1 mL, 2.55 mmol) furnish the title compound (0.24 g, 0.59 mmol, 46%). ^1H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.31-3.39 (m, 1H), 6.69 (s, 1H), 6.94-7.01 (m, 1H), 7.26 (s, 1H), 7.30-7.42 (m, 3H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.2.

Example 39.

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

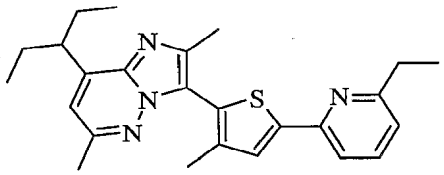


A slurry of 0.05 g/mL of Reike® Zn in THF (0.26 g, 4.01 mmol) and 1-bromo-4-fluoro-benzene (0.29 mL, 2.68 mmol) is heated at a reflux overnight. The solution is filtered under nitrogen. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.35 g, 0.89 mmol) and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

chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.091 g, 0.22 mmol, 25%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.38 (m, 1H), 6.68 (s, 1H), 7.08 (d, J = 8.8 Hz, 2H),7.18 (s, 1H), 7.59 (dd, J = 8.5, 5.3 Hz, 2H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.3.

Example 40.

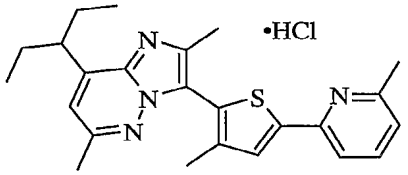
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-ethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, 2-bromo-6-ethyl pyridine (0.26 g, 1.41 mmol), 1.56 M *n*-Bu-Li (0.94 mL, 1.47 mmol), 0.5 M $ZnCl_2$ in THF (3.0 mL, 1.53 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) produce the title compound (0.15 g, 0.36 mmol, 28%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.34 (t, J = 7.5 Hz, 3H), 1.75-1.94 (m, 4H), 2.16 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 2.85 (q, J = 16.2, 7.5 Hz, 2H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.53 (s, 1H), 8.59 (t, J = 7.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.3; found: 419.3.

Example 41.

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

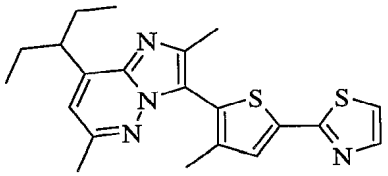


Using a procedure similar to Example 33, 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36

mmol), MeOH (6 mL) and AcCl (0.098 mL, 1.36 mmol) furnish the title compound (0.11 g, 0.25 mmol, 42%). ^{1}H NMR ($CDCl_3$), δ 0.96 (t, J = 7.2 Hz, 6H), 1.74-1.89 (m, 2H), 1.89-2.02 (m, 2H), 2.22 (s, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 3.08 (s, 3H), 3.88-3.98 (m, 1H), 7.23 (s, 1H), 7.40 (d, J = 6.9 Hz, 1H), 7.71 (d, J = 4.8 Hz, 1H), 8.06 (s, 1H), 8.82 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{29}ClN_4S$ $(M+H)^+$: 441.3; found: 405.2.

Example 42.

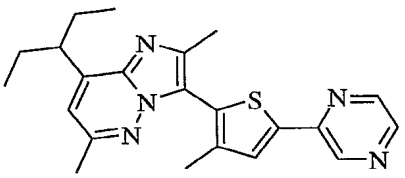
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.46 g, 1.17 mmol), 0.5 M 2-thiazolylzinc bromide in THF (4.7 mL, 2.35 mmol) and $PdCl_2$(dppf) (0.043 g, 0.059 mmol) furnish the title compound (0.32 g, 0.81 mmol, 70%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 7.70 (s, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.47 (s, 1H), 7.78 (d, J = 3.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 397.1.

Example 43.

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

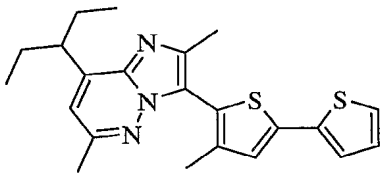


Using a procedure similar to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) (example Rupp-2), 2-chloropyrazine (0.11 mL, 1.22 mmol), 1.42 M *n*-Bu-Li (1.52 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), and $PdCl_2$(dppf)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

mmol) furnish the title compound (0.19 g, 0.49 mmol, 48%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.20 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.63 (s, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.51 (t, J = 1.9 Hz, 1H), 8.96 (d, J = 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 44.

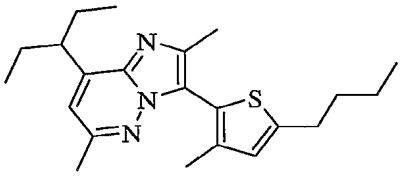
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 0.5 M 2-thiophenlyzinc bromide in THF (3.0 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) furnish the title compound (0.25g, 0.63 mmol, 83%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.14 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.02 (dd, J = 5.0, 3.6 Hz, 1H), 7.11 (s, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.19 (dd, J = 5.0, 1.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_3S_2$ $(M+H)^+$: 396.7; found: 396.2.

Example 45.

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

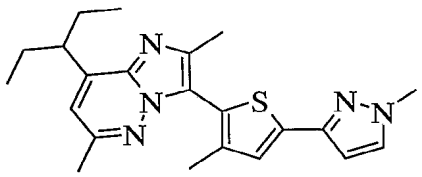


Using a procedure similar to Example 25 from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.1.02 mmol), 1.34 M *n*-Bu-Li (1.60 mL, 2.14 mmol), 0.5 M $ZnCl_2$ (4.3 mL, 2.14 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound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

($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 0.97 (t, J = 7.5 Hz, 3H), 1.40-1.51 (m, 2H), 1.67-1.92 (m, 6H), 2.07 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 3.30-3.38 (m, 1H), 6.64 (s, 1H), 6.70 (s, 1H) LC/MS (m/z): calcd. for $C_{22}H_{31}N_3S$ $(M+H)^+$: 370.3; found: 370.2.

Example 46.

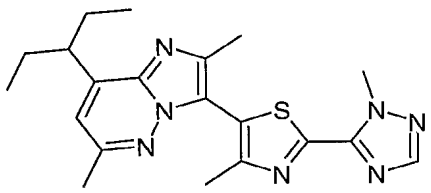
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.42 M *n*-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 3-bromo-1-methyl-*1H*-pyrazole (Pavlik, J.; Kurzweil, E.; *J. Org. Chem.*, 1991, 56, 22, 6313) (0.20 g, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.041g, 0.10 mmol, 10%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 3.95 (s, 3H), 6.47 (d, J = 2.2 Hz, 1H), 6.67 (s, 1H), 7.25 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 47.

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

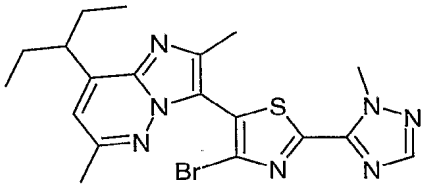


82 mg of 1-Methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78C to room temperature for 10min and cooled to –78°C

again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78C to room temperature for 15 min. 265 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.66 mmol) and 27 mg of PdCl2(dppf) (0.033 mmol) are added and the vial is capped with a Teflon cap and heated at 80°C for 2 days. The reaction is cooled to room temperature and quenched with sat. NH4Cl and extracted with CH2Cl2. The separated CH2Cl2 layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt : 2 M NH3 in MeOH=10:2:1) to give 57 mg of the title product. Yield 22%. mass spectrum (m/e):396(M+1). ^{1}H-NMR (CDCl3): δ 7.96 (s, 1H), 6.77 (s, 1H), 4.45 (s, 3H), 3.36 (m, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 2.47 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.3Hz, 6H).

Example 48.

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

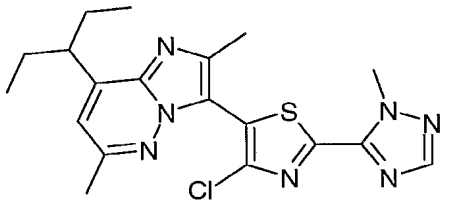


82 mg of 1-methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78°C to room temperature for 10min and cooled to –78°C again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78°C to room temperature for 15min. 152 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.33 mmol) and 27 mg of PdCl2(dppf) (0.033 mmol) are added and the vial is capped with a Teflon cap and heated at 80°C for 2days. The reaction is cooled to room temperature and quenched with sat. NH4Cl and extracted with CH2Cl2. The separated CH2Cl2 layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt:2M NH3 in MeOH=10:2:1) to give 88mg of the title product. Yield 54%.

mass spectrum (m/e):461(M+1). ^{1}H-NMR (CDCl3): 7.98 (s, 1H), 6.77 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 2.55 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

Example 49.

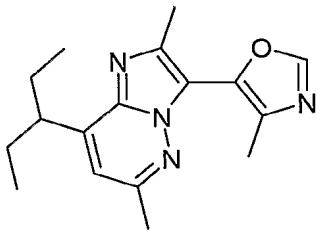
Preparation of 3-[4-chloro-2-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



175 mg of 3-[4-Bromo-2-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.38 mmol) and 56 mg of copper chloride (0.57 mmol) are placed into 4 ml vial with 3.0 ml of dry DMF and the vial is capped with a Teflon cap. The vial is heated at 130°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and hexane:AcOEt=8:1) to give 91 mg of crude product. The pure product is recrystalized from Et2O/Hexane. 73 mg (46%). mass spectrum (m/e):416(M+1). ^{1}H-NMR (CDCl3): 7.98 (s, 1H), 6.80 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

Example 50.

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

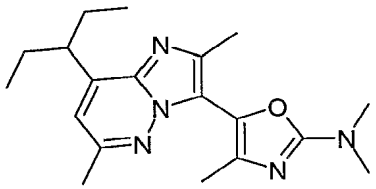


686 mg of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 mmol), 830 mg of 4-methyl-oxazole. (10 mmol), 105 mg of triphenylphosphine (0.4 mmol) and 1.30 g of cesium carbonate (4.0 mmol) are placed into tube with 10 ml of dry

DMF. N2 gas is bubbled in for 20min and 92 mg of Pd2dba3 (0.1 mmol) is added. The tube is sealed and heated at 130°C overnight. After being cooled to room temperature, water and CHCl2 are added to the mixture. The CHCl2 layer is separated, washed with sat. NaCl , dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=5:1) to give 234 mg of the title product. Yield 39%. mass spectrum (m/e):299(M+1). ^{1}H-NMR (CDCl3): 8.06 (s, 1H), 6.75 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.50 (s, 3H), 2.29 (s, 3H), 1.86 (m, 4H), 0.90 (t, J=7.4Hz, 6H).

Example 51.

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



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

230 mg of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo[*1,2-b*]pyridazine (0.77 mmol) is dissolved in 20 ml of CH2Cl2 and 178 mg of NBS (1.0 mmol) is added. The reaction mixture is stirred at room temperature overnight. The reaction mixture is washed with sat. Na2S2O3, sat. NaCl, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 36 mg of the title compound. Yield 12%. mass spectrum (m/e):378(M+1). ^{1}H-NMR (CDCl3): 6.82 (s, 1H), 3.39 (m, 1H), 2.58 (s, 3H), 2.53 (s, 3H), 2.26 (s, 3H), 1.85 (m, 1H), 0.89 (t, J=7.4Hz, 6H).

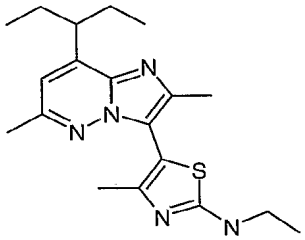
B. N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-oxazol-2-yl}-dimethylamine.

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

Teflon cap and heated at 110°C for 3days. The reaction mixture is cooled to room temperature, concentrated, and applied onto a silica-gel chromatography column (Hexane :AcOEt:2M NH3 in MeOH=10:2:1) to give 24 mg of the title product. Yield 89%. mass spectrum (m/e):342(M+1). ^{1}H-NMR (CDCl3): 6.71(s, 1H), 3.34 (m, 1H), 3.13 (s, 6H), 2.56 (s, 3H), 2.49 (s, 3H), 2.14 (s, 3H), 1.84 (m, 4H), 0.89 (t, J=7.5Hz, 6H).

Example 52.

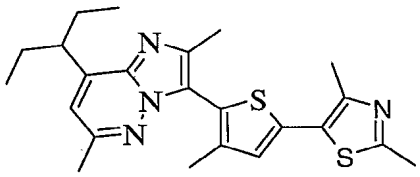
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[(4-methyl-2-ethylamino)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



The title compound is prepared essentially as described in Example 51B. employing 2.0 ml of ethylamine 2.0 M in THF and 182 g of cesium carbonate (0.56 mmol), 78%. mass spectrum (m/e):358 (M+1); 1H-NMR (CDCl3): 6.69(s, 1H), 5.23(br, 1H), 3.38(m, 3H), 2.56(s, 3H), 2.46(s, 3H), 2.17(s, 3H), 1.85(m, 4H), 1.35(t, 3H, J=7.2Hz), 0.90(t, 6H, J=7.2Hz).

Example 53.

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

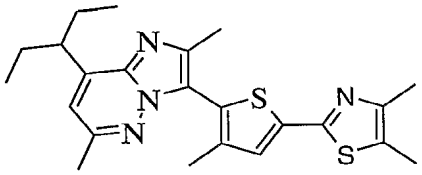


To a –78 °C mixture of 2,4-dimethylthiazole (0.23 g, 2.04 mmol) and THF (3 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.09 mmol). The mixture is stirred at –78°C for 15 minutes. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-

2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (20 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by silica gel chromatography (0%-15% EtOAc/hexane gradient) furnish the title compound (0.21 g, 0.49 mmol, 49%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.14 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 2.57 (s, 3H), 2.66 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.00 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 54.

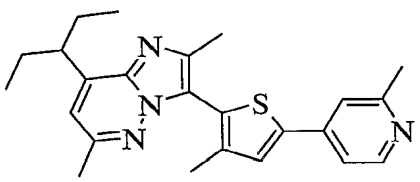
Preparation of 3-[5-(4,5-dimethyl-thiazol-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, from 4,5-dimethylthiazole (0.22 mL, 2.04 mmol), 1.56 M *n*-Bu-Li (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.27 g, 0.64 mmol, 63%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.13 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.49 (s, 3H), 2.51(s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.32 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 55.

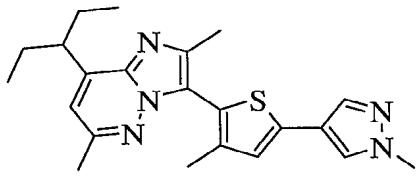
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-pyridin-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, from 4-bromo-2-methyl pyridine (Fukaya et. el. *Chem. Pharm. Bull.*, 1990, 38, 2446) (0.21 g, 1.22 mmol), 1.56 M *n*-Bu-Li (0.69 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.2 mL, 1.12 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.058 g, 0.14 mmol, 14%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.16 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 2.58 (s, 3H), 3.27-3.37 (m, 1H), 6.68 (s, 1H), 7.29 (d, J = 5.3 Hz, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 8.46 (t, J = 5.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.2.

Example 56.

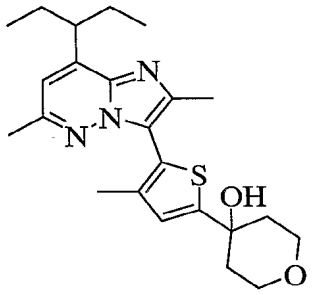
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 31, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.42 M *n*-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-1-methyl-*1H*-pyrazole (0.25 g, 1.53 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound (0.092g, 0.23 mmol, 23%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 6H), 1.73-1.92 (m, 4H), 2.12 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 3.92 (s, 3H), 6.66 (s, 1H), 6.98 (s, 1H), 7.54 (s, 1H), 7.68 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 57.

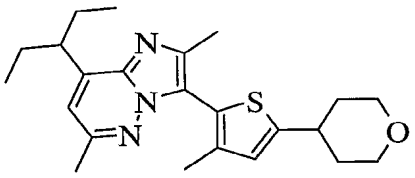
Preparation of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-tetrahydro-pyran-4-ol.



To a -78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.53 mmol) and THF (10 mL) is added 1.56 M *n*-Bu-Li (1.03 mL, 1.61 mmol). After 30 minutes tetrahydro-pyran-4-one (0.21 mL, 2.29 mmol) is added over 5 minutes. The solution is stirred at –78°C for 2 hours, warmed to ambient temperature, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-100% EtOAc/hexane gradient) furnish the title compound (0.38 g, 0.92 mmol, 60%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 1.91-2.00 (m, 2H), 2.11 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.51 (s, 3H), 3.30-3.39 (m, 1H), 3.83-3.98 (m, 5H), 6.66 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3O_2S$ $(M+H)^+$: 414.3; found: 414.2.

Example 58.

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



Method A.

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

(10 mL) is added TFA (0.79 mL, 10.28 mmol) and Et_3SiH (0.25 mL, 1.57 mmol). The solution is concentrated, dissolved in EtOAc (30 mL), washed with sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient), is dissolved in EtOH (25 mL), 10 % Pd/C (0.07 g, 0.066 mmol) is added and the solution stirred under an atmosphere of H_2. After 2 hours the solution is filtered thru celite® and concentrated. The residue is purified by ISCO column chromatography (30% EtOAc in hexane) furnish the title compound (0.033 g, 0.083 mmol, 14%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.95 (m, 4H), 1.97-2.04 (m, 2H), 2.09 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.52 (s, 3H), 3.00-3.11 (m, 1H), 3.30-3.40 (m, 1H), 3.54 (dt, J = 11.8, 2.2 Hz, 2H), 4.08 (dd, J = 11.8, 2.2 Hz, 2H), 6.65 (s, 1H), 6.75 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3OS$ $(M+H)^+$: 398.7; found: 398.2.

Method B.

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

To a -78°C solution of 2-bromo-3-methyl-thiophene (2.0 g, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.32 mL, 18.63 mmol). After 30 minutes at –78°C tetrahydro-pyran-4-one (2.3 mL, 23.07 mmol) is added and the solution is warmed to ambient temperature. The solution is washed with sat. NH_4Cl (30 mL). The aqueous phases is extracted with EtOAc. The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (30%-100% EtOAc/hexane gradient) furnish the title compound (2.3 g, 8.30 mmol, 47%). ^1H NMR ($CDCl_3$), δ 1.82 (m, 2H), 2.00 (s, 3H), 2.06-2.15 (m, 3H), 2.16 (s, 3H), 3.77-3.84 (m, 2H), 3.87 dt, J = 11.3, 2.2 Hz, 2H), 6.67 (s, 1H). LC/MS (m/z): calcd. for $C_{10}H_{13}BrO_2S$ $(M+H)^+$: 277.0; found: 260.9.

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

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

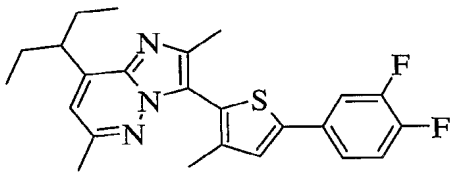
thru celite and concentrated. The residue is purified by ISCO column chromatography (5%-10% EtOAc/hexane gradient) furnish the title compound (1.53 g, 5.86 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 1.69-1.82 (m, 2H), 1.84-1.92 (m, 2H), 2.14 (s, 3H), 2.84-2.98 (m, 1H), 3.49 (dt, J = 11.8, 2.2 Hz, 2H), 4.00-4.07 (m, 2H), 6.51 (s, 1H).

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

Using a procedure similar to Example 25, 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydropyran (0.83 g, 3.19 mmol), 1.56 M *n*-Bu-Li (2.04 mL, 3.19 mmol), $ZnCl_2$ (6.4 mL, 3.19 mmol), 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.56 mmol) and $Pd(PPh_3)_4$ (0.092 g, 0.008 mmol) furnish the title compound (0.072 g, 0.18 mmol, 11%). Spectrum identical to that from Method A.

Example 59.

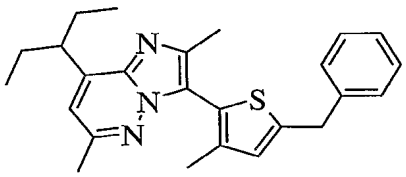
Preparation of 3-[5-(3,4-difluoro-phenyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) and 0.5 M solution of 3,4-difluorophenylzinc bromide in THF (5.1 mL, 2.55 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-80% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.18 g, 0.42 mmol, 33%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.13-7.21 (m, 1H), 7.18 (s, 1H), 7.31-7.36 (m, 1H), 7.39-7.46 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_2N_3S$ $(M+H)^+$: 426.3; found: 426.2.

Example 60.

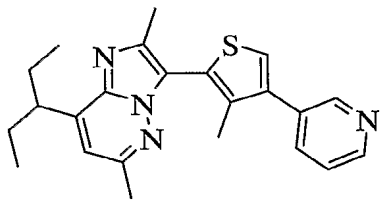
Preparation of 3-(5-benzyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of benzylzinc bromide in THF (4.6 mL, 2.29 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 40-65% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.062 g, 0.15 mmol, 20%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.51 (s, 3H), 3.29-3.39 (m, 1H), 4.16 (s, 2H), 6.65 (s, 1H), 6.68(s, 1H), 7.22-7.29 (m, 1H), 7.31-7.36 (m, 4H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 404.2.

Example 61.

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

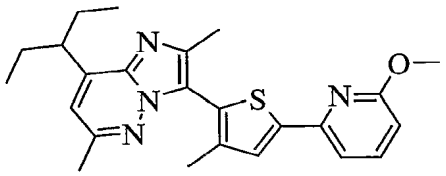


A solution of 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.64 mmol), pyridine-3-boronic acid (0.086 g, 0.70 mmol), 2 M Na_2CO_3 (0.48 mL, 0.96 mmol) and, *n*-PrOH (3 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (2.7 mg, 0.0013 mmol) and PPh_3 (0.010 g, 0.038 mmol) are added and the solution is heated at 90 °C overnight. The solution is diluted with EtOAc (30 mL), washed with 10% Na_2CO_3 (30 mL), water (30 mL), brine (30 mL),

dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO (20-40% EtOAc gradient) furnish the title compound (0.051 g, 0.13 mmol, 20%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.09 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.29-3.40 (m, 1H), 6.69 (s, 1H), 7.33-7.43 (m, 1H), 7.47 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 8.61 (bs, 1H), 8.78 (bs, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2; found: 391.4.

Example 62.

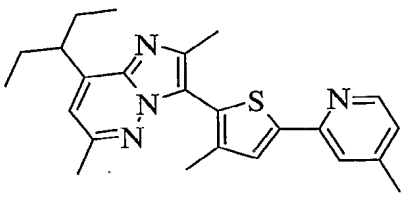
Preparation of 8-(1-ethyl-propyl)-3-[5-(6-methoxy-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 6-methoxy-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.12 g, 0.29 mmol, 38%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 3.98 (s, 3H), 6.61 (d, J = 7.5 Hz, 1H), 6.70(s, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 63.

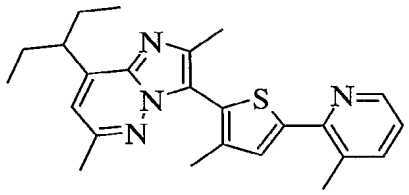
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(4-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.21 g, 0.52 mmol, 68%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.40 (s, 3H), 2.52 (s, 6H), 3.30-3.40 (m, 1H), 6.67 (s, 1H), 6.97(d, J = 4.8 Hz, 1H), 7.49 (s, 1H), 7.52 (s, 1H), 8.42 (d, J = 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 64.

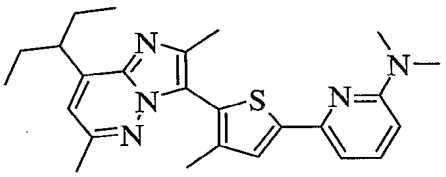
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine) (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 3-methyl-2-pyridylzinc bromide in THF (5.0 mL, 2.50 mmol) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 2.63 (s, 3H), 3.29-3.39 (m, 1H), 6.67 (s, 1H), 7.06-7.14 (m, 1H), 7.44 (s, 1H), 7.74 (dd, J = 7.5, 0.9 Hz, 1H), 8.47 (dd, J = 4.9, 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 65.

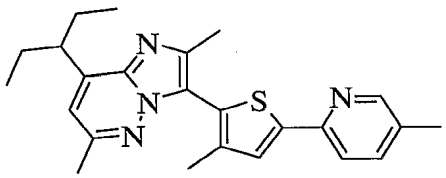
Preparation of (6-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-dimethyl-amine.



Using a procedure similar to Example 39, from Rieke® Zn in THF (0.20 g, 3.06 mmol), (6-bromo-pyridin-2-yl)-dimethyl-amine (Newkomw et. el. *J. Org. Chem.*, 1988, 3, 786) (0.41 mL, 2.04 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.35 g, 0.89 mmol), and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16 g, 0.37 mmol, 36%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.21 (s, 6H), 3.30-3.40 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.95 (d, J = 7.4 Hz, 1H), 7.45 (dd, J = 8.4, 7.4 Hz, 1H), 7.46 (s, 1H). LC/MS (m/z): calcd. for $C_{25}H_{31}N_5S$ $(M+H)^+$: 434.3; found: 434.3.

Example 66.

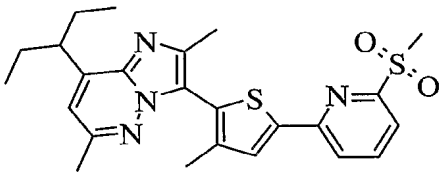
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.23 g, 0.57 mmol, 74%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.16 (s, 3H), 2.35 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.48(s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 8.39-8.40 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 67.

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



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

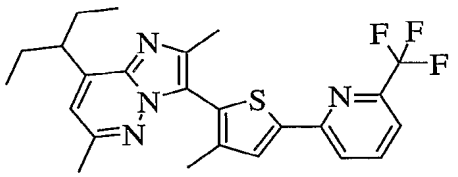
To a solution of 2-bromo-6-methylsulfanyl-pyridine (Testaferri et. el *Tetrahedron*, 1985, 41, 1373) (2.15 g, 10.53 mmol) and CH_2Cl_2 (30 mL) is added 56-87% mCPBA (12 g, 42.15 mmol). The solution is cooled with ice to ambient temperature and the solution is stirred for 2 hour, washed with sat. $Na_2S_2O_3$ (15 mL), sat. $NaHCO_3$ (2 X 15 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by recrystalization from EtOAc /hexane furnish the title compound (1.71 g, 7.24 mmol, 69%). ^1H NMR ($CDCl_3$), δ 3.26 (s, 3H), 7.73 (dd, J = 8.0, 0.9 Hz, 1H), 7.82 (dd, J = 8.0, 7.5 Hz, 1H), 8.05 (dd, J = 7.5, 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_6H_6BrNO_2S$ $(M+H)^+$: 235.9; found: 235.9.

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

Using a procedure similar to Example 25, 2-bromo-6-methanesulfonyl-pyridine (0.29 mL, 1.22 mmol), 1.3 M *n*-Bu-Li (0.82 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.13 g, 0.28 mmol, 27%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30 (s, 3H), 3.30-3.38 (m, 1H), 6.70 (s, 1H), 7.64 (s, 1H), 7.83 (dd, J = 7.6, 0.8 Hz, 1H), 7.89 (dd, J = 7.9, 0.8 Hz, 1H), 7.93 (dd, J = 7.9, 7.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4O_2S_2$ $(M+H)^+$: 469.3; found: 469.2.

Example 68.

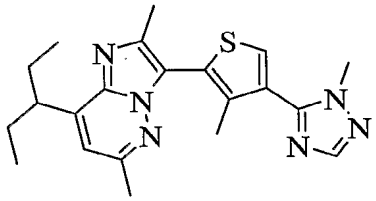
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 2-chloro-6-trifluoromethyl-pyridine (0.29 mL, 1.22 mmol), 1.34 M *n*-Bu-Li (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.20 g, 0.44 mmol, 43%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.50 (dd, J = 7.5, 0.9 Hz, 1H), 7.65 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.84 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 69.

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

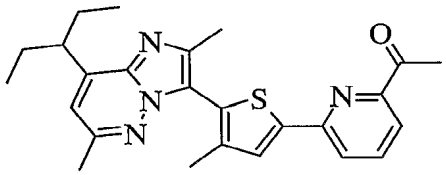


To a slurry of 0.05 g/ mL of Reike® Zn in THF (3.0 mL, 2.29 mmol) is added a solution of 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution was heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution was transferred to a flask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

NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (50%-100% Et_2O) to furnish the title compound (0.058 g, 0.15 mmol, 19%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.11 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.68 (s, 1H), 7.64 (s, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.2; found: 395.4.

Example 70.

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



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

Using a procedure similar to Example 25, 2,6-dibromo-pyridine (0.91 g, 3.82 mmol), 1.34 M *n*-Bu-Li (1.50 mL, 2.00 mmol), $ZnCl_2$ (4.0 mL, 2.00 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.75 g, 1.92 mmol) and $PdCl_2$(dppf) (0.070 g, 0.096 mmol) furnish the title compound (0.26 g, 0.55 mmol, 29%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.31 (dd, J = 7.5, 1.3 Hz, 1H), 7.49-7.57 (m, 2H), 7.58 (s, 1H).

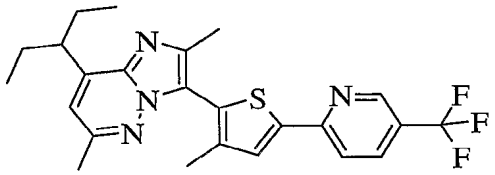
B. 1-(6-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-ethanone.

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

temperature. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15-20% EtOAc/hexane gradient) furnish the title compound (0.030 g, 0.069 mmol, 13%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.19 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 2.77 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.59 (s, 1H), 7.77-7.85 (m, 2H), 7.87 (dd, J = 6.8, 2.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{28}N_4OS$ $(M+H)^+$: 433.3; found: 433.2.

Example 71.

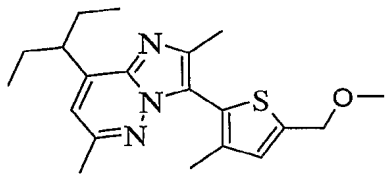
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 2-bromo-5-trifluoromethyl-pyridine (2.14 mL, 1.07 mmol), 1.34 M *n*-Bu-Li (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.17 g, 0.37 mmol, 36%). ^1H NMR ($CDCl_3$), δ 0.90 (t, J = 7.3 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.19 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.70 (s, 1H), 7.63 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.4, 2.2 Hz, 1H), 7.79-7.82 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 72.

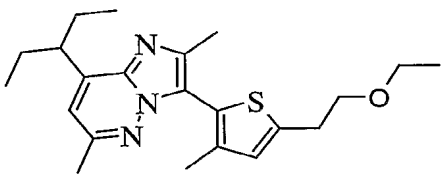
Preparation of 8-(1-ethyl-propyl)-3-(5-methoxymethyl-3-methyl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and THF (3 mL) is added 1.34 M *n*-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes iodo-methoxy-methane (0.097 mL, 1.15 mmol) is added and the solution warmed to ambient temperature. After 1 hour the solution is diluted with EtOAc (40 mL) washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.12 g, 0.34 mmol, 44%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.09 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.28-3.37 (m, 1H), 3.44 (s, 3H), 4.61 (s, 2H), 6.65 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{27}N_3OS$ $(M+H)^+$: 358.3; found: 358.3.

Example 73.

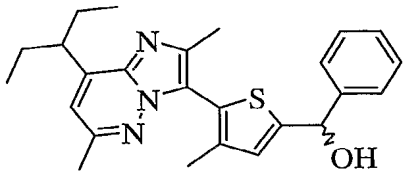
Preparation of 3-[5-(2-ethoxy-ethyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 72, from of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 1.34 M *n*-Bu-Li (0.53 mL, 0.84 mmol), 1-bromo-2-ethoxy-ethane (0.13 mL, 1.15 mmol) and KI (0.013 g, 0.076 mmol) furnish the title compound (0.11 g, 0.29 mmol, 38%). ^{1}H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.23 (t, J = 7.0 Hz, 3H), 1.72-1.90 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.09 (t, J = 7.0 Hz, 2H), 3.28-3.37 (m, 1H), 3.55 (q, J = 7.0 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 6.64 (s, 1H), 6.77 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{31}N_3OS$ $(M+H)^+$: 386.3 found: 386.3.

Example 74.

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



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

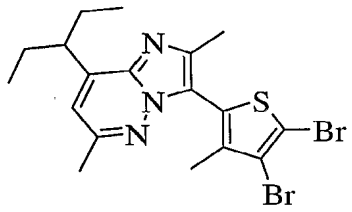
To a –78°C solution of 2-bromo-3-methyl-thiophene (4.7 g, 26.54 mmol) and Et_2O (100 mL) is added 2.0 M LDA (14.6 mL, 29.2 mmol). After 1 hour benzaldehyde (3.0 mL, 29.2 mmol) is added and the solution warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (3.29 g, 11.62 mmol, 44%). ^1H NMR ($CDCl_3$), δ 2.11 (s, 3H), 3.38-3.46 (m, 1H), 5.90 (s, 1H), 6.54 (s, 1H), 7.30-7.45 (m, 5H). LC/MS (m/z): calcd. for $C_{12}H_{11}BrOS$ $(M+H)^+$: 281.0, 283.0; found: 264.9, 266.9.

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

Using a procedure analogous to Example 30C, from 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.1.15 mmol), (5-bromo-4-methyl-thiophen-2-yl)-phenyl-methanol (0.33 g, 1.15 mmol), 2 M Na_2CO_3 (0.86 mL, 1.72 mmol) *n*-PrOH (1 mL), $Pd(OAc)_2$ (0.0052 g, 0.023 mmol), and PPh_3 (0.018 , 0.069 mmol). The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 25-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.017 g, 0.041 mmol, 3.5%). ^1H NMR ($CDCl_3$), δ 0.86 (t, $J = 7.5$ Hz, 6H), 1.72-1.90 (m, 4H), 2.04 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 2.75 (bs, 1H), 3.26-3.38 (m, 1H), 6.05 (s, 1H), 6.65 (s, 1H), 6.76 (s, 1H), 7.30-7.45 (m, 3H), 7.50-7.56 (m, 1H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3OS$ $(M+H)^+$: 420.3; found: 420.3.

Example 75.

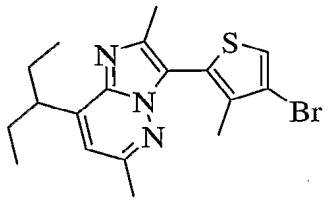
Preparation of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.00 g, 10.20 mmol) and AcOH (40 mL) is added Br_2 (0.57 mL, 11.21 mmol) and the solution heated at 110 °C overnight. Br_2 (0.57 mL, 11.21 mmol) is added and the solution heated at 110 °C for 2 hours. The solution is poured into 5 M NaOH (200 mL) and ice (200 mL). The slurry is extracted with EtOAc (2 x 150 mL). The combined organic layers are washed with water (200 mL), 20% $NaHSO_3$ (200 mL), sat. $NaHCO_3$ (200 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (5%-15% EtOAc gradient) furnish the title compound (2.66 g, 5.64 mmol, 55%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.12 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 3.25-3.35 (m, 1H), 6.69 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{21}Br_2N_3S$ $(M+H)^+$: 470.0; found: 470.3.

Example 76.

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

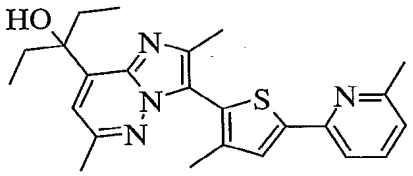


To a –78 °C solution of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 g, 0.47 mmol) and THF (3 mL) is added 1.6 M *n*-BuLi (0.31 mL, 0.49 mmol). After 20 minutes the solution is quenched with water (1 mL), warmed to ambient temperature, diluted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

by ISCO (5%-10% EtOAc gradient) furnish the title compound (0.056 g, 0.14 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.68 (s, 1H), 7.44 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 392.3.

Example 77.

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



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

To a –78°C solution of 2-bromo-3-methyl-thiophene (2.0 mL, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.76 mL, 19.52 mmol). After 45 minutes 0.5 M $ZnCl_2$ (39.0 mL, 19.50 mmol) is added and the solution stirred for 30 minutes. 2-Bromo-6-methyl-pyridine (2.4 mL, 21.29 mmol) and $Pd(PPh_3)_4$ (0.50 g, 0.44 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (20 mL). The aqueous layer is extracted with CH_2Cl_2 (30 mL). The combined organic layers are washed with sat. NH_4Cl (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (2.34 g, 8.73 mmol, 49%). ^{1}H NMR ($CDCl_3$), δ 2.21 (s, 3H), 2.54 (s, 3H), 6.99 (d, J = 7.9 Hz, 1H), 7.23 (s, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.53 (dd, J = 7.9, 7.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{11}H_{10}BrNS$ $(M+H)^+$: 267.0, 269.0; found:267.7, 269.5.

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

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (below) (0.50 g, 3.39 mmol), 2-(5-bromo-4-methyl-thiophen-2-yl)-6-methyl-pyridine (1.00 g, 3.73 mmol), Cs_2CO_3 (2.32 g, 7.13 mmol) and DMF (5 mL) is de-gassed for 15 minutes with N_2. $Pd_2(dba)_3$ (0.15 g, 0.16 mmol) and PPh_3 (0.17 g, 0.65 mmol) is added and the solution is heated at 130°C overnight. The solution is diluted with CH_2Cl_2 (30 mL) washed with water (2 x 25 mL), brine (25 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (100% EtOAc), followed by recrystalization from acetonitrile / water furnish the title compound (0.45 g, 1.35 mmol, 39%). ^{1}H NMR ($CDCl_3$), δ 2.13 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 2.57 (s, 3H), 6.90 (d, J = 9.2 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 8.0, 7.5 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{19}H_{18}N_4S$ $(M+H)^+$: 335.1; found: 335.1.

C. 1-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-propan-1-one.

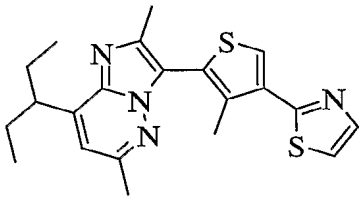
To a –78°C solution of 2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.34 g, 1.02 mmol) and THF (9 mL) is added 2.0 M LDA (0.61 mL, 1.22 mmol). After 3 minutes, *N*-methoxy-*N*-methyl-propionamide (Wolberg et. el. *Chem. Eur. J.*, 2001, 7, 4562) (1.17 g, 1.42 mmol) is added and the solution stirred for 20 minutes, warmed to ambient temperature and stirred for 30 minutes. The solution is diluted with EtOAc (50 mL) washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.10 g, 0.26 mmol, 25%). ^{1}H NMR ($CDCl_3$), δ 1.28 (t, J = 7.0 Hz, 3H), 2.13 (s, 3H), 2.54 (s, 3H), 2.58 (s, 6H), 3.59 (q, J = 7.0 Hz, 2H), 7.03 (d, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.55 (bs, 1H), 7.58 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{22}N_4OS$ $(M+H)^+$: 391.2; found: 391.2.

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

To a –0°C solution of 1-{2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-propan-1-one (0.040 g, 0.10 mmol) and Et_2O (5 mL) is added 3.0 M ethyl magnesium bromide (0.68 mL, 2.05 mmol). The solution is warmed to ambient temperature, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.016 g, 0.038 mmol, 37%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.92-2.01 (m, 4H), 2.14 (s, 3H), 2.46 (s, 3H), 2.53 (s, 3H), 3.57 (s, 3H), 6.39 (s, 1H), 6.66 (s, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.57 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 78.

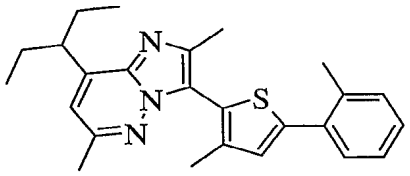
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 g, 0.64 mmol) and $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (3.82 mL, 1.91 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) furnish the title compound (0.19 g, 0.48 mmol, 76%). ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.36 (s, 3H), 2.47 (s, 3H), 2.50 (, 3H), 3.29-3.39 (m, 1H), 6.69 (s, 1H), 7.33 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 3.3 Hz, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.2; found: 397.3.

Example 79.

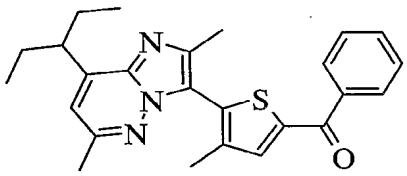
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-o-tolyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 g, 0.38 mmol) and $PdCl_2$(dppf) (0.014 g, 0.019 mmol) and 0.5M solution of 2-methylphenylzinc iodide in THF (3 mL, 1.53 mmol) furnish the title compound (0.069 g, 0.17 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.19 (s, 3H), 2.53 (s, 3H), 2.54 (s, 3H), 2.55 (s, 3H), 3.32-3.40 (m, 1H), 6.68 (s, 1H), 7.02 (s, 1H), 7.22-7.30 (m, 3H), 7.48-7.53 (m, 1H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 404.3.

Example 80.

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

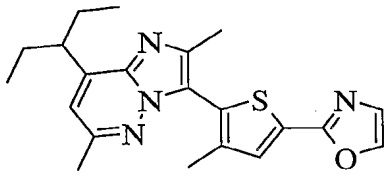


To a -78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and THF (5 mL) is added 1.30 M *n*-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes *N*-methoxy-*N*-methyl-benzamide (0.13 mL, 0.84 mmol) is added, the solution is warmed to ambient temperature, and stirred overnight. The solution is diluted with EtOAc (20 mL), washed with sat. NH_4Cl (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 0.16 mmol, 21%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.54 (s,

3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.49-7.54 (m, 2H), 7.56 (s, 1H), 7.57-7.62 (m, 1H), 7.89-7.94 (m, 2H). LC/MS (m/z): calcd. for $C_{25}H_{27}N_3OS$ $(M+H)^+$: 418.2; found: 418.2.

Example 81.

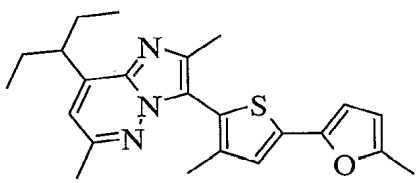
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-oxazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of oxazole (0.14 g, 2.04 mmol) and THF (3 mL) is added 1.6 M *t*-Bu-Li in hexane (1.32 mL, 2.14 mmol). The mixture is stirred at –78°C for 15 minutes. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 20-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) to furnish the title compound (0.020 g, 0.053 mmol, 5%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.69 (s, 1H), 7.19 (s, 1H), 7.59 (s, 1H), 7.65 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4OS$ $(M+H)^+$: 381.3; found: 381.1.

Example 82.

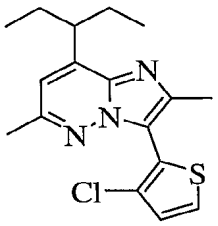
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-furan-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a 0°C mixture of 2-methylfuran (0.18 mL, 2.04 mmol) and Et_2O (2 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.14 mmol). The mixture is heated at a reflux for 30 minutes, cooled to 0°C, and 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65°C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) furnish the title compound (0.20 g, 0.51 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.12 (s, 3H), 2.35 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.62 (dd, J = 3.1, 0.9 Hz, 1H), 6.40 (d, J = 3.1 Hz, 1H), 6.66 (s, 1H), 7.12 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{27}N_3OS$ $(M+H)^+$: 394.3; found: 394.2.

Example 83.

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

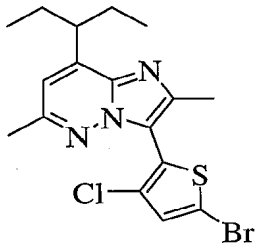


To a flask of 2-bromo-3-chloro-thiophene (Lemaire et. el., *Synth. Commun.*, 1994, 24, 95) (2.53 g, 12.82 mmol) is added 0.05 g/mL Reike® zinc in THF (25 mL, 19.24 mmol). The solution is heated at a reflux for 2 hours. The excess zinc is allowed to settle and the solution transferred to a flask containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example KW1-A03735-193) (2.01 g, 6.41 mmol) and $PdCl_2$(dppf) (0.23 g, 0.32 mmol). The solution is heated at a reflux overnight, quenched with sat. NH_4Cl (25 mL) and extracted with EtOAc (2 X 25 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (2%-15% EtOAc/hexane gradient) furnish the title compound (1.32 g, 6.68 mmol, 62%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m,

4H), 2.48 (s, 3H), 2.49 (s, 3H), 3.37-3.36 (m, 1H), 6.67 (s, 1H), 7.07 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H). LC/MS (m/z): calcd. for $C_{17}H_{20}ClN_3S$ $(M+H)^+$: 334.1; found: 334.1.

Example 84.

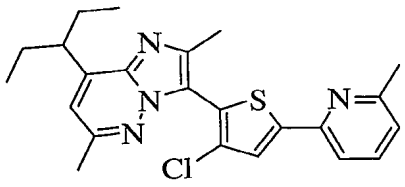
Preparation of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. (1.15 g, 3.44 mmol) and CH_2Cl_2 (12 mL) is added NBS (0.64 g, 3.62 mmol). The solution is stirred at ambient temperature overnight, washed with water (2 x 75 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated to furnish the title compound (1.36 g, 3.29 mmol, 96%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.49 (s, 3H), 2.53 (s, 3H), 3.26-3.36 (m, 1H), 6.70 (s, 1H), 7.07 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.1; found: 412.0.

Example 85.

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



Method A.

To a flask of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027 g, 0.036 mmol) is added 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (2.9 mL, 1.45

mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. NH_4CL (40 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.072 g, 0.17 mmol, 23%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.58 (s, 3H), 3.30-3.39 (m, 1H), 6.70 (s, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.60 (dd, J = 7.7, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{25}ClN_4S$ $(M+H)^+$: 425.2; found: 425.2.

Method B.

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

To a solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.50 g, 7.60 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (23.00 mL, 11.39 mmol) is added $Pd(PPh_3)_4$ (0.18 g, 0.15 mmol). The solution is heated at 40°C overnight, diluted with Et_2O (50 mL), washed with sat. NH_4Cl (40 mL), dried over $MgSO_4$, filtered on concentrated. The residue is purified by ISCO column chromatography (5%-20% EtOAc/hexane gradient) furnish the title compound (0.45 g, 2.15 mmol, 28%). ^1H NMR ($CDCl_3$), δ 2.56 (s, 3H), 7.02 (d, 7.7 Hz, 1H), 7.13 (d, J = 0.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 0.9 Hz, 1H), 7.54 (dd, J = 7.9, 7.7, 1H).

B. 2-(5-bromo-4-chloro-thiophen-2-yl)-6-methyl-pyridine.

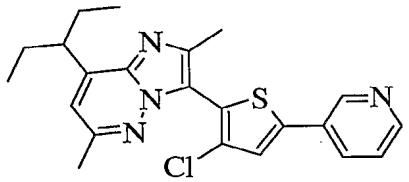
To a 0°C solution of 2-(4-chloro-thiophen-2-yl)-6-methyl-pyridine (example Rupp-96) (0.45 g, 1.45 mmol) and CH_2Cl_2 (10 mL) is added Br_2 (0.15 mL, 2.91 mmol). The solution is warmed to ambient temperature and stirred for 1 hour. The solution is washed with sat. $NaHCO_3$ (10 mL), sat. $Na_2S_2O_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.59 g, 2.04, 95%). ^1H NMR ($CDCl_3$), δ 2.55 (s, 3H), 7.05 (d, 7.9 Hz, 1H), 7.29 (s, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 7.9, 7.9, 1H). LC/MS (m/z): calcd. for $C_{10}H_7BrClNS$ $(M+H)^+$: 288.0; found: 287.9.

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

A solution of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.39 g, 1.78 mmol), 2-(5-bromo-4-chloro-thiophen-2-yl)-6-methyl-pyridine (0.59 g, 2.04 mmol), Cs_2CO_3 (1.23 g, 3.77 mmol), and DMF (5 mL), is de-gassed with N_2 for 15 minutes. PPh_3 (0.089 g, 0.34 mmol) and $Pd_2(dba)_3$ (0.079 g, 0.86 mmol) is added and the solution heated at 110°C for 48 hours. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (19 x 300 C18 Symmetry column, 20-45% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.078 g, 0.18 mmol, 10%). Spectrum identical to Method A.

Example 86.

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



Method A.

A solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), pyridine-3-boronic acid (0.082 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol) and, *n*-PrOH (1 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.0012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added and the solution is heated at 88°C overnight. The solution is diluted with EtOAc (15 mL), washed with water (10 mL), sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15-40% EtOAc/hexane gradient) furnish the title compound (0.095 g, 0.23 mmol, 38%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.32-7.37 (m, 2H), 7.85-7.90 (m, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.2; found: 411.2.

Method B.

A. 3-(4-Chloro-thiophen-2-yl)-pyridine.

A solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.45 g, 7.34 mmol), pyridine-3-boronic acid (0.95 g, 7.71 mmol), 2 M Na_2CO_3 (5.50 mL, 11.01 mmol) and, *n*-PrOH (3 mL), is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.033 g, 0.15 mmol) and PPh_3 (0.12 g, 0.44 mmol) are added and the solution is heated at 85°C for 48 hours, diluted with CH_2Cl_2 (50 mL), washed with 10 % Na_2CO_3 (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.74 g, 3.78 mmol, 51%). ^{1}H NMR ($CDCl_3$), δ 7.12-7.13 (m, 1H), 7.20 (d, J = 1.4 Hz, 1H), 7.31 (dd, J = 8.0, 4.9 Hz, 1H), 7.78-7.82 (m, 1H), 8.55 (d, J = 4.9 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H).

B. 3-(5-Bromo-4-chloro-thiophen-2-yl)-pyridine.

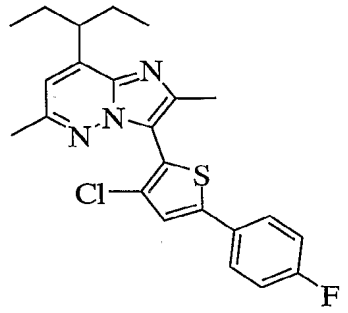
Using a procedure similar to Example 85 Method B. step B, 3-(4-chloro-thiophen-2-yl)-pyridine (0.74 g, 3.78 mmol), and Br_2 (0.39 mL, 7.56 mmol) furnish the title compound (0.99 g, 3.61 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 7.13 (s, 1H), 7.34 (dd, J = 8.1, 4.4 Hz, 1H), 7.74-7.78 (m, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.78 (s, 1H).

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

Using a procedure similar to Example 85 Method B Step C, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 2.30 mmol), 3-(5-bromo-4-chloro-thiophen-2-yl)-pyridine) (0.76 g, 2.76 mmol), Cs_2CO_3 (1.57 g, 4.83 mmol), PPh_3 (0.11 g, 0.44 mmol) and $Pd_2(dba)_3$ (0.10 g, 0.11 mmol). The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.35 g, 0.85 mmol, 37%). Spectrum identical to Method A.

Example 87.

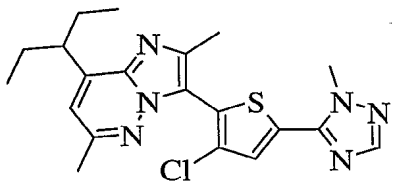
Preparation of 3-[3-chloro-5-(4-fluoro-phenyl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), 4-flourophenylboronic acid (0.093 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol), *n*-PrOH (2 mL), $Pd(OAc)_2$ (0.0068 g, 0.030 mmol) and PPh_3 (0.016 g, 0.061 mmol) furnish the title compound (0.041 g, 0.096 mmol, 16%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.07-7.13 (m, 2H), 7.22 (s, 1H), 7.54-7.60 (m, 2H). LC/MS (m/z): calcd. for $C_{23}H_{23}ClFN_3S$ $(M+H)^+$: 428.2; found: 428.1.

Example 88.

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



Method A.

To a –78 °C solution of 1-methyl-1,2,4-triazole (0.18 mL, 2.33 mmol) and THF (3 mL) is added a 1.56 M solution of *n*-Bu-Li in hexanes (1.49 mL, 2.33 mmol). The solution is stirred at –78°C for 30 minutes, 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g,

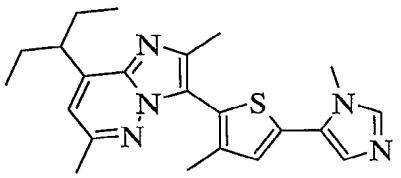
0.78 mmol) and $PdCl_2$(dppf) (0.028 g, 0.039 mmol) is added and the solution heated at 60 °C for 2 days, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-10% EtOAc/hexane gradient) furnish the title compound (0.19 g, 0.46 mmol, 59%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.37 (m, 1H), 4.16 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.1.

Method B.

A 5-L reaction flask equipped with a cooling bath, air stirrer, gas dispersion tube and thermometer probe is charged with 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-1H-[1,2,4]triazole (162.0 g, 0.745 moles), 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (250.1 g, 0.898 moles), NMP (800 mL), KOAc (366.0 g), TBABr (50.5 g), and additional NMP (700 mL) to form a mixture. While stirring, N_2 is bubbled through the mixture for 1 hour. A mixture of $Pd(OAc)_2$ (8.37 g) and TDBPP (24.56 g) are added in one portion, then heated to 120 °C for 3 hours. The reaction is cooled to 50 °C and transferred to a 12 L flask. The mixture is cooled to 20-25 °C, then added de-ionized H_2O (3.5 L) is added dropwise to precipitate out a sticky solid that gradually solidifies with stirring overnight. The solids are filtered, washed with de-ionized H_2O (2 x 2L), and fried on the filter plate for 30-60 minutes. The crude solids (595 g) are warmed in EtOAc (6.0 L) to 30 °C, then filtered through GFF paper to remove insolubles. The filtrate is dried over Na_2SO_4, treated with Darco (30.0 g), heated to 35 °C, filtered, and concentrated to give brown solids (432 g). The crude solids are eluted through a silica plug (1.0 kg) with CH_2Cl_2 (4.0 L), followed by EtOAc (16.0 L). Similar fractions are combined and concentrated under vacuum to approximately 6.0 L, then treated with Darco overnight with stirring. After filtering off the Darco through GFF paper, the filtrate is concentrated to solids (336 g). The solids are crystallized from EtOAc: heptane (1:2) to afford the title compound as a pale yellow solid (187 g, 60.5%, >98% area-% by reverse phase: Zorbax SB-C8, 4.6 mm x 250 mm, 5 microns, UV = 218 nm, flow rate 1.0 mL/min., oven temp. 25°C, isocratic = 30% water (0.1% TFA) & 70% AcCN.

Example 89.

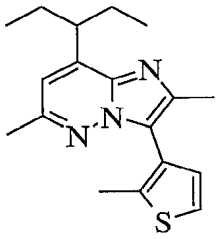
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-*3H*-imidazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.34M *n*-Bu-Li (0.80 mL, 1.07 mmol), 0.5M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 5-iodo-1-methyl-*1H*-imidazole (0.24 g, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.061g, 0.15 mmol, 15%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.24-3.38 (m, 1H), 3.61 (s, 3H), 6.68 (s, 1H), 7.02 (s, 1H), 7.23 (s, 1H), 7.55 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 90.

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



A. 4,4,5,5-Tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane.

A mixture of 3-bromo-2-methyl-thiophene (Saika et. el. *Chem. Soc. Chem. Communication*, 18, 1994, 2133; Steinkopf et. el.; *Justus Liebigs Ann. Chem.*, 513, 1934, 281; 3.1 g, 17.51 mmol), DMSO (50 mL), 4,4,5,5,4',4',5',5'-Octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (4.90g, 19.26 mmol), and KOAc (5.20 g, 52.58 mmol) is de-gassed with N_2 for 15 minutes. $PdCl_2$(dppf) (0.70 g, 0.88 mmol) is added and the solution stirred at ambient temperature overnight, then warmed to 85°C for 3 hours. The solution is diluted with water (200 mL), extracted with EtOAc (2 x 100 mL). The

combined organic layers washed with water (2 x 200 mL), brine (200 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (5%-20% EtOAc/hexane gradient) furnish the title compound (1.52 g, 6.78 mmol, 39%). ^1H NMR ($CDCl_3$), δ 1.34 (s, 12H), 2.72 (s, 3H), 7.04 (d, J = 5.0 Hz, 1H), 7.22 (d, 5.0 Hz, 1H).

B. 2-Methyl-thiophene-3-boronic acid.

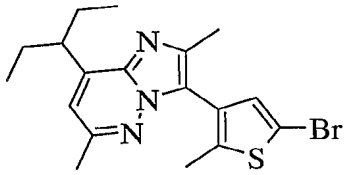
To a solution of 4,4,5,5-tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (1.52 g, 6.78 mmol), acetone (15 mL) and water (15 mL) is added $NaIO_4$ (2.90 g, 13.56 mmol). The solution is stirred at ambient temperature for 24 hours, then heated to a reflux for 24 hours. The solution is concentrated dissolved in EtOAc (1450 mL), washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.75g, 5.49 mmol, 78%). ^1H NMR ($CDCl_3$), δ 2.93 (s, 3H), 7.10 (d, J = 5.3 Hz, 1H), 7.51 (d, 5.3 Hz, 1H).

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

(1.65 g, 4.80 mmol), 2-methyl-thiophene-3-boronic acid (0.75 g, 5.28 mmol), 2 M Na_2CO_3 (3.60 mL, 7.20 mmol) and *n*-PrOH (20 mL) is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.022 g, 0.096 mmol) PPh_3 (0.076 g, 0.29 mmol) is added and the solution heated at 60°C for 24 hours, then heated at 90°C for 24 hours. The solution is concentrated, diluted in EtOAc (50 mL) washed with 10% Na_2CO_3 (40 mL), water (40 mL), brine (40 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.78 g, 2.49 mmol, 52%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.94 (m, 4H), 2.38 (s, 3H), 2.44 (s, 3H), 2.50 (s, 3H), 3.30-3.40 (m, 1H), 6.64 (s, 1H), 7.11 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 5.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.2; found: 314.2.

Example 91.

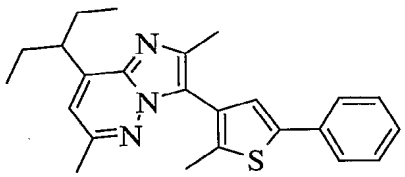
Preparation of 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine. (0.76 g, 2.42 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.60 g, 3.37 mmol). The solution is stirred at ambient temperature for 2 hours and concentrated. The solution is dissolved in Et_2O (30 mL) washed with water (3 x 30 mL), brine (30 mL) dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.95 g, 2.42 mmol, >99%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.31 (s, 3H), 2.42 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 392.1.

Example 92.

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

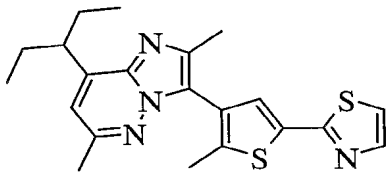


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) and 0.5 M solution of phenylzinc iodide in THF (2.0 mL, 1.02 mmol). The residue is purified by column chromatography (0-10% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.081 g, 0.21 mmol, 41%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.40 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.32-3.41 (m, 1H), 6.66 (s, 1H), 7.23-7.30 (m, 1H),

7.32 (s, 1H), 7.34-7.41 (m, 2H), 7.57-7.63 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.2; found: 390.2.

Example 93.

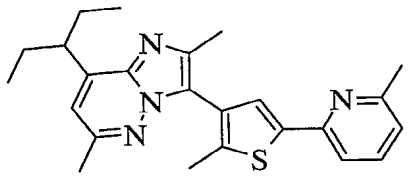
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol), 0.5 M 2-thiazolylzinc bromide in THF (8.1 mL, 4.05 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) furnish the title compound (0.20 g, 0.50 mmol, >99%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.40 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.60 (s, 1H), 7.22 (d, J = 3.2 Hz, 1H), 7.52 (s, 1H), 7.75 (d, J = 3.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.1; found: 397.2.

Example 94.

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

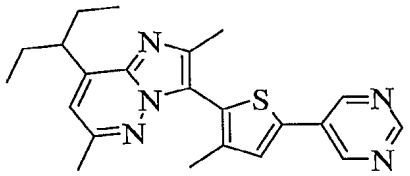


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.24 g, 0.61 mmol) and $PdCl_2$(dppf) (0.022 g, 0.031 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (3.7 mL, 1.84 mmol) furnish the title compound (0.086 g, 0.21 mmol, 34%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.39 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.57 (s, 3H), 3.31-3.40 (m, 1H), 6.65 (s, 1H), 6.97 (d, J = 7.8 Hz,

1H), 7.41 (d, J = 7.8 Hz, 1H), 7.50-7.56 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.2; found: 405.2.

Example 95.

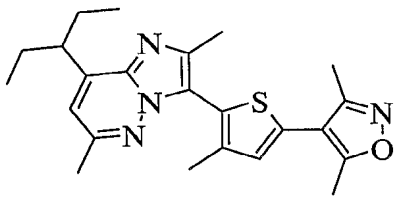
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-5-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 74B, from of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol), 5-pyrimidine boronic acid (0.076 g, 0.61 mmol), 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), $Pd(OAc)_2$ (0.0023 g, 0.011 mmol), PPh_3 (0.0080 g, 0.0031 mmol), and *n*-PrOH (2 mL) is furnished the title compound (0.084 g, 0.21 mmol, 42%). ^{1}H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.17 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.69 (s, 1H), 7.74 (s, 1H), 8.95 (s, 2H), 9.10 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 96.

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

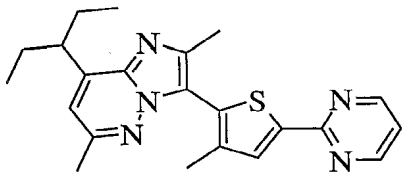


To a flask of 4-iodo-3,5-dimethyl-isoxazole (0.34 g, 1.53 mmol) is added a solution of Rieke® zinc 5g/100 mL in THF (3 mL, 2.29 mmol). The slurry is heated at a reflux for 4 hours, the zinc is allowed to settle and the solution transferred to a flask of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol). The solution is

heated at 50 °C overnight, diluted with EtOAc (20 mL), washed with 0.1 M HCl (15 mL), water (15 mL), brine (15 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.78-1.96 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 2.53 (s, 3H), 2.56 (s, 3H), 2.61 (s, 3H), 3.33-3.42 (m, 1H), 6.72 (s, 1H), 6.98 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4OS$ $(M+H)^+$: 409.3; found: 409.2.

Example 97.

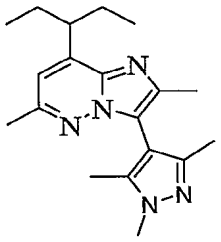
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



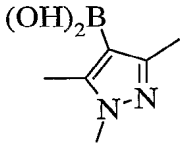
A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 2-tributylstannanyl-pyrimidine (0.34 g, 0.92 mmol) and THF (5 mL) is de-gassed with N_2 for 10 minutes Triphenylarsine (0.047 g, 0.15 mmol) and $Pd_2(dba)_3$ (0.035 g, 0.038 mmol) is added and the solution heated at 55°C for 48 hours and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient), dissolved in acetonitrile (20 mL), washed with hexane (3 x 20 mL) and concentrated to furnished the title compound (0.097 g, 0.25 mmol, 32%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.74-1.92 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.08 (t, J = 4.8, 1H), 7.93 (s, 1H), 8.69 (s, 2H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 98.

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



A. 1,3,5-Trimethylpyrazole-4-boronic acid.



To a dry flask is added 300 mg (1.59 mmol) of 4-bromo-1,3,5-trimethyl pyrazole to 4.0 ml THF. The mixture is cooled to -78^0C and 1eq of n-BuLi (1.6 M) is added via syringe. The mixture is stirred 1.5 hrs, and 0.19ml of trimethylborate (1.08 eq) is added. The reaction mixture is stirred 2 hrs, allowing bath to reach -10^0C, then 1.5 ml of 5N HCl is added and stirred 30 minutes longer. The aqueous layer is extracted 3 times with ethyl acetate. The combined organics are dried over MgSO4, filtered, and evaporated to an oil. The oil is dissolved in methanol/methylene chloride and re-evaporated. The residue is triturated with acetone/ethyl acetate then filtered to obtain title compound as a white solid 92.1 mg (37.6%). ^{1}H-NMR (DMSO-d_6): δ5.92 (s); 3.72 (s, 3H); 2.34 (s, 3H); 2.26 (s, 3H) ppm.

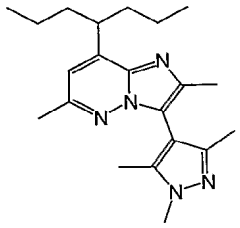
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.

3-Iodo-2,6-dimethyl-8-(1-ethyl-propyl)-imidazo[*1,2-b*]pyridazine (200mg, 0.582 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (233mg, 1.53 mmol), Pd(PPh3)4 (13.4mg, 0.01 mmol) are combined in a microwave pressure tube. Then 0.58 ml of 2N Na2CO3 and 3.0ml of dimethoxyethane/H20/ethanol (7:3:2) solution is added. The mixture is microwaved at 155^0C for 20minutes. Water is added and the mixture is extracted four times with ethyl acetate. The combined organics are dried over MgSO4, filtered, then

evaporated to a residue which is chromatographed using hexanes, then 1:1 hexanes: ethyl acetate, then 100% ethyl acetate to give the title compound (6.4%) as a yellow oil. ^{1}H-NMR (DMSO-d_6): δ6.86 (s, 1H); 3.73 (s, 3H); 3.06-3.10 (m, 1H); 2.41 (s, 3H); 2.22 (s, 3H); 2.03 (s, 3H); 1.93 (s, 3H); 1.74-1.83 (m, 4H); 0.77 (t, J = 7.26 Hz, 6H) ppm. MS/ ES+ = 327 (100%, M+2).

Example 99.

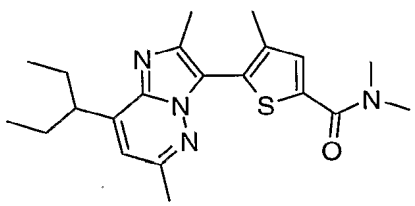
Preparation of 2,6-Dimethyl-8-(1-propyl-butyl)-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.



3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine (75 mg, 0.20 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (80 mg, 0.52 mmol), 2N Na2CO3 solution (0.22 ml), and 5.0mg (0.0004 mmol) of Pd(PPh3)4 are combined in microwave pressure vessel with 1.5ml of dimethylether/H2O/ethanol (7:3:2) solution. The mixture is microwaved at 140^{0}C for 25 minutes. The mixture is evaporated and chromatographed on silica gel column using hexanes then 3:1 hexane:ethyl acetate, then 1:1 hexane:ethyl acetate to give the title compound (22.8%) as a clear oil. ^{1}H-NMR (DMSO-d_6): δ6.88 (s, 1H); 3.72 (s, 3H); 3.06-3.10 (m, 1H); 2.40 (s, 3H); 2.21 (s, 3H); 2.02 (s, 3H); 1.92 (s, 3H); 1.60-1.76 (m, 4H); 1.08-1.21 (m, 4H); 0.82 (t, J = 7.49 Hz, 6H) ppm. MS/ ES+ = 354 (100%, M+1).

Example 100.

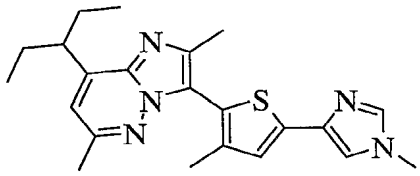
Preparation of 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid dimethylamide.



Using a procedure analogous to Example 23 B, 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (151 mg, 0.42 mmol) and 2.0 M dimethylamine (2.0 mL, 4 mmol) give the title compound (161 mg, 0.42 mmol, 100%). 1H NMR (CDCl3): δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.94 (m, 4H), 2.14 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.15-3.50 (m, 7H), 6.72 (s, 1H), 7.30 (s, 1H). ES-MS (m/z): calcd for C21H28N4OS (M+H)+: 385.6 found: 385.3.

Example 101.

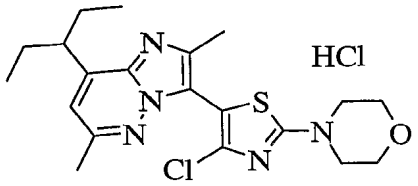
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-Imidazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31. from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.34 M *n*-BuLi (0.80 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 3-iodo-1-methyl-*1H*-imidazole (0.24 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.030g, 0.076 mmol, 8%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, *J* = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.13 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.31-3.40 (m, 1H), 3.72 (s, 3H), 6.66 (s, 1H), 7.09 (d, *J* = 1.3 Hz, 1H), 7.19 (s, 1H), 7.86 (d, *J* = 1.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.2; found: 394.2.

Example 102.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine, hydrochloride salt.

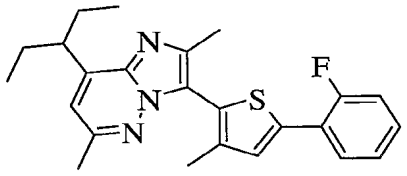


IPA (225.0 mL) is added to compound N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (18.8 g, 0.0448 mmol,

below) in a 1 L 1-neck round-bottomed flask The starting material slurry is heated to 50 °C on a Buchi bath, at which time a hazy solution resulted. Concentrated (12 M) aqueous HCl (3.73 mL, 0.0448 mmole, 1.0 eq) is added all at once, and the hazy solution is stirred at 50 °C on the Buchi for 10 minutes, then evaporated to a yellow solid under vacuum. After 20 minutes at room temperature under vacuum (weight of 20.9 g), acetone (100 mL) is added and the resulting yellow slurry is stirred at room temperature for 1 hour, then cooled with an ice bath and stirred for an additional 1 hour. The slurry is filtered, rinsed with acetone, and dried overnight under vacuum at 40°C to provide pale yellow-white crystalline solid 19.18 g (94%). ^{1}H NMR (DMSO): δ 7.52 (s, 1H), 3.73 (t, J = 4.6, 4H), 3.49 (t, J = 5.2 Hz, 4H), 3.39 (m, 1H), 2.57 (s, 3H), 2.49 (s, 3H), 1.77 (m, 4H), 0.80 (t, J = 7.4 Hz, 6H).

Example 103.

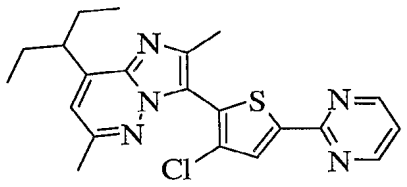
Preparation of 8-(1-ethyl-propyl)-3-[5-(2-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 30 B, 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.18 g, 0.50 mmol), 1-bromo-2-fluoro-benzene (0.072 g, 0.65 mmol), and 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), *n*-PrOH (2 mL), and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) furnish the title compound (0.022 g, 0.054 mmol, 11%). ^{1}H NMR ($CDCl_3$), δ 0.93 (t, *J* = 7.4 Hz, 6H), 1.71-1.96 (m, 4H), 2.19 (s, 3H), 2.66 (s, 3H), 2.67 (s, 3H), 3.41-3.50 (m, 1H), 7.15 (s, 1H), 7.15-7.23 (m, 2H), 7.28-7.35 (m, 1H), 7.45 (d, *J* = 1.4 Hz, 1H), 7.66 (dt, *J* = 7.8, 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.2; found: 408.2.

Example 104.

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



A. 3-(3-Chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a –78 °C solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 g, 5.97 mmol) and THF (30 mL) is added 1.6 M *n*-BuLi (4.1 mL). After 30 minutes $B(OMe)_3$ (0.74 mL, 6.59 mmol) is added, the solution is warmed to ambient temperature and stirred overnight. 1 M HCl (30 mL) is added and the solution stirred for 20 minutes. The solution is made basic with 5 M NaOH. The organic layer is extracted with 1 M NaOH (30 mL). The combined aqueous layers are made acidic with 5 M HCl, K_3PO_4•3 H_2O is added and the PH adjusted to 5.5 using 1 M NaOH. The combined aqueous layers are extracted with EtOAc (200 mL), washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (2.20 g, 5.82 mmol, 97%). LC/MS (m/z): calcd. for $C_{17}H_{21}BClN_3O_2S$ $(M+H)^+$: 378.7; found: 378.0.

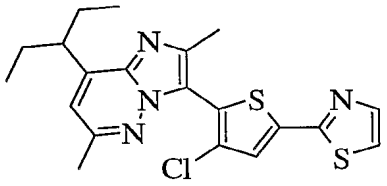
B. 3-(3-Chloro-5-pyrimidin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), and *i*-PrOH (3 mL) are degassed with N_2 for 15 minutes. $Pd(OAc)_2$ (7.4 mg, 0.033 mmol) and PPh_3 (0.026 g, 0.099 mmol) are added and the solution is heated at 90 °C overnight. The solution is diluted with EtOAc (35 mL), washed with 10% Na_2CO_3 (35 mL), brine (35 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.077 g, 0.19 mmol, 29%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H),

3.27-3.40 (m, 1H), 6.71 (s, 1H), 7.16 (t, J = 5.0 Hz, 1H), 8.00 (s, 1H), 8.74 (d, J = 5.0 Hz, 2H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.2.

Example 105.

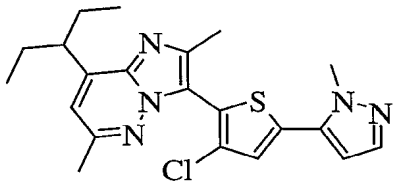
Preparation of 3-(3-chloro-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.099 g, 0.24 mmol, 35%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.71 (s, 1H), 7.33 (t, J = 3.3 Hz, 1H), 7.49 (s, 1H), 7.81 (d, J = 3.3 Hz, 2H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 417.1; found: 417.1.

Example 106.

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

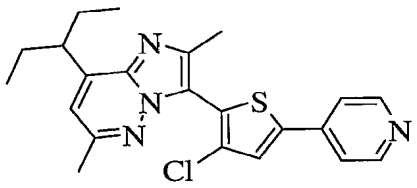


To a –78 °C solution of 1-methyl-*1H*-pyrazole (0.12 g, 1.45 mmol) and THF (4 mL) is added 1.6 M *n*-BuLi (0.91 mL, 1.45 mmol). After 45 minutes 0.5 M $ZnCl_2$ (2.9 mL, 1.45 mmol) is added and the solution is warmed to ambient temperature. After 30 minutes 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example Rupp-88) (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027

g, 0.036 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.15 g, 0.36 mmol, 50%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 6H), 3.26-3.36 (m, 1H), 4.05 (s, 3H), 6.45 (d, J = 1.9 Hz, 1H), 6.71 (s, 1H), 7.14(s, 1H), 7.49 (d, J = 1.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}ClN_5S$ $(M+H)^+$: 414.2; found: 414.2.

Example 107.

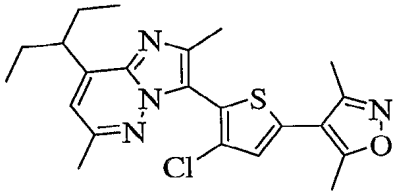
Preparation of 3-(3-chloro-5-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-bromo-pyridine hydrochloride (0.26 g, 1.32 mmol), 2 M Na_2CO_3 (1.00 mL, 1.99 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.16 g, 0.59 mmol, 59%). ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 6.72 (s, 1H), 7.45-7.49 (m, 3H), 8.63 (d, J = 1.3 Hz, 1H), 8.64 (d, J = 1.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.1; found: 411.1.

Example 108.

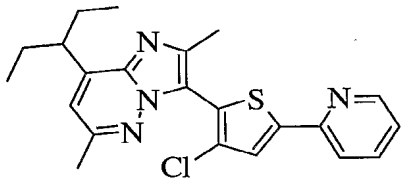
Preparation of 3-[3-chloro-5-(3,5-dimethyl-isoxazol-4-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-iodo-3,5-dimethyl-isoxazole (0.30 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.14 g, 0.50 mmol, 50%). ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.43 (s, 3H), 2.53 (s, 6H), 2.57 (s, 3H), 3.27-3.38 (m, 1H), 6.71 (s, 1H), 7.01 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}ClN_4OS$ $(M+H)^+$: 429.2; found: 429.2.

Example 109.

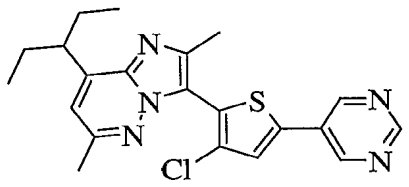
Preparation of 3-(3-chloro-5-pyridin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 g, 0.61 mmol) and $PdCl_2$(dppf) (0.022 g, 0.030 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide (2.40 mL, 1.21 mmol) and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) followed by recrystallization from CH_3CN furnish the title compound (0.15 g, 0.36 mmol, 60%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.17-7.23 (m, 1H), 7.56 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.70-7.76 (m, 1H), 8.59 (d, J = 4.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 412.0; found: 412.4.

Example 110.

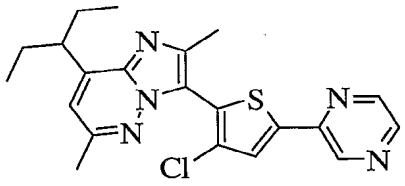
Preparation of 3-(3-chloro-5-pyrimidin-5-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.053 g, 0.13 mmol, 20%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.27-3.37 (m, 1H), 6.73 (s, 1H), 7.40 (s, 1H), 8.97 (s, 2H), 9.18 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 411.2.

Example 111.

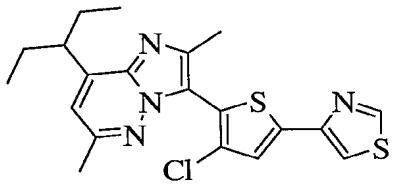
Preparation of 3-(3-chloro-5-pyrazin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40g, 1.06 mmol), 2-iodo-pyrazine (0.16 g, 1.59 mmol), 2 M Na_2CO_3 (1.06 mL, 2.12 mmol) and *i*-PrOH (5 mL), $Pd(OAc)_2$ (0.012 g, 0.053 mmol), and PPh_3 (0.042 g, 0.16 mmol) furnish the title compound (0.15 g, 0.36 mmol, 34%). ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.25-3.37 (m, 1H), 6.71 (s, 1H), 7.66 (s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 8.51-8.53 (m, 1H), 8.96 (d, J = 1.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.3.

Example 112.

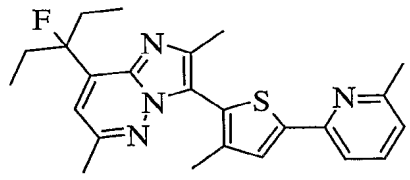
Preparation of 3-(3-chloro-5-thiazol-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a 0 °C solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.45 mmol) and THF (2 mL) is added 0.05 g/mL of Reike® Zn (3.80 mL, 2.91 mmol). The solution is heated at a reflux for 1 hour, and the excess Zn allowed to settle for 1 hour at ambient temperature. The solution is transferred to a flask of 4-bromo-thiazole (Kelly, T. et al. *Tetrahedron Lett.* 1995, 51, 9293) (0.29 g, 1.74 mmol). $PdCl_2$(dppf) (0.027 g, 0.036 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (40 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) to furnish the title compound (0.098 g, 0.24 mmol, 16%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.70 (s, 1H), 7.45 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 8.85 (d, J = 2.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.3.

Example 113.

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

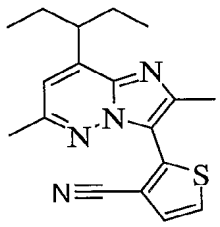


To a –78 °C solution of 3-{2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol (0.23 g, 0.55 mmol) and CH_2Cl_2 (3 mL) is added a solution of [bis(2-methoxyethyl)amino]sulfur triflouride (0.14 g, 0.60 mmol) and CH_2Cl_2 (2 mL). The solution is warmed to ambient temperature and

stirred overnight. The solution is washed with sat. $NaHCO_3$ (5 mL) and concentrated. The reside is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.13g, 0.31 mmol, 57%). ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 6H), 2.14 (s, 3H), 2.16-2.31 (m, 2H), 2.46 (s, 3H), 2.54 (s, 3H), 2.56 (s, 3H), 2.59-2.70 (m, 2H), 6.98 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 7.8, 7.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{27}FN_4S$ $(M+H)^+$: 423.2; found: 423.4.

Example 114.

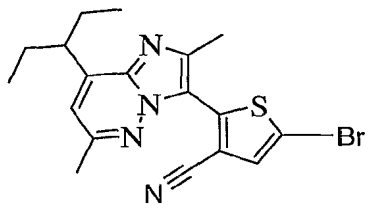
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution 0.05 g/mL of Reike® Zn (31 mL, 23.93 mmol) is added 2-bromo-thiophene-3-carbonitrile (Fournari, P. et al. Bull. Soc. Chim. Fr., 1967, 4115) (2.25 g, 11.96 mmol) and THF (5 mL). The solution is heated at a reflux for 2 hours, cooled to ambient temperature and the excess Zn allowed to settle. The solution is transferred via a cannula into a flask of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.5 g, 7.98 mmol) and $PdCl_2$(dppf) (0.29 g, 0.040 mmol). The mixture is heated at 65°C overnight, diluted with EtOAc (75 mL), washed with sat. NH_4Cl (2 x 75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (1.10 g, 3.39 mmol, 42%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.55 (s, 3H), 2.61 (s, 3H), 3.25-3.34 (m, 1H), 6.75 (s, 1H), 7.35 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 5.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{20}N_4S$ $(M+H)^+$: 325.5; found: 325.2.

Example 115.

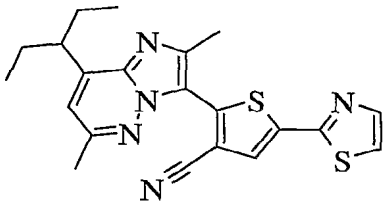
Preparation of 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.83 g, 2.56 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.48 g, 2.69 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (1.03 g, 2.55 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.56 (s, 3 H), 2.60 (s, 3H), 3.24-3.32 (m, 1H), 6.76 (s, 1H), 7.30 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{19}BrN_4S$ $(M+H)^+$: 404.4; found: 404.1.

Example 116.

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

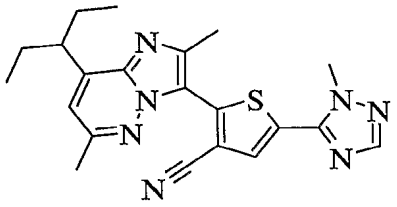


To a flask containing 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added a solution of 0.5 M 2-thiazolylzinc bromide (6.0 mL, 3.10 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.39 mmol, 64%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3H), 2.66 (s, 3H), 3.25-3.35 (m, 1H), 6.78 (s, 1H), 7.38 (d, J = 3.5

Hz, 1H), 7.70 (s, 1H), 7.84 (d, J = 3.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{21}N_5S_2$ $(M+H)^+$: 408.6; found: 408.1.

Example 117.

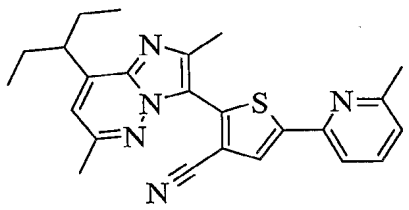
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile.



To a –78 °C solution of 1-methyl-1,2,4-triazole (0.14 mL, 1.86 mmol) and THF (5 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (1.20 mL, 1.86 mmol) after 30 minutes a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (example Rupp-122) (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), and is chromatographed (50 x 250 C18 X-Terra RP column, 30-90% 10 mM NH_4HCO_3/water/5 % ACN: ACN gradient). The residue is dissolved in Et_2O (25 mL), washed with sat. $NaHCO_3$ (25 mL), dried over MgSO4, filtered and concentrated to furnish the title compound (0.013 g, 0.032 mmol, 5%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3 H), 2.67 (s, 3H), 3.26-3.34 (m, 1H), 4.17 (s, 3H), 6.79 (s, 1H), 6.78 (s, 1H), 7.92 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{23}N_7S$ $(M+H)^+$: 406.5; found: 406.2.

Example 118.

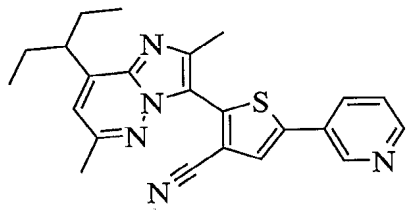
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-(6-methyl-pyridin-2-yl)-thiophene-3-carbonitrile.



To a flask containing 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.024 g, 0.033 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.50 mL, 1.24 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-25% EtOAc/hexane gradient), furnish the title compound (0.11 g, 0.26 mmol, 39%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.76-1.92 (m, 4H), 2.57 (s, 3 H), 2.58 (s, 3H), 2.65 (s, 3H), 3.26-3.35 (m, 1H), 6.75 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 7.9, 7.5 Hz, 1H), 7.74 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}N_5S$ $(M+H)^+$: 416.6; found: 416.2.

Example 119.

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

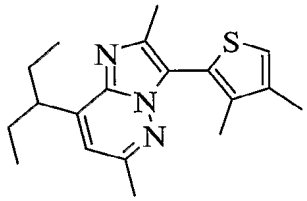


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol), 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol), and THF (2 mL) is added 1.7 M *t*-BuLi (1.85 mL, 3.15 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.21 g, 0.52 mmol) and $Pd(PPh_3)_4$ (0.03 g, 0.026 mmol) are added and the solution

heated at 55 °C for 1 hour, cooled to ambient temperature and stirred overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (2 x 40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-40% EtOAc/hexane gradient), furnish the title compound (0.15 g, 0.37 mmol, 71%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.58 (s, 3 H), 2.66 (s, 3H), 3.26-3.35 (m, 1H), 6.78 (s, 1H), 7.34-7.46 (m, 1H), 7.56 (s 1H), 7.91 (d, J = 7.1 Hz, 1H), 8.62 (s, 1H), 8.91 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{23}N_5S$ $(M+H)^+$: 402.6; found: 402.4.

Example 120.

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



A. 2-Bromo-3,4-dimethyl-thiophene.

To a solution of 3,4-dimethyl-thiophene (2.0 g, 17.82 mmol) (Minato et. al., *Tetrahedron* 1982, 38, 3347) in CH_2Cl_2 (20 mL) is added NBS (3.3 g, 18.72 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated. The residue is purified by ISCO column chromatography (100% hexane) furnish the title compound (3.0 g, 16.70 mmol). ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.17 (s, 3H), 6.85 (s, 1H).

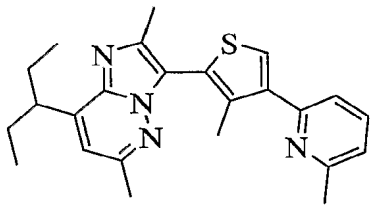
B. 3-(3,4-Dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3,4,3',4'-tetramethyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine, respectively.

To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.30 g, 10.58 mmol), 2-bromo-3,4-dimethyl-thiophene (3.03 g, 15.88 mmol) and Cs_2CO_3 (7.24 g, 22.23 mmol) and DMF (50 mL) is de-gassed with N_2 for 20 minutes. $Pd_2(dba)_3$ (0.48 g, 0.053 mmol) and PPh_3 (0.56 g, 0.21 mmol) are added and the solution is heated at 120°C overnight. The solution is diluted with EtOAc (200 mL), washed with water (3 x

200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated. The residue is purified by ISCO column chromatography (10% -15% EtOAc/hexane gradient) furnish 2.04 g of a brown oil which is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN gradient) furnish the title compound (0.41 g, 1.25 mmol, 12%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.94 (m, 4H), 2.00 (s, 3 H), 2.24 (d, J = 1.0 Hz, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.65 (s, 1H), 7.10 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{25}N_3S$ $(M+H)^+$: 328.5; found: 328.3.

Example 121.

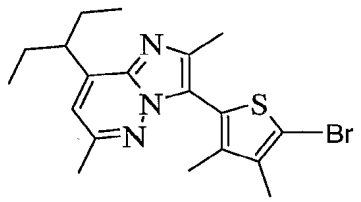
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (below) (0.25 g, 0.64 mmol) and $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.5 mL, 1.27 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) and is chromatographed (50 x 250 C18 Symmetry column, 10-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient). The residue is dissolved in Et_2O (20 mL), washed with sat. $NaHCO_3$ (15 mL) dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.20 (s, 3 H), 2.47 (s, 3H), 2.49 (s, 3H), 2.61 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 7.5, 7.8 Hz, 1H), 7.72 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.3.

Example 122.

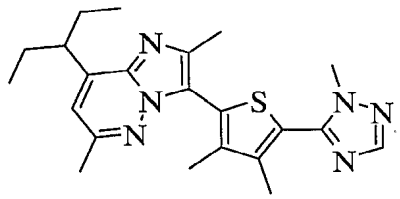
Preparation of 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.41 g, 1.25 mmol) and CH_2Cl_2 (30 mL) is added NBS (0.23 g, 1.32 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (0.41 g, 1.01 mmol, 80%). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 6H), 1.72-1.94 (m, 4H), 2.02 (s, 3 H), 2.18 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.67 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{24}BrN_3S$ $(M+H)^+$: 407.4; found: 407.3.

Example 123.

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

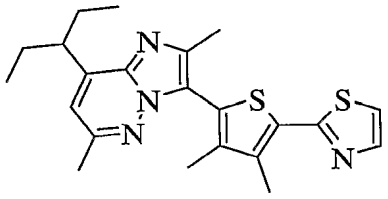


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.056 mL, 0.74 mmol) and THF (2 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (0.46 mL, 0.74 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. The solution is cooled to 0 °C, a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $PdCl_2$(dppf) (0.009 g, 0.012 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried

over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), followed by a second purification by ISCO column chromatography (100% Et_2O) furnish the title compound (0.07 g, 0.17 mmol, 70%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3 H), 2.29 (s, 3H), 2.47 (s, 3H), 2.51 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.69 (s, 1H), 8.00 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{28}N_6S$ $(M+H)^+$: 409.6; found: 409.2.

Example 124.

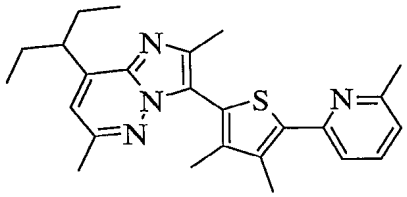
Preparation of 3-(3,4-dimethyl-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and THF (1 mL) is added 1.6 M *n*-BuLi (0.16 mL). The solution is stirred for 45 minutes and 0.5 M $ZnCl_2$ in THF (0.52 mL, 0.26 mmol) is added. The solution is warmed to ambient temperature and stirred for 30 minutes. 2-Bromo-thiazole (0.044 mL, 0.49 mmol), and $PdCl_2$(dppf) (0.009 g, 0.012 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient), furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.49 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.29-3.39 (m, 1H), 6.68 (s, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.86 (d, J = 3.1 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{26}N_4S_2$ $(M+H)^+$: 411.6; found: 411.2.

Example 125.

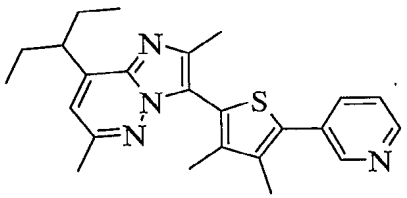
Preparation of 3-[3,4-dimethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $PdCl_2$(dppf) (9 mg, 0.012 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (0.98 mL, 0.49 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.029 g, 0.069 mmol, 29%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.04 (s, 3 H), 2.45 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 2.59 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.0, 7.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.6; found: 419.4.

Example 126.

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

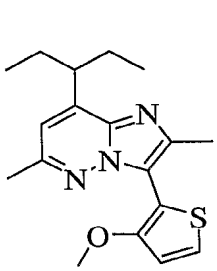


To a –78 °C solution of 3-iodo-pyridine (0.15 g, 0.74 mmol) and 0.5 M $ZnCl_2$ in THF (1.5 mL, 0.75 mmol) is added *t*-BuLi (0.88 mL, 1.49 mmol). The slurry is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) are added and the solution stirred at ambient

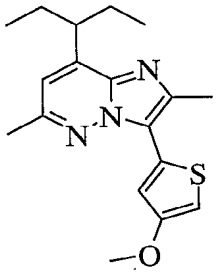
temperature for 2 days, diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.29 (s, 3H), 2.49 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.36 (dd, J = 8.0, 4.5 Hz, 1H), 7.79-7.83 (m 1H), 8.57 (d, J = 4.5 Hz, 1H), 8.79 (d, J = 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.6; found: 405.2.

Example 127 & 128.

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



Ex. 127.



Ex. 128.

To a solution of 3-methoxy-thiophene (2.19 g, 19.14 mmol) in Et_2O (50 mL) is added 1.6 M *n*-BuLi (12.20 mL, 19.46 mmol). The solution is heated at a reflux for 30 minutes and cooled to ambient temperature. As solution of 0.5 M $ZnCl_2$ (38.9 mL, 19.5 mmol) and THF (50 mL) is added and the solution is stirred for 30 minutes. 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 g, 6.38 mmol) and $PdCl_2$(dppf) (0.23 g, 0.032 mmol) are added and the solution is heated at 65 °C for 4 hours, diluted with EtOAc (250 mL), washed with sat. NH_4Cl (250 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-25% EtOAc/hexane gradient) furnish the title compounds (1.50 g, 4.55 mmol, 71%) and (0.23 g, 0.70 mmol, 11%), respectively.

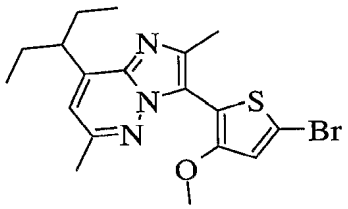
Example 127: ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.59 (s, 3H), 2.70 (s, 3H), 3.26-3.35 (m, 1H), 3.86 (s, 3H), 6.32 (d, J = 1.6 Hz, 1H), 6.67 (s, 1H),

7.41 (d, J = 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 128: ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 6H), 1.71-1.88 (m, 4H), 2.47 (s, 3H), 2.49 (s, 3H), 3.26-3.35 (m, 1H), 3.84 (s, 3H), 6.62 (s, 1H), 6.96 (d, J = 5.5 Hz, 1H), 7.39 (d, J = 5.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 129.

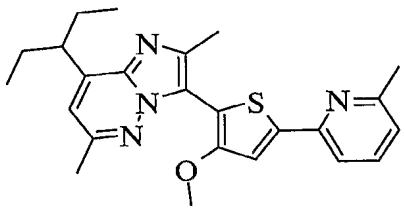
Preparation of 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.78 g, 2.37 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.44 g, 2.49 mmol). The solution is stirred for 1 hour, washed with water (3 x 10 mL), concentrated and purified by ISCO column chromatography (5%-15% EtOAc/hexane gradient) to furnish the title compound (0.87 g, 2.13 mmol, 90%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.82 (s, 3H), 6.65 (s, 1H), 6.97 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3OS$ $(M+H)^+$: 408.1; found: 408.3.

Example 130.

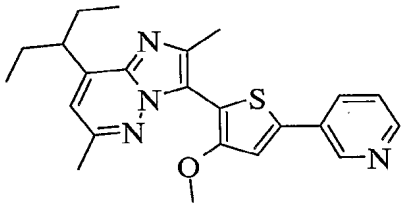
Preparation of 8-(1-ethyl-propyl)-3-[3-methoxy-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) and $PdCl_2$(dppf) (0.018 g, 0.024 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.47 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.50 (s, 3 H), 2.51 (s, 3H), 2.55 (s, 3H), 3.26-3.37 (m, 1H), 3.90 (s, 3H), 6.63 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.49 (s, 1H), 7.54 (dd, J = 7.4, 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.6; found: 422.4.

Example 131.

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

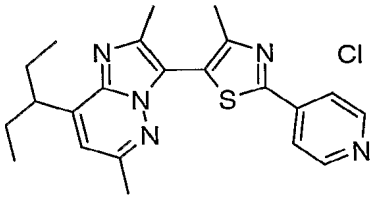


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol) and 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol) is added *t*-BuLi (2.27 mL, 3.85 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.26 g, 0.64 mmol) and $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) are added and the solution heated at 50 °C for 1 hour, cooled to ambient temperature and stirred overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-50% EtOAc/hexane gradient), furnish the title compound (0.16 g, 0.39 mmol, 61%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 3 H), 2.55 (s, 3H), 3.28-3.38 (m, 1H), 3.93, (3H), 6.67 (s, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.88-

7.92 (m, 1H), 8.55 (d, J = 4.5 Hz, 1H), 8.92 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4OS$ $(M+H)^+$: 407.6; found: 407.4.

Example 132.

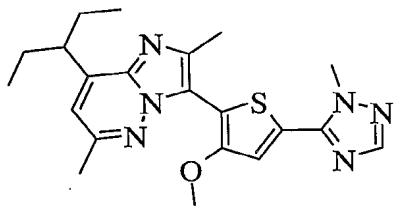
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-4-yl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



A mixture of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (500 mg, 1.27 mmol), 4-pyridineboronic acid (500 mg, 4 mmol), $Pd(PPh_3)_4$ (100 mg, 0.08 mmol), toluene (2 mL), MeOH (1mL), and K_2CO_3 (2 M aqueous solution, 3.5mL) is heated at 100 °C for 18 hours. Ethyl acetate (20mL) is added, and the organic layer is separated, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification is performed via silica gel chromatography using a 3:1 mixture of hexanes and ethyl acetate to obtain the free amine of the title compound (200 mg, 40%). The purified product is dissolved in ethyl acetate and a freshly prepared solution of hydrogen chloride (0.5 M in ethyl acetate, 2 mL) is added. The solvent is removed in vacuo to give the title compound ^{1}H-NMR ($CDCl_3$), δ 8.2 (m, 2H); 7.05 (m,2H); 6.55 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. MS/ES$^+$ = 391 (100%, M+1).

Example 133.

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



A. 5-Bromo-1-methyl-*1H*-[1,2,4]triazole.

To a –78 °C solution of 1-methyl-*1H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 M *n*-BuLi (8.70 mL, 13.86 mmol). After 45 minutes 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added, the solution is warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 161.9.

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

To a solution of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.75 g, 2.28 mmol) and CH_3CN (10 mL) is added NIS (0.54 g, 2.39 mmol). The solution is stirred overnight, concentrated, diluted with EtOAc (30 mL), washed with water (30 mL), sat. NH_4Cl (30 mL), 20% ($NaHSO_3$) (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.91 g, 2.00 mmol, 88%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.83 (s, 3H), 6.64 (s, 1H), 7.12 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}IN_3OS$ $(M+H)^+$: 456.4; found: 456.0.

C. 5-Bromo-1-methyl-1*H*-[1,2,4]triazole.

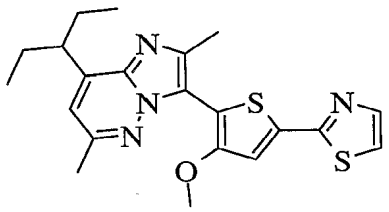
To a –78 °C solution of 1-methyl-1*H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 M *n*-BuLi (8.70 mL, 13.86 mmol). After 45 minutes 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added, the solution warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 161.9.

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

To a slurry of 0.05 g/ mL of Reike® Zn in THF (2.8 mL, 2.11 mmol) is added 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution is heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution is transferred to a flask containing 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g, 0.70 mmol) and $Pd(PPh_3)_4$ (0.041 g, 0.035 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (30 mL). The aqueous phase is extracted with EtOAc (20 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The reside is purified by ISCO column chromatography (20%-65% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) furnish the title compound (0.19 g, 0.46 mmol, 62%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.51 (s, 3 H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.92 (s, 3H), 4.15 (s, 3H), 6.67 (s, 1H), 7.48 (s, 1H), 7.89 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6OS$ $(M+H)^+$: 411.5; found: 411.3.

Example 134.

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

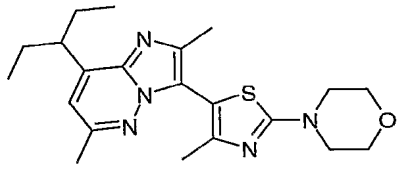


To a flask containing 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.45 g, 0.99 mmol) and $PdCl_2$(dppf) (0.057 g, 0.078 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (9.9 mL, 4.94 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.29 g, 0.70 mmol, 71%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-

1.90 (m, 4H), 2.51 (s, 3H), 2.53 (s, 3H), 3.28-3.37 (m, 1H), 3.93 (s, 3H), 6.67 (s, 1H), 7.28 (d, J = 3.3 Hz, 1H), 7.41 (s, 1H), 7.80 (d, J = 3.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4OS_2$ $(M+H)^+$: 413.6; found: 414.3.

Example 135.

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



110 mg of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.28 mmol) and 122 mg of morpholine (1.4 mmol) are dissolved in 3.0 ml of THF and 182 mg of cesium carbonate (0.56 mmol) is added. The mixture is put in 4 ml vial with a Teflon® lined cap and heated at 110°C overnight. The reaction mixture is concentrated and applied to a silica-gel column chromatography column with hexane:EtOAc = 3:1 eluent to give 98 mg of the title compound (88%). mass spectrum (m/e): 400(M+1); ^{1}H-NMR(CDCl3): δ 6.70(s, 1H), 3.87(t, 4H, J=4.8Hz), 3.56(t, 4H, J=4.8Hz), 3.35(m, 1H) 2.56(s, 3H), 2.46(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.6Hz)

The following compounds are prepared essentially as described in Example 135. with 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
136.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	2M Methyl-amine/THF	6.71 (s, 1H), 5.44 (s, NH), 3.35 (m, 1H), 3.06 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.6 Hz, 6H).	344
137.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dimethylamine	2M Dimethyl-amine/THF	6.70 (s, 1H), 3.36 (m, 1H), 3.17 (s, 6H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	358
138.	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	N-Methyl-ethylamine	6.70 (s, 1H), 3.59 (q, J = 7.6 Hz, 2H), 3.37 (m, 1H), 3.15 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.5 Hz, 2H), 0.90 (t, J = 7.1 Hz, 6H).	372
139.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-diethylamine	Diethyl-amine	6.71 (s, 1H), 3.56 (q, J = 7.1 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.3 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	386

140.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(furan-2-ylmethyl)-methylamine	N-Methyl-(furan-2-yl)-methyl-amine	7.44 (s, 1H), 6.69 (s, 1H), 6.38 (s, 2H), 4.72 (s, 2H), 3.36 (m, 1H), 3.14 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).	424
141.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl}thiomorpholine	Thio-morpholine	6.71 (s, 1H), 3.92 (m, 4H), 3.37 (m, 1H), 2.80 (m, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	416
142	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-amine	2-methoxy-ethylamine	6.71 (s, 1H), 5.90 (s, NH), 3.66 (t, J = 5.4 Hz, 2H), 3.56 (t, J = 4.6 Hz, 2H), 3.44 (s, 3H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	388
143	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	i-propyl-amine	6.69 (s, 1H), 5.15 (s, NH), 3.74 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 1.35 (d, J = 5.4 Hz, 6H), 0.90 (t, J = 7.4 Hz, 6H).	372
144.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-pyrrolidine	Pyrrolidine	6.68 (s, 1H), 3.55 (m, 4H), 3.36(m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 2.09 (m, 4H), 1.86 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).	384

145.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	n-propyl-amine	6.70 (s, 1H), 5.21 (s, NH), 3.39 (t, J = 7.2 Hz, 2H), 3.29 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.85 (m, 4H), 1.74 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.4 Hz, 6H).	372
146	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-benzylamine	Benzyl-amine	7.47-7.23 (m, 5H), 6.70 (s, 1H), 5.52 (s, NH), 6.70 (s, 2H), 3.34 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H).	420
147	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxy-ethyl)-ethylamine	N-(2-Methoxy-ethyl)-ethylamine		416
148	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-n-propylamine	N-(2-meth-oxyethyl)-n-propyl-amine	6.69 (s, 1H), 3.72 (m, 4H), 3.47 (t, J = 7.4 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.87 (m, 6H), 0.99 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	430
149	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidine	piperidine	6.68 (s, 1H), 3.53 (t, J = 4.7 Hz, 4H), 3.36 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.86 (m, 4H), 1.71 (m, 6H), 0.90 (t, J = 7.4 Hz,	398

			6H).	
150	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-pentylamine	3-amino-pentane	6.70 (s, 1H), 5.24 (s, NH), 3.32 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 1.94 (s, 3H), 1.85 (m, 4H), 1.72 (m, 2H), 1.60 (m, 2H), 1.02 (t, J = 7.5 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	400
151	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-cyclo-propylamine	Cyclo-propylamine	6.70 (s, 1H), 6.51 (s, NH), 3.35 (m, 1H), 2.67 (m, 1H), 2.57(s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H), 0.82 (m, 2H), 0.77 (m, 2H).	370
152	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-allylamine	Allylamine	6.70 (s, 1H), 6.0 (m, 1H), 5.60 (s, NH), 5.38 (dd, J = 1.3, 17.4 Hz, 1H), 5.27 (dd, J = 1.2, 10.3 Hz, 1H), 4.0 (d, J = 5.2 Hz, 2H), 3.45 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 6.8 Hz, 6H).	370
153	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,2,3,6-tetra-hydro-pyridine	1,2,3,6-tetra-hydro-pyridine	6.70 (s, 1H), 5.96 (m, 1H), 5.81 (m, 1H), 4.02 (t, J = 3.1 Hz, 2H), 3.72 (t, J = 5.5 Hz, 2H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.35 (m, 2H), 2.19 (s, 3H), 1.87 (m,	396

			4H), 0.90 (t, J = 7.4 Hz, 6H).	
154	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-ethyl-n-propyl-amine	6.69 (s, 1H), 3.58 (q, J = 7.1 Hz, 2H), 3.43 (t, J = 7.5 Hz, 2H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.80 (m, 4H), 1.30 (t, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	400
155	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-methyl-n-propyl-amine	6.68 (s, 1H), 3.46 (t, J = 8.3 Hz, 2H), 3.35 (m, 1H), 3.16 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.80 (m, 2H), 1.00 (t, J = 7.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	386
156	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	N-Methyl-2-propyl-amine	6.70 (s, 1H), 4.40 (m, 1H), 3.36 (m, 1H), 2.99 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.29 (d, J = 6.4 Hz, 6H), 0.90 (t, J = 7.1 Hz, 6H).	386
157	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-2-propyn-1-amine	N-Methyl-2-Propyn-1-amine	6.70 (s, 1H), 4.40 (d, J = 2.5 Hz, 2H), 3.35 (m, 1H), 3.17 (s, 3H), 2.56 (s, 3H), 2.45 (s, 3H), 2.34 (m, 1H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	382

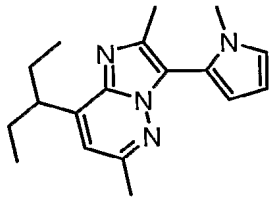
158	N-Methyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-amino-propionitrile	N-Methyl-3-amino-propio-nitrile	6.71 (s, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.37 (m, 1H), 3.25 (s, 3H), 2.9 (t, J = 6.4 Hz, 2H), 2.58 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).	397
159	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- cyclopropyl-methylamine	Cyclo-propyl-methyl-amine	6.68 (s, 1H), 5.35 (s, NH), 3.34 (m, 1H), 3.19 (t, J = 6.3 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H), 1.86 (m, 4H), 1.19 (m, 1H), 0.91 (t, J = 7.1 Hz, 6H), 0.61 (m, 2H), 0.31 (m, 2H).	384
160	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methylsulfanyl)-ethylamine	2-methyl-sulfanyl-ethylamine	6.72 (s, 1H), 5.58 (s, NH), 3.58 (m, 2H), 3.35 (m, J = 7.3, 14.4, 1H), 2.85 (m, 2H), 2.57 (s, 3H), 2.46 (s, 3H), 2.17 (s, 6H), 1.85 (m, 4H), 0.90 (t, J = 6.7 Hz, 6H).	404
161	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine	N-{[1,3]di-oxolan-2-yl-methyl}-methyl-amine	6.72 (s, 1H), 5.22 (m, 1H), 4.05 (m, 2H), 3.94 (m, 2H), 3.73 (d, J = 4.5 Hz, 2H), 3.35 (m, J = 6.6, 14.1 Hz, 1H), 3.23 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).	430
162	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-	N-Methyl-2-propen-1-yl-amine	6.71 (s, 1H), 5.93 (m, 2H), 5.30 (m, 2H), 4.16 (d, J = 5.9 Hz, 2H), 3.39 (m, 1H),	384

	3-yl]-4-methyl-thiazol-2-yl}- N-Methyl-2-propen-1-yl-amine		3.12 (s, 3H), 2.58 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).	
163	(R)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(R)-(tetrahydro-furan-2-ylmethyl)-amine	6.70 (s, 1H), 5.44 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 2H), 0.90 (t, J = 7.3 Hz, 6H).	414
164	(S)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(S)-(tetrahydro-furan-2-ylmethyl)-amine	6.69 (s, 1H), 5.45 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.59 (m, 1H), 3.34 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 1H), 0.90 (t, J = 7.2 Hz, 6H).	414
165	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxyethyl)-methylamine	N-Methyl-2-methoxy-ethyl-amine	6.70 (s, 1H), 3.74 (t, J = 4.2 Hz, 2H), 3.71 (t, J = 4.1 Hz, 2H), 3.43 (s, 3H), 3.37 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	402
166	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-	N-Methyl-benzyl-amine	7.43-7.32 (m, 5H), 6.69 (s, 1H), 4.76 (s, 2H), 3.35 (m, 1H), 3.10 (s, 3H), 2.57(s, 3H), 2.48 (s, 3H), 2.21 (s,	434

	yl}-N-methyl-benzylamine		3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).	
167	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethyl-benzylamine	N-Ethyl-benzyl-amine	7.41-7.31 (m, 5H), 6.68 (s, 1H), 4.76 (s, 2H), 3.54 (q, J = 7.3, 2H), 3.36 (m, 1H), 2.56(s, 3H), 2.49 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	448
168	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(1-methoxy-2-butyl)-amine	1-Methoxy-2-amino-butane		416
169	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methyl-isobutylamine	N,2-Di-methyl- n-propyl-amine		400
170	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isobutyl-amine	2-Methyl-n-propyl-amine		386

Example 171.

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



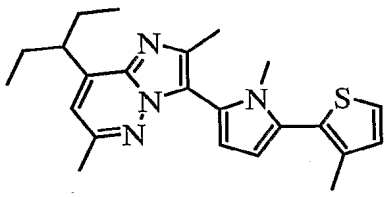
A THF solution (10 mL) of N-methylpyrrole (Aldrich, 800 μL, 9.0 mmol) is cooled to -78 °C under N_2 then treated with *tert*-BuLi (1.7 M in pentane, 5.3 mL, 9.0 mmol). The solution is warmed to room temperature for 30 minutes then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 18 mL, 9.0 mmol). The resulting mixture is warmed to room temperature and treated with a THF slurry (5 mL) containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.02 gm, 3.0 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 140 mg, 0.17 mmol). The mixture is heated to 60 °C overnight, then poured into sat'd aq NH_4Cl (50 mL) and extracted with diethyl ether (75 mL). The organic extract is ished with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (407.5 mg, 46% yield) as an oil.

ES-MS (m/z): calc'd for $C_{18}H_{24}N_4$: 296.20; found 297.5 $(M+H)^+$

^{1}H NMR (400 mHz, $CDCl_3$): δ 6.86 (s, 1H), 6.65 (s, 1H), 6.32-6.28 (m, 2H), 3.50 (s, 3H), 3.35 (br s, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 1.87-1.75 (m, 4H), 0.87 (t, J = 7.0 Hz, 6H).

Example 172.

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



A. 3-(5-Bromo-1-methyl-^1H-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

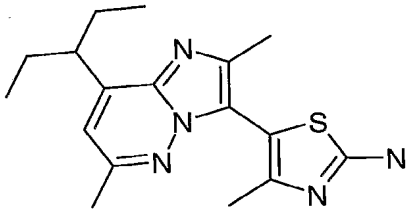
A THF solution (10 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-^1H-pyrrol-2-yl)-imidazo[*1,2-b*]pyridazine (414 mg, 1.40 mmol) is cooled to 0 °C and treated with a THF solution of NBS (250 mg, 1.40 mmol). Within 5 min, the reaction mixture is treated with sat Na_2SO_3 (1 mL) then concentrated. The resulting residue is diluted with ethyl acetate (50 mL) and ished with 50% aq sat'd Na_2SO_3 (2x50 mL). The organic extract is dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (374 mg, 71% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{23}BrN_4$: 374.11; found 375 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.33 (d, J = 4.0 Hz, 1H), 6.30 (d, J = 4.0 Hz, 1H), 3.40 (s, 3H), 3.36 (br s, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H).

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

A THF slurry (5 mL) of 3-(5-bromo-1-methyl-^1H-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (143 mg, 0.38 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 19 mg, 0.023 mmol) is treated with 3-methyl-2-thienyl zinc bromide (Aldrich, 0.5 M in THF, 3.8 mL, 1.9 mmol) then heated to 60 °C for 1 hr. The resulting mixture is poured into sat'd NH_4Cl (25 mL) and extracted with diethyl ether (35 mL). The organic extract is washed with aq. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 15% ethyl acetate in hexane) to elute the product. The material is purified a second time by flash chromatography using hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the product. Only the fractions containing pure desired product, as judged by MS analysis, are collected and give the title compound (82.6 mg, 55% yield) as an oil. ES-MS (m/z): calc'd for $C_{23}H_{28}N_4S$: 392.20; found 393.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.28 (d, J = 5.3 Hz, 1H), 6.96 (d, J = 4.8 Hz, 1H), 6.67 (br s, 1H), 6.39 (d, J = 3.5 Hz, 1H), 6.37 (d, J = 4.0 Hz, 1H), 3.35 (br s, 1H), 3.33, (s, 3H), 2.52 (s, 3H), 2.51 (s, 3H), 2.26 (s, 3H), 1.89-1.76 (m, 4H), 0.87 (t, J = 7.5 Hz, 6H).

Example 173.

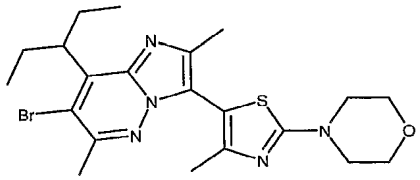
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-ylamine.



50 mg of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.13 mmol) and 10 mg of copper (I) oxide are added to 3 ml of 2 M NH3 in MeOH and vial is capped with a Teflon® lined cap, heated at 130°C for overnight. The reaction mixture is concentrated under N2 gas and applied onto a silica-gel chromatography column (Hexane: AcOEt: 2 M NH3 in MeOH = 20:20:1) to give 22 mg of the title compound. Yield 54%: mass spectrum (m/e): 330(M+1); ^{1}H-NMR(CDCl3): 6.72(s,1H), 5.24(br, 2H), 3.40(m, 1H), 2.56(s, 3H), 2.47(s, 3H), 2.18(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.4Hz).

Example 174.

Preparation of N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.



A. 7-Bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

547 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine (1.74 mmol) and 341 mg of NBS (1.92 mmol) are dissolved in 20 ml of CHCl3 and stirred at room temperature overnight. The reaction mixture is washed with sat. $Na_2S_2O_3$, sat. NaCl, dried over Na_2SO_4 and evaporated. The crude materials are

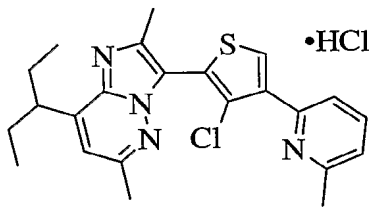
applied onto a silica-gel chromatography column (Hexane:AcOEt=8:1) to give 218 mg of the title compound. Yield 27%. mass spectrum (m/e): 473(M+1); ^{1}H-NMR(CDCl3): 3.44(m, 1H), 2.70(s, 3H), 2.45 (s, 3H), 2.37(s, 3H), 2.03(m, 4H), 0.90(m, 6H).

B. N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.

72 mg of 7-bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 mmol) and 66 mg of morpholine (0.76 mmol) and 97 mg of cesium carbonate (0.3 mmol) are put in 4 ml vial with 3 ml of dry THF. The vial is capped with a Teflon® lined cap and heated at 100°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1) to give 30 mg of the title compound. Yield 42%.: mass spectrum (m/e): 479(M+1); ^{1}H-NMR(CDCl3): 3.87(t, 4H, J=5.0Hz), 3.55(t, 4H, J=5.0Hz), 3.45(m, 1H), 2.70(s, 3H), 2.44(s, 3H), 2.40(m, 2H), 2.18(s, 3H), 2.01(m, 2H), 0.88(t, 6H, J=7.3Hz).

Example 175.

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

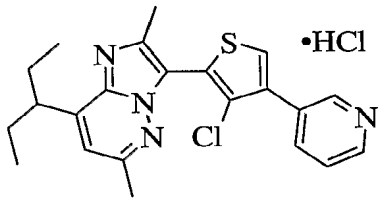


Reike® Zn (0.5 g/ mL solution in THF (1.9 mL,, 1.45 mmol) is added to a flask containing 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the resulting solution is transferred to a flask containing 2-bromo-6-methyl-pyridine (0.12 g, 0.73 mmol) and $PdCl_2$(dppf) (0.018 g, 0.024 mmol). The reaction is heated at 65 °C overnight, diluted with ethyl acetate (20 mL), and washed with a sat. solution of NH_4Cl (15 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by silica gel chromatography using a hexanes and ethyl acetate gradient. The resulting product is dissolved in

dichloromethane (5 mL), treated with a 1 M solution of HCl in EtOH (0.35 mL, 0.35 mmol) and concentrated. The residue is recrystallized from ethyl acetate and hexanes furnish the title compound (0.033 g, 0.072 mmol, 11%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.3 Hz, 6H), 1.73-2.02 (m, 4H), 2.68 (s, 3H), 2.81 (s, 3H), 3.21 (s, 3H), 3.88-3.98 (m, 1H), 7.25 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.33 (dd, J = 7.5, 7.1 Hz, 1H), 9.26 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{23}H_{26}Cl_2N_4S$ $(M+H)^+$: 424.2; found: 424.2.

Example 176.

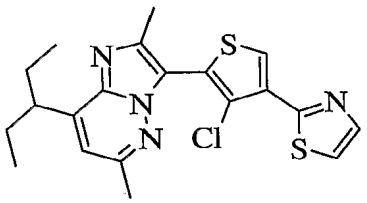
Preparation of 3-(3-chloro-4-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



Using a procedure analogous to Example 175, 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.97 mmol), Reike® Zn (0.5 g/ mL solution in THF, 2.5 mL, 1.94 mmol), 3-iodo-pyridine (0.30 g, 1.45 mmol), $PdCl_2$(dppf) (0.035 g, 0.048 mmol), and a 1 M solution of HCl in EtOH (0.61 mL, 0.61 mmol) furnish the title compound (0.076 g, 0.17 mmol, 18%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.0 Hz, 6H), 1.71-1.88 (m, 2H), 1.88-2.01 (m, 2H), 2.68 (s, 3H), 2.81 (s, 3H), 3.85-3.96 (m, 1H), 5.28 (s, 1H), 7.27 (bs, 1H), 8.09 (bs, 1H), 8.23 (bs, 1H), 8.70 (bs, 1H), 8.89 (bs, 1H), 9.18 (bs, 1H). LC/MS (m/z): calcd. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 177.

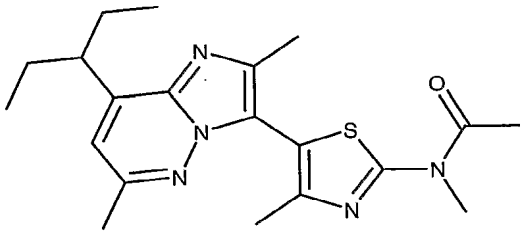
Preparation of 3-(3-chloro-4-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 175, 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), Reike® Zn (0.5 g/ mL solution in THF, 1.6 mL, 1.21 mmol), 2-bromo-thiazole (0.11 mL, 1.21 mmol), and $PdCl_2$(dppf) (0.022 g, 0.030 mmol) furnish the title compound (0.012 g, 0.29 mmol, 6.8%). ^{1}H-NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.52 (s, 6H), 3.27-3.43 (m, 1H), 6.73 (s, 1H), 7.43 (d, J = 3.3 Hz, 1H), 7.94 (d, J = 3.3 Hz, 1H), 8.30 (s,1H) ppm. LC/MS (m/z): calcd. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.2.

Example 178.

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

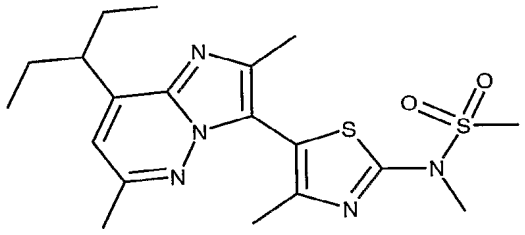


60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH_2Cl_2 and 16 mg of acetylchloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1 and Hexane :AcOEt=2:1) to give 33.8 mg of the title compound. Yield 50%: mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.03(s,1H), 3.79(s, 3H),

3.47(m, 1H), 2.54 (s, 3H), 2.47(s, 3H), 2.46(s, 3H), 2.31(s, 3H), 1.86(m, 4H), 0.91(t, 6H, J=7.4Hz).

Example 179.

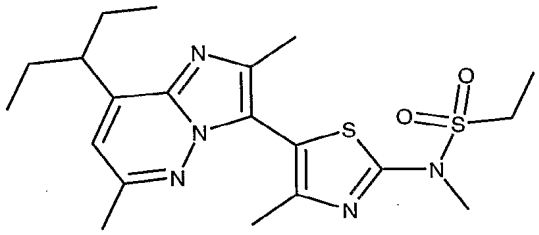
Preparation of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methanesulfonyl-methylamine.



60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH2Cl2 and 23 mg of methanesulfonyl chloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied to silica-gel chromatography (Hexane :AcOEt = 2:1) to give 53.8 mg of the title compound. Yield 75%. mass spectrum (m/e): 422(M+1); ^{1}H-NMR(CDCl3): 6.96(s, 1H), 3.60(s, 3H), 3.34(m, 1H), 3.19(s, 3H), 2.56(s, 3H), 2.48(s, 3H), 2.29(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.4Hz).

Example 180.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethanesulfonyl-methylamine.

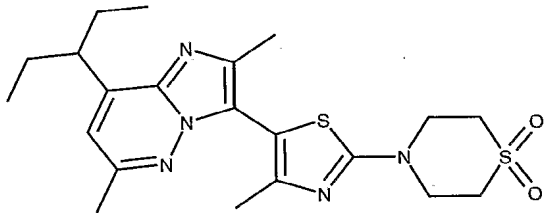


The title compound is prepared by a procedure analogous to Example 178. employing 50 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.15 mmol), 51 mg of triethylamine (0.5 mmol) and 39 mg of ethanesulfonylchloride (0.3 mmol). 48.9 mg, Yield 75%: mass spectrum

(m/e): 436(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.62(s, 3H), 3.42(q, 2H, J=7.4Hz), 3.35(m, 1H), 2.55(s, 3H), 2.48(s, 3H), 2.28(s, 3H), 1.85(m, 4H), 1.46(t, 3H, J=7.4Hz), 0.90(t, 6H, J=7.5Hz).

Example 181.

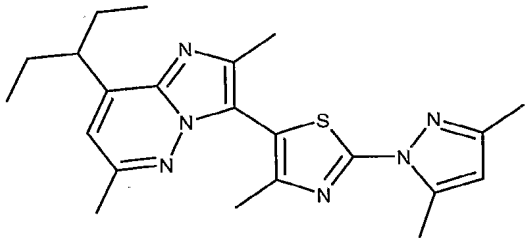
Preparation of 3-[2-(1,1-dioxo-thiomorpholin-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}thiomorpholine(0.14 mmol) is dissolved in 3 ml of CH_2Cl_2 and 62 mg of mCPBA (0.36 mmol) is added. The reaction mixture is stirred at room temperature for 30 min. The reaction mixture is diluted with CH_2Cl_2, washed with sat. NaHCO3 and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt:2 M NH3 in MeOH=10:3:1) to give 20.3 mg of the title compound. Yield 33%: mass spectrum (m/e): 448(M+1). ^{1}H-NMR: 6.72 (s, 1H), 4.16 (t, J = 4.7 Hz, 4H), 3.35 (m, 1H), 3.23 (t, J = 5.2 Hz, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).

Example 182.

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



A. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-hydrazine.

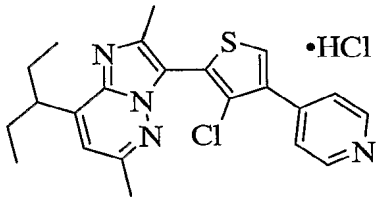
The title compound is prepared essentially as described in Example 135 using hydrazine. MS found (M+1) 345.

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

28 mg of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-hydrazine (0.08 mmol) and 80 mg of 2,4-pentanedione (0.8 mmol) are dissolved in 1.0 ml of AcOH and heated at 100°C for 2 h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane : AcOEt = 5:1) to give 23 mg of the title compound. Yield 70%: mass spectrum (m/e): 409 (M+1). 6.72 (s, 1H), 6.03 (s, 1H), 3.36 (m, J = 7.1, 14.1 Hz, 1H), 2.75 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.32(s, 3H), 2.31(s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).

Example 183.

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

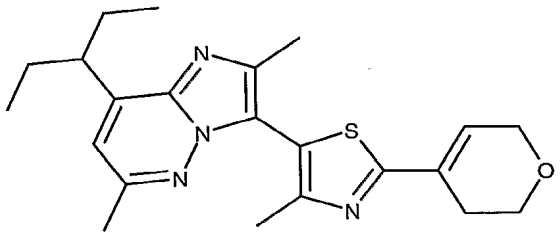


A solution of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), 4-pyridyl-boronic acid (0.82, 0.67 mmol), a 2 M solution of Na_2CO_3 (0.5 mL, 0.91 mmol), and *n*-PrOH (2.5 mL) are degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added, and the solution heated at a 90 °C overnight. The solution is diluted with ethyl acetate (40 mL) and washed with a 10 % solution of Na_2CO_3 (30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO flash chromatography (20%-30% EtOAc gradient). The resulting product is dissolved in dichloromethane (5 mL), treated with a 1 M solution of HCl in

EtOH (0.35 mL, 0.35 mmol), and concentrated. The residue is recrystallized from acetonitrile and ethyl acetate furnish the title compound (0.15 g, 0.34 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.5 Hz, 6H), 1.73-1.88 (m, 2H), 1.89-2.04 (m, 2H), 2.68 (s, 3H), 2.82 (s, 3H), 3.87-3.97 (m, 1H), 7.28 (s, 1H), 8.26-8.34 (m, 3H), 8.95 (d, J = 5.3 Hz, 2H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 184.

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



A. 4-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-tetrahydro-pyran-4-ol.

370 mg of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.93 mmol) is dissolved in 10 ml of dry THF and cooled to –78°C. 0.6 ml of n-BuLi 2.0 M in hexane (1.2 mmol) is added and stirred at –78°C for 30 min. 141 mg of tetrahydro-*4H*-pyran-4-one (1.41 mmol) is added and stirred at –78°C for 2 h. The reaction mixture is diluted with AcOEt, washed with sat. NH4Cl , dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt : 2 M NH3 in MeOH =10:3:1) to give 152 mg of the title compound. Yield 40%.: mass spectrum (m/e): 415(M+1). ^{1}H NMR ($CDCl_3$): δ 6.74 (s, 1H), 3.99 (t, J = 2.2 Hz, 4H), 3.97 (t, J = 2.2 Hz, 4H), 3.35 (m, 1H), 3.20 (s, OH), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 1.88 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).

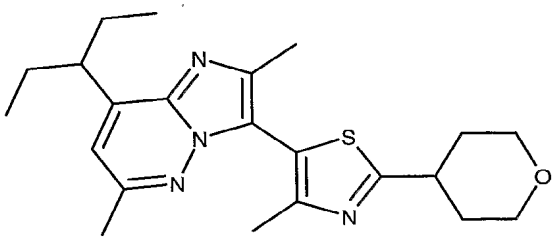
B. 3-[2-(3,6-Dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

150 mg of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-tetrahydro-pyran-4-ol (0.36 mmol) is dissolved in 5 ml of CH2Cl2

and 112 mg of triethylsilane (0.96 mmol) and 717 mg of trifluoroacetic acid (6.3 mmol) are added. The reaction mixture is stirred at room temperature for 1h. The reaction mixture is stirred under reflux for 1 h and cooled down to room temperature. The solvent is removed in *vacuo*. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt: 2 M NH3 in MeOH =10:3:1) to give 64 mg of the title compound. Yield 45%. mass spectrum (m/e): 397(M+1). 6.94 (s, 1H), 6.71 (s, 1H), 4.41 (d, J = 2.6 Hz, 2H), 3.98 (t, J = 5.3 Hz, 2H), 3.43 (m, 1H), 2.62(s, 3H), 2.75 (m, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 1.86 (m, 4H), 0.92 (t, J = 8.2 Hz, 6H).

Example 185.

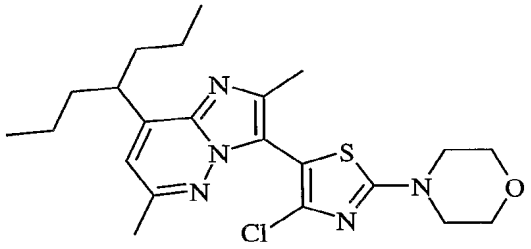
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(tetrahydro-pyran-4-yl)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



Add 3-[2-(3,6-dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (55 mg, 0.14 mmol), 5% palladium on carbon (55 mg) and absolute ethanol (50 ml) to a pressure vessel. Purge the reaction vessel with nitrogen, purge the reaction vessel with hydrogen, pressurize the reaction mixture with hydrogen (415 KPa), seal the vessel, agitate the reaction and heat to 40 °C. Continue the reaction for 18 hours then turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the 5% palladium on carbon. The filtrate is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt : 2 M NH_3 in MeOH = 10:3:1) to give 12.8 mg of the title compound. Yield 23%. mass spectrum (m/e): 399(M+1). ^{1}H NMR ($CDCl_3$): δ 6.73 (s, 1H), 4.14 (m, 2H), 3.60 (m, 2H), 3.34 (m, 2H), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 2.16 (m, 2H), 2.02 (m, 2H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 186.

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



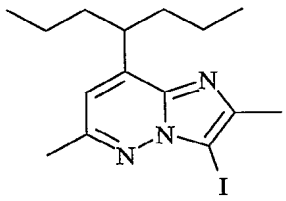
A. 6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine.

6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine can be made using chemistry described in J. Heterocylic Chem. **1991**, *28*, 583. A 250 mL three neck round bottom flask is charged with 3-amino-6-methyl pyridazine (2.5 g, 0.229 moles, 1.0 equiv), water (70 mL), and acetonitrile (50 mL). Concentrated sulfuric acid (3.51 g, 1.91 mL, 0.0344 moles, 1.5 equiv), silver nitrate (3.87 g, 0.0229 moles, 1.0 equiv), and valproic acid (7.21 g, 7.95 mL, 0.050 moles, 2.2 equiv) are added to the reaction mixture. The reaction is heated to 75 °C. As the reaction mixture is heating, a solution of $(NH_4)_2S_2O_8$ (7.85 g, 0.0344 moles, 1.5 equiv) in 40 mL of water is slowly added via an addition funnel over a period of 30 minutes. The reaction mixture is heated at 70-80 °C for two more hours. The reaction mixture is cooled and dichoromethane is added. The reaction is made basic with a 30% aqueous NaOH solution and filtered through a short Celite® plug. The organic layer is separated, and the aqueous layer is extracted two more times with dichoromethane. The combined organic extracts are dried over Na_2SO_4. The solvent is evaporated and the crude material is purified using silica gel chromatography with a 2.0 N solution of NH_3 in MeOH and methylene chloride as eluent. Yield = 0.61 g (13%). MS (APCI): 208 (M+1).

B. 2,6-Dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.

A 250 mL round bottom flask is charged with 6-methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine (0.611 g, 0.00295 moles, 1 equiv), ethanol 2B (30 mL), and chloroacetone (0.382 g, 0.328 ml, 0.00412 moles, 1.4 equiv). The reaction mixture is heated at 75 °C overnight and then cooled to room temp. $NaHCO_3$ (0.371 g, 0.00442 moles, 1.5 equiv) is slowly added to the reaction mixture that is then heated to 100 °C overnight. The reaction mixture is cooled and the solvent is evaporated. Dichloromethane is added and the reaction mixture is passed through filter paper. The solvent is evaporated to obtain a brown oil which is purified via silica gel chromatography. The material is eluted with a hexanes and ethyl acetate gradient to obtain 0.511 g of the final products. Two peaks are identified in the lc/ms. The mixture is used "as is" in the next reaction. MS (APCI): 246 (M+1).

C. 3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



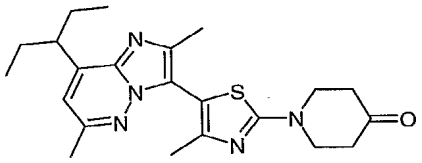
A 50 mL round bottom flask is charged with 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.51 g, 0.0021 moles) and acetonitrile (3 mL). The reaction mixture is placed on an ice bath and NIS (0.468 g, 0.00208 moles) is added neat. The reaction is stirred overnight and the ice bath melts. The next day, the reaction mixture is partitioned between dichloromethane and a saturated aqueous solution of $NaHCO_3$. The organic layer is collected and the aqueous layer is extracted two more times with dichloromethane. The organic extracts are combined, washed with brine, and dried over Na_2SO_4. The solvent is evaporated and the crude material is purified via silica gel chromatography eluting with hexanes and then a 25:75 mixture of ethyl acetate and hexanes. Yield = 0.435 g (56%). MS (APCI): 372 (M+1).

D. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.

A 15 mL round bottom flask is charged with 3-iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.200 g, 0.000539 moles), 4-(4-chloro-thiazol-2-yl)-morpholine (0.165 g, 0.000808 moles), Cs_2CO_3 (0.361 g, 0.00108 moles, 2.0 equiv), $Pd(dba)_2$ (0.0092 g, 0.0000161 moles, 0.03 equiv), PPh_3 (0.00847 gram, 0.000323 moles, 0.060 equiv) and DMF (2.0 mL). Nitrogen is bubbled through the reaction mixture for 15 minutes; then, the reaction mixture is heated at 130 °C overnight. The next day, the reaction mixture is partitioned between Et_2O and a saturated solution of NH_4Cl. The aqueous layer is extracted twice more with Et_2O. The organic extracts are combined, washed 2-3 times with H_2O, washed once with brine, and dried over Na_2SO_4. The solvents are evaporated in vacuo and the crude reaction mixture is purified via silica gel chromatography. Yield = 0.1737 g (72%). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, *J* = 7 Hz, 6H), 1.14- 1.37 (m, 4H), 1.74 (q, *J* = 8 Hz, 4H), 2.54 (s, 3H), 2.50 (s, 3H), 3.48 (m, 1H), 3.53 (t, *J* = 5 Hz, 4H), 3.83 (t, *J* = 5 Hz, 4H), 6.71(br s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{30}ClN_5OS$ $(M+H)^+$: 448; found: 448.

Example 187.

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



A. 8-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane.

100 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 mmol), 182 mg of 4-piperidineethylene ketal (1.27 mmol) and 244 mg of Cs2CO3 (0.75 mmol) are put into 4.0 ml vial with 2.0 ml of THF. The vial is capped with a Teflon® lined cap and heated at 110°C for 3 days. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 116 mg of the title compound. Yield 100%. mass spectrum

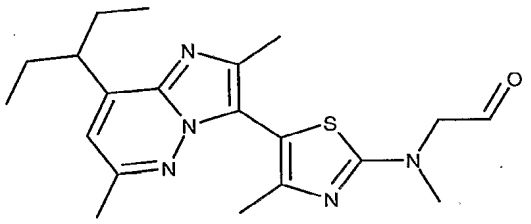
(m/e): 456(M+1). ^{1}H NMR ($CDCl_3$): δ 6.69 (s, 1H), 4.05 (s, 4H), 3.70 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.90-1.78 (m, 8H), 0.90 (t, J = 7.2 Hz, 6H).

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

70 mg of 8-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane (0.15 mmol) is dissolved in 10.ml of conc. HCl and stirred at room temperature for 2 h. The reaction mixture is neutralized with sat. NaHCO3, extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=2:1) to give 33.2 mg of the title compound . Yield 52%. mass spectrum (m/e): 412(M+1). ^{1}H NMR ($CDCl_3$): δ 6.70 (s, 1H), 3.94 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.67 (t, J = 6.5 Hz, 4H), 2.57 (s, 3H), 2.47 (s, 3H), 2.21 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).

Example 188.

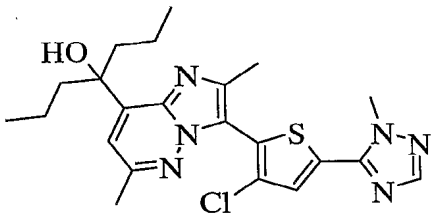
Preparation of ({5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methyl-amino)-acetaldehyde.



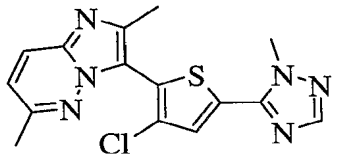
85 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine (0.2 mmol) is dissolved in 2 ml of conc. HCl and stirred at 50°C for 30 min. The mixture is cooled to room temperature and neutralized with sat. NaHCO3. The mixture is extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (CH2Cl2:MeOH=20:1) to give 73.4 mg of the title compound. Yield 76%. mass spectrum (m/e): 386(M+1). 9.79 (s, 1H), 6.72 (s, 1H), 4.39 (s, 2H), 3.36 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).

Example 189.

Preparation of 4-{3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

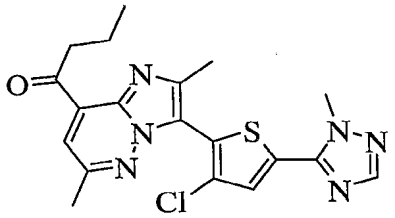


A. 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.32 g, 2.17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}*H*-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_3 (0.057 g, 0.22 mmol) are added and the solution is heated at 135°C for 4 hours. The solution is diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC/MS (m/z): calcd. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

B. 1-{3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one.



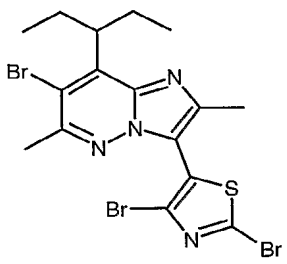
A solution of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.58 mmol), *N*-methoxy-*N*-methyl-butylamide (Wolberg, M. et. al. *Chem. Europ. J.* 2001, 7, 4562.) (0.084 g, 0.64 mmol) in THF (3 mL) is cooled to a -78 °C, and a 2.0 M solution of LDA in heptane/ THF/ ethyl benzene (0.58 mL, 1.16 mmol) is added. The solution is warmed to ambient temperature, diluted with dichloromethane (20 mL), and washed with a sat. NH_4Cl solution (15 mL). The organic layer is dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-100% EtOAc gradient) to furnish the title compound (0.11 g, 0.27 mmol, 46%). ^{1}H-NMR ($CDCl_3$), δ 1.04 (t, J = 7.0 Hz, 3H), 1.76-1.86 (m, 2H), 2.56 (s, 3H), 2.59 (s, 3H), 3.51 (t, J = 7.1 Hz, 2H), 4.15 (s, 3H), 7.36 (s, 1H), 7.49 (s, 1H), 7.90 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{19}H_{19}ClN_6OS$ $(M+H)^+$: 415.1; found: 415.3.

C. 4-{3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

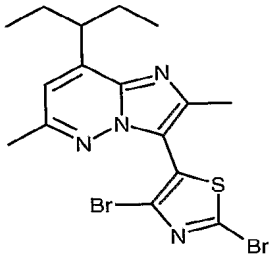
A solution of 1-{3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one (0.15 g, 0.36 mmol) and THF (5 mL) is cooled to 0°C, and a 2.0 M propyl magnesium bromide solution in diethylether (0.22 mL, 0.43 mmol) is added. The reaction is warmed to ambient temperature, diluted with ethyl acetate (30 mL), and washed with a sat. NH_4Cl solution (30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) to furnish the title compound (0.016 g, 0.017 mmol, 47%). ^{1}H-NMR ($CDCl_3$), δ 0.90 (t, J = 7.4 Hz, 6H), 1.12-1.29 (m, 2H), 1.37-1.54 (m, 2H), 1.86-2.04 (m, 4H), 2.50 (s, 3H), 2.54 (s, 3H), 4.15 (s, 3H), 6.11 (bs, 1H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6OS$ $(M+H)^+$: 459.2; found: 459.3.

Example 190, 191, and 192.

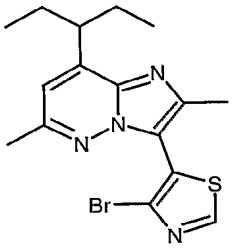
Preparation of 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



190.



191.



192.

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

2.41 g (7 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 3.00 g of thiazole (35.2 mmol), 378 mg of triphenylphosphine (1.44 mmol) and 4.71 g of Cs2CO3 (14.5 mmol) are combined with 25 ml of DMF and N2 gas is bubbled in for 30 min. 330 mg of Pd2dba3 (0.36 mmol) is added and the tube is sealed. The reaction tube is heated at 130°C overnight. To the reaction mixture is added water and CH2Cl2, and the CH2Cl2 layer is separated, washed with sat. NaCl and dried over Na2SO4. The solvents are removed *in vauo* and crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt = 3:1) to give 1.48 g of the title compound. Yield 70%. mass spectrum (m/e): 301(M+1); ^{1}H-NMR(CDCl3): 8.93(s, 1H), 8.52(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.76(s, 3H), 2.66(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.5Hz).

B. 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

1.05 g (3.5 mmol) of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine and 1.56 g of NBS (8.75 mmol) are dissolved in 50 ml of CH2Cl2 and stirred at room temperature for 3 days. The reaction mixture is diluted with CH2Cl2 and washed with sat. $Na_2S_2O_3$ and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 20:1→8:1) to give three products:

149 mg of 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (9%);

936 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (58%); and

77 mg of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (6%).

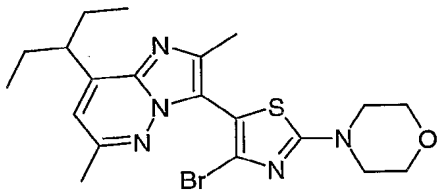
7-Bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 538(M+1); ^{1}H-NMR(CDCl3): 3.45(m, 1H), 2.71(s, 3H), 2.52(s, 3H), 2.38(m, 2H), 2.02(m, 2H), 0.88(t, 6H, J=7.5Hz);

3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 459(M+1); ^{1}H-NMR(CDCl3): 6.79(s, 1H), 5.33(m, 1H), 2.57(s, 3H), 2.55(s, 3H), 1.87(m, 4H), 0.90(t, 6H, J=7.5Hz); and

3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 380(M+1); ^{1}H-NMR(CDCl3): 9.01(s, 1H), 6.77(s, 1H), 3.35(m, 1H), 2.55(s, 3H), 2.54(s, 3H), 1.87(m, 4H), 0.91(t, 6H, J=7.5Hz).

Example 193.

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



100 mg (0.22 mmol) of 3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol), 96 mg of morpholine (1.1 mmol) and 215 mg of Cs2CO3(0.66 mmol) are put in a 4 ml vial with dry THF, and the vial is

capped with a Teflon cap. The vial is heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt :2 M NH3 in MeOH = 9:3:1) to give 72.7 mg of the title compound. Yield 71%. mass spectrum (m/e): 465(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.87(t, 4H, J=5.1Hz), 3.58(t, 4H, J=5.1Hz), 3.35(m, 1H), 2.57(s, 3H), 2.53(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.5Hz).

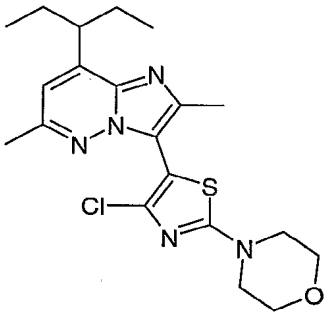
The following compounds are prepared essentially as described in Example 193. Examples 194-197 use 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol) and the named amine. Example 198. uses 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
194	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-methyl-amine	Methyl-amine	6.75 (s, 1H), 5.85 (s, NH), 3.37 (m, 1H), 3.07 (d, J = 5.3 Hz, 3H), 2.59 (s, 3H), 2.55 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	409
195	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	Dimethyl-amine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J=7.3Hz)	423
196	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-2-methoxy-ethyl-methyl-amine	6.71 (s, 1H), 3.76 (m, 2H), 3.71 (m, 2H), 3.42 (s, 3H), 3.35 (s, 1H), 3.21 (s, 3H), 2.57(s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	467

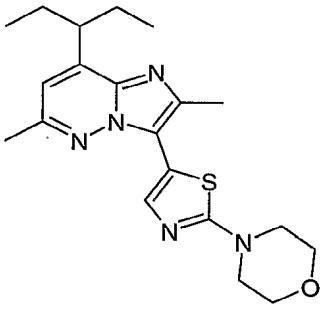
197	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-methyl-i-propyl-amine	6.72 (s, 1H), 4.43 (m, 1H), 3.36 (m, 1H), 3.0 (s, 3H), 2.57 (s, 3H), 2.54 (s, 3H), 1.86 (m, 4H), 1.31 (s, 3H), 1.29 (s, 3H), 0.90 (t, J = 7.4 Hz, 6H).	451
198	N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-bromo-thiazol-2-yl}-morpholine	Morpholine	3.87 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 7.8 Hz, 4H), 3.43 (m, 1H), 2.71(s, 3H), 2.50 (s, 3H), 2.38 (m, 2H), 2.01 (m, 2H), 0.88 (t, J = 7.5 Hz, 6H).	544

Example 199 and 200.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine and N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine.



199.



200.

Method A

40 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 25 mg of CuCl (0.25 mmol) are put in a 4 ml vial with 2 ml of dry DMF and capped with a Teflon cap. The vial is heated at 120°C overnight. The reaction mixture is filtered, washed with CH2Cl2 and the filtrate is concentrated. The crude product mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 2:1 and Hexane : AcOEt = 8:1) to give two products:

4.2 mg of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (12%), and

7.2 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (22%).

N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine mass spectrum (m/e): 420(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.88(t, 4H, J=5.0 Hz), 3.57(t, 4H, J=5.0Hz), 3.35(m, 1H), 2.57(s, 3H), 2.52(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.5Hz.

N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.75(s, 1H), 6.70(s, 1H), 3.91(t, 4H, J=5.0Hz), 3.61(t, 4H, J=5.0Hz), 3.34(m, 1H), 2.67(s, 3H), 2.61(s, 3H), 1.85(m, 4H), 0.88(t, 6H, J=7.5Hz).

Method B N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine.

A 20L reactor flask under nitrogen is charged with 2900 ml of dry and degassed DMF then with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[1,2-b]pyridazine (287 g, 0.836 mol), 2-morpholino-4-chlorothiazole (205.4 g, 1.01 mol, 1.2 equv.), $Pd(OAc)_2$ (3.74 g, 7.91 mmol, 0.01 equiv.), triphenylphosphine (8.77g, 33.1 mmol, 0.04 equiv.), Copper iodide (8 g, 41.59 mmol, 0.05 equiv.) and cesium carbonate (544.9 g, 1.65 mol). The reaction mixture is heated at 120°C. After 16 h at 120°C, 1.87 g of $Pd(OAc)_2$ and 4.38 g of triphenylphosphine more is added. After 1 h, the mixture is cooled, quenched with NH_4Cl solution (4300 mL) and extracted with MTBE (2900 mL), the aqueous phase is extracted twice more with 2000 ml of MTBE. The organic phases are washed with sat NaCl aq (2000 mL), then treated with charcoal 72 g in flask bottle and filtered on Celite®. The filtrate is concentrated under vacuum to afford 373.8 g (79.3%) of the title compound which is 81.4%-area HPLC analysis the rest being solvent and with no detectable Example 200 by-product.

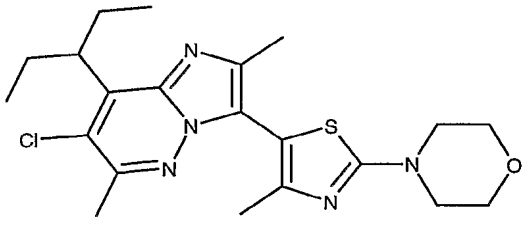
The following title compounds are prepared essentially as described in Examples 199 and 200 Method A:

Example #	Name	Starting material	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
201	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.51 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).	378
202	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	7.74 (s, 1H), 6.67 (s, 1H), 3.35 (m, 1H), 2.23 (s, 6H), 2.67(s, 3H), 2.61 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	344
203	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	6.71 (s, 1H), 3.76 (t, J = 5.3 Hz, 2H), 3.71 (t, J = 5.1 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 3.20 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	423
204	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	7.72 (s, 1H), 6.68 (s, 1H), 3.80 (t, J = 5.7 Hz, 2H), 3.72 (t, J = 5.7 Hz, 2H), 3.42 (s, 3H), 3.35 (m, 1H), 3.26 (s, 3H), 2.67 (s, 3H), 2.61 (s, 3H), 1.84	388

	methylamine	methylamine	(m, 4H), 0.88 (t, J = 7.7 Hz, 6H).	
205	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	6.71 (s, 1H), 4.48 (m, J = 7.4, 13.2 Hz, 1H), 3.34 (m, J = 7.6, 14.4 Hz, 1H), 3.04 (s, 3H), 2.76 (s, 3H), 2.61 (s, 3H), 1.85 (m, 4H), 1.31 (d, J = 7.1 Hz, 6H), 0.88 (t, J = 7.3 Hz, 6H).	407
206	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-isopropyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	7.72 (s, 1H), 6.67 (s, 1H), 4.48 (m, 1H), 3.33 (m, 1H), 3.03 (s, 3H), 2.66 (s, 3H), 2.60 (s, 3H), 1.84 (m, 4H), 1.31 (d, J = 6.8, 6H), 0.88 (t, J = 7.2 Hz, 6H).	371

Example 207.

Preparation of N-{5-[7-chloro-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.

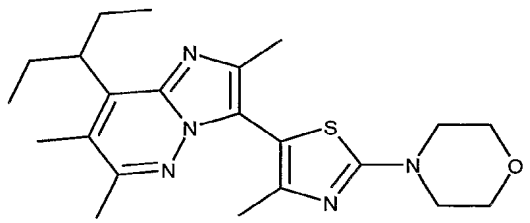


50 mg of N-{5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine (0.1 mmol) is dissolved in 2.0 ml of

dry DMF and 31 mg of CuCl (0.3 mmol) is added. The vial is capped with a Teflon® lined cap and heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 39.2 mg of the title compound. Yield 87%. mass spectrum (m/e): 435(M+1). 3.88 (t, J = 4.8 Hz, 4H), 3.57 (t, J = 5.1 Hz, 4H), 2.64(s, 3H), 2.44 (s, 3H), 2.18 (s, 3H), 2.00 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 208.

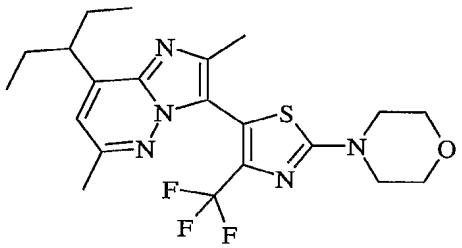
Preparation of N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6,7-trimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.



50 mg of N-{5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine (0.1 mmol) is dissolved in 4 ml of Et2O and cooled to –78°C. 0.09 ml of n-BuLi 1.6M in hexane (0.15 mmol) is added at –78°C and stirred at –78°C for 20 min. 43 mg of iodomethane (0.3 mmol) is added to the mixture and stirred at –78°C and allowed to come to room temperature overnight. The reaction is quenched with sat. NH4Cl and extracted with Et2O. The separated organic layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=3:1) to give 29.6 mg of the title compound. Yield 69%. mass spectrum (m/e): 414(M+1). ^{1}H NMR ($CDCl_3$): δ 3.87 (t, J = 4.6 Hz, 4H), 3.56 (t, J = 4.6 Hz, 4H), 3.35 (m, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.01 (m, 4H), 0.88 (m, 6H).

Example 209.

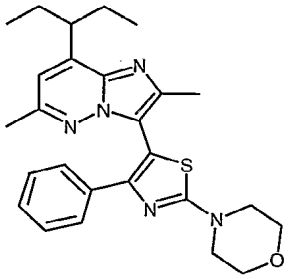
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-trifluoromethyl-thiazol-2-yl}-morpholine.



170 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.37 mmol) and 100 mg of sodium trifluoroacetate (0.74 mmol) are dissolved in 3 ml of DMF/toluene = 2/1. N2 gas is bubbled into the mixture for 20 min and 141 mg of CuI (0.74 mmol) is added. The vial is sealed and heated in the microwave at 210°C for 30 min. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and CH3CN : CH2Cl2 : Hexane = 5 : 45 : 50) to give 64.3 mg of the title compound. Yield 38%. mass spectrum (m/e): 454(M+1). ^{1}H NMR ($CDCl_3$): δ 6.72 (s, 1H), 3.88 (m, 4H), 3.60 (m, 4H), 3.32 (m, 1H), 2.54 (s, 3H), 2.47 (s, 3H), 1.85 (m, 4H), 0.89 (t, J = 7.0 Hz, 6H).

Example 210.

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

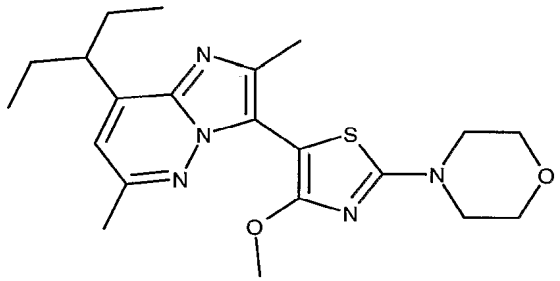


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 40 mg of phenylboronic acid (0.33 mmol) and 0.27 ml of 2 M Na2CO3aq.(0.55 mmol) are put in 2.5 ml of DME / water / EtOH = 7 / 3 / 1. N2 gas is bubbled in the mixture for 20 min and 20 mg of Pd(PPh3)4

(0.017 mmol) is added. The vial is sealed and heated at 160°C for 30 min in Microwave. The reaction mixture are added CH2Cl2 and water and the organic layer is separated, washed with brine, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt = 10:1) to give 27 mg of the title compound. Yield 54% mass spectrum (m/e): 462(M+1). δ 8.29(m, 1H), 7.60(m, 2H), 7.44(m, 1H), 7.22(m, 1H), 6.70 (s, 1H), 3.90 (t, J = 4.6 Hz, 4H), 3.64 (t, J = 5.0 Hz, 4H), 3.36 (m, 1H), 2.52 (s, 3H), 2.09 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 211.

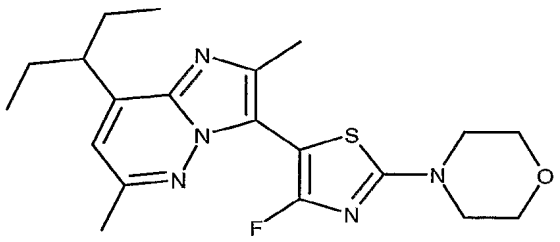
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-morpholine.



100 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol), 24 mg of sodium methoxide (0.44 mmol) and 21 mg of CuI (0.11 mmol) are put into 4 ml vial with MeOH 3 ml and capped with a Teflon® lined cap. The reaction vial is heated at 130°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane : THF = 10 : 1) to give 32.8 mg of the title compound. Yield 36%. Mass spectrum (m/e): 416(M+1). ^{1}H NMR ($CDCl_3$): δ 6.64 (s, 1H), 3.96 (s, 3H), 3.86 (t, J = 4.7 Hz, 4H), 3.53 (m, 4H), 3.34 (m, 1H), 2.82 (s, 3H), 2.48 (s, 3H), 1.82 (m, 4H), 0.85 (t, J = 7.4 Hz, 6H).

Example 212.

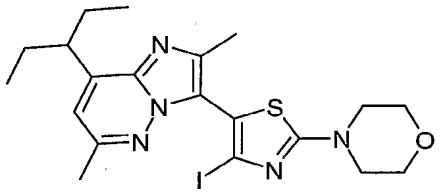
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-fluoro-thiazol-2-yl}-morpholine.



50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol) is dissolved in 4 ml of diethylether and cooled to –78°C and 0.1 ml of n-BuLi 1.6M in hexane (0.16 mmol) is added at –78°C and stirred at –78°C for 20 min. 104 mg of N-fluorobenzene sulfonimide (0.33 mmol) in 2 ml of toluene is added at –78°C and stirred at room temperature for 1h. sat. NH4Cl is added, and the mixture is extracted with Et2O, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 4.1 mg of the title compound. Yield 10%. Mass spectrum (m/e): 404 (M+1). 6.71 (s, 1H), 3.87 (t, J = 4.6 Hz, 4H), 3.55 (t, J = 5.0 Hz, 4H), 3.34 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 1.84 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 213.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-morpholine.

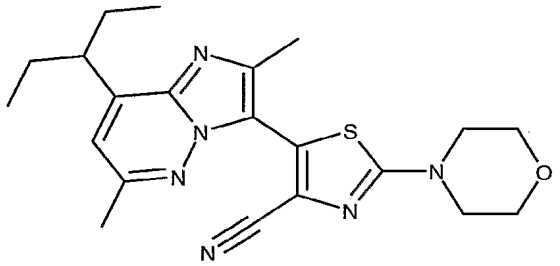


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 30 mg of CF_3CO_2Na (0.22 mmol) and 42 mg of CuI (0.22 mmol) are put into 4 ml vial with DMF / toluene = 2:1. The vial is capped with a Teflon cap and heated at 150°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt = 5 : 1) to give 54 mg of the

title compound. 96%. Mass spectrum (m/e): 512 (M+1). ^{1}H NMR ($CDCl_3$): δ 6.71 (s, 1H), 3.87 (t, J = 5.4 Hz, 4H), 3.58 (t, J = 5.4 Hz, 4H), 3.36 (m, 1H), 2.57 (s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 5.4 Hz, 6H).

Example 214.

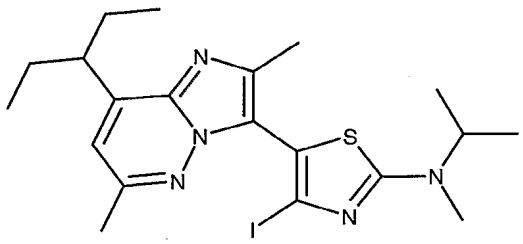
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-2-morpholin-4-yl-thiazole-4-carbonitrile



50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), and 30 mg of CuCN (0.33 mmol) are put into 4 ml vial with 2 ml of DMF and the vial is capped with a Teflon cap. The vial is heated at 150°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=5:1) to give 12.3 mg of the title compound. Yield 28%. Mass spectrum (m/e): 411(M+1). 6.77 (s, 1H), 3.89 (t, J = 4.8 Hz, 4H), 3.61 (t, J = 5.0 Hz, 4H), 3.32 (m, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 215.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-N-isopropyl-methylamine.

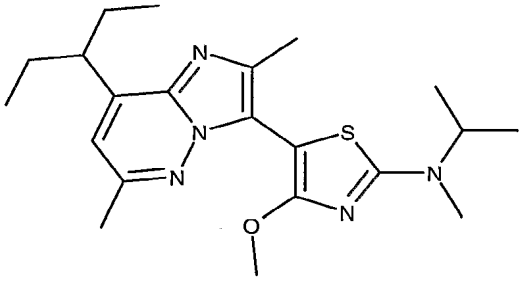


The title compound is prepared essentially as described in Example 213, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-

bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 17.9 mg. Yield 22%: mass spectrum (m/e):498 (M+1). ^{1}H NMR ($CDCl_3$): δ 6.71 (s, 1H), 4.41 (m, 1H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.53 (s, 3H), 1.84 (m, 4H), 1.29 (d, J = 5.8 Hz, 6H), 0.90 (t, J = 7.2 Hz, 6H).

Example 216.

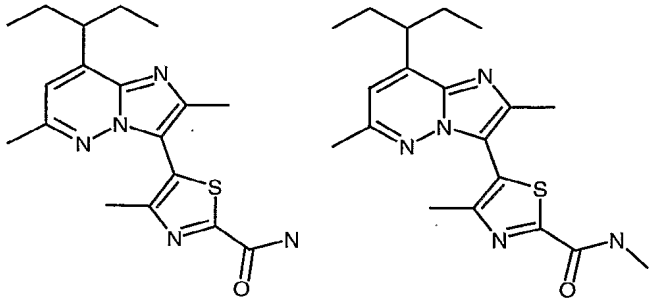
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-N-isopropyl-methylamine.



The title compound is prepared essentially as described in Example 211, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 52.7. Yield 36%: mass spectrum (m/e):402(M+1). ^{1}H NMR ($CDCl_3$): δ 6.63 (s, 1H), 4.44 (m, 1H), 3.96 (s, 3H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H), 1.83 (m, 4H), 1.29 (d, J = 6.7 Hz, 6H), 0.88 (t, J = 8 Hz, 6H).

Example 217 and 218.

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



217. 218.

180 mg of 8-(1-Ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.46 mmol) and 124 mg of copper(I) cyanide are put into 4 ml vial with 2 ml of dry DMF. The vial is closed with a Teflon can and heated at 130°C overnight. The crude reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 1:1 →1:3) to give

52.1 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (32%) and

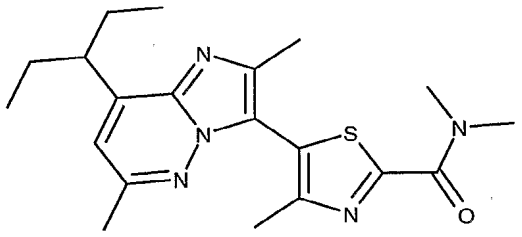
7.6 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid methylamide.

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide: mass spectrum (m/e): 358(M+1) ^{1}H NMR ($CDCl_3$): δ 7.21 (s, NH), 6.76 (s, 1H), 5.59 (s, NH), 3.34 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.42 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H). and

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid methylamide: mass spectrum (m/e): 372(M+1). ^{1}H NMR ($CDCl_3$): 8.77 (s, NH), 6.75 (s, 1H), 4.06 (s, 3H), 3.35 (m, 1H), 2.55 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 219.

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

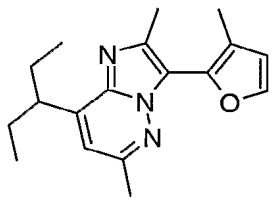


5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (46 mg, 0.13 mmol) and 28 mg of sodium *tert*-Butoxide (0.30 mmol) are put into 4 ml of dry DMSO and stirred at room temperature for 5 min. 141 mg of iodomethane (1.0 mmol) is added and stirred at room temperature for 1 h.

Water is added, and the mixture is extracted with CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=3:1) to give 22.3 mg of the title compound. Yield 45%: mass spectrum (m/e):386(M+1). 6.75 (s, 1H), 3.70 (s, 3H), 3.35 (m, 1H), 3.21 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.41 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).

Example 220.

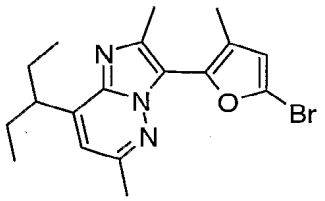
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 3-methylfuran (Acros, 232 mg, 2.83 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol). After addition of the nBuLi, the solution is warmed to 0 °C for 15 minutes, then to room temperature for an additional 5 minutes. The reaction mixture is then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 5.8 mL, 2.9 mmol). The resulting mixture is warmed to room temperature and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (400 mg, 1.17 mmol) and $PdCl_2(dppf) - CH_2Cl_2$ complex (Aldrich, 95 mg, 0.12 mmol). The mixture is heated to 60 °C for 4 hours, then poured into 1 N HCl (60 mL) and extracted with ethyl acetate (2x60 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound as an oil pyridazine (149 mg, 43% yield). ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.5 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 7.59 (d, J = 1.8 Hz, 1H), 6.71 (s, 1H), 6.47 (d, J = 1.8 Hz, 1H), 3.36 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.10 (s, 3H), 1.92-1.79 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).

Example 221.

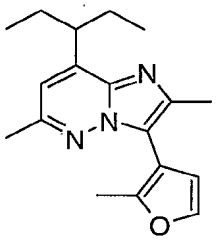
Preparation of 3-(5-bromo-3-methyl-furan-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (4 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine (32.4 mg, 0.11 mmol) is cooled to 0 °C under a $CaSO_4$ drying tube and treated with NBS (20.1 mg, 0.11 mmol). After 15 minutes at 0 °C, the mixture is warmed to room temperature. After an additional 10 minutes, the reaction mixture is poured into H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (26.3 mg, 64% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 6.72 (s, 1H), 6.40 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.49 (s, 3H), 2.07 (s, 3H), 1.93-1.77 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H).

Example 222.

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



A. 3-Bromo-2-methyl furan.

A THF solution (10 mL) of 2,3-dibromofuran (Lancaster, 5.54 gm, 24.5 mmol) under N_2 is treated with $PdCl_2(PPh_3)_2$ (860 mg, 1.2 mmol) and stirred for 10 minutes at

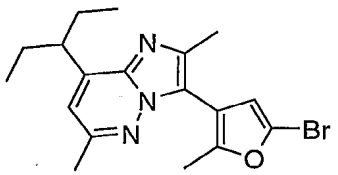
room temperature. The solution is then treated with CH_3ZnCl (Aldrich, 2.0 M in THF, 15 mL, 30 mmol). The resulting mixture is stirred at room temperature overnight then poured into 1 N HCl and extracted into diethyl ether. The organic extract is washed with sat. NaCl, dried over Na_2SO_4, and filtered. The filtrate is then distilled and the product is collected at 120-125 °C to give the title compound as a colorless oil (1.71 gm, 43% yield). ^1H NMR (400 mHz, $CDCl_3$): δ 7.25 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 2.28 (s, 3H).

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

A THF solution (10 mL) of 3-bromo-2-methyl furan (prepared as described above) (1.06 gm, 6.58 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 4.1 mL, 6.6 mmol). After 10 minutes at -78 °C, the mixture is treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 13.2 mL, 6.6 mmol). The resulting mixture is warmed to room temperature then treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.13 gm, 3.29 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 257 mg, 0.31 mmol). The mixture is heated to 60 °C for 4 hours, then poured into sat. NH_4Cl (50 mL) and extracted with diethyl ether (2x50 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (685 mg, 70% yield) as an oil. ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 7.45 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.60 (d, J = 2.0 Hz, 1H), 3.35-3.31 (m, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H), 1.88-1.75 (m, 4H), 0.86 (t, J = 7.5 Hz, 6H).

Example 223.

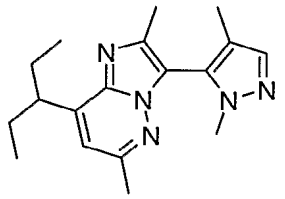
Preparation of 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (2 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine (42.3 mg, 0.14 mmol) under a $CaSO_4$ drying tube is treated with N-bromosuccinimide (27.6 mg, 0.16 mg). After 30 minutes the reaction mixture is poured into H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the title product (36.9 mg, 70% yield) as a white solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.3 (M+H); ^{1}H NMR (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.50 (s, 1H), 3.33 (m, 1H), 2.53 (s, 3H), 2.44 (s, 3H), 2.29 (s, 3H), 1.90-1.73 (m, 4H), 0.86 (t, J = 7.3 Hz, 6H).

Example 224.

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

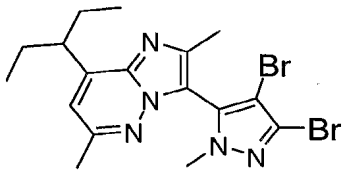


n-BuLi (1.3 ml, 2.09 mmol) is stirred in THF (4 ml), under N_2, and cooled to –72^{0}C. 1,4-dimethyl-*1H*-pyrazole (170 mg, 2.04 mmol, in THF, 1 ml) is added slowly, stirred for 5 min. then allowed to warm to ambient temp. and stirred for 45 min. The mixture is cooled to –72°C and a zinc chloride solution (4.3 ml, 2.14 mmol, 0.5 M in toluene) added, warmed to ambient temp. and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 40 mg, 0.05 mmol). The mixture is heated to 65^{0}C overnight, cooled to ambient temp., added to water and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50 % ethyl acetate in hexane) to elute the product. The title compound is obtained (0.7% yield). ES-MS (m/z): calc'd for $C_{18}H_{25}N_5$: 311.4; found 312.2 $(M+H)^+$. ^{1}H NMR (400 mHz, $CDCl_3$):

δ 7.51 (s, 1H), 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.53 (s, 3H), 2.43 (s, 3H), 2.00 (s, 3H), 1.87 (m, 4H), 0.92 (m, 6H)..

Example 225.

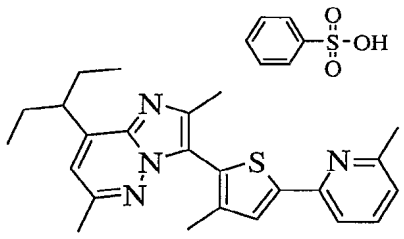
Preparation of 3-(4,5-dibromo-2-methyl-*2H*-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (300 mg, 1.4 mmol), 3,4,5-tribromo-1-methyl-^{1}H-pyrazole (700 mg, 2.1 mmol) and cesium carbonate (900 mg, 2.8 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (14 mg) is added and the mixture heated to 130°C overnight. The mixture is added to water and extracted twice with EtOAc. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (204 mg, 32% yield). ES-MS (m/z): calc'd for $C_{17}H_{21}Br_2N_5$: 455.2; found 455.9 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.51 (s, 3H), 2.45 (s, 3H), 1.84 (m, 4H), 0.88 (t, 6H).

Example 226.

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

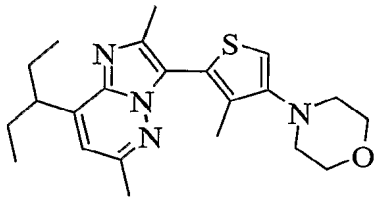


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.23 g, 0.57 mmol) and MeOH (1

mL) is added a solution of benzenesulfonic acid (0.096 g, 0.57 mmol) and MeOH (1 mL). The solution is concentrated to furnish the title compound (0.32 g, 0.57 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.0 Hz, 6H), 1.59-1.82 (m, 4H), 2.06 (s, 3H), 2.61 (s, 6H), 2.88 (s, 3H), 3.22-3.32 (m, 1H), 6.79 (bs, 2H), 7.25 (s, 1H), 7.33-7.42 (m, 3H), 7.49 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.4 Hz, 2H), 7.92 (dd, J = 7.4, 1.6 Hz, 1H) 8.23 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.4.

Example 227.

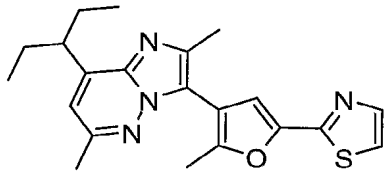
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-morpholin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30g, 0.76 mmol), morpholine (0.10 mL, 1.15 mmol), $Pd_2(dba)_3$ (0.035 g, 0.038 mmol), and 2-dicyclohexylphosphino-biphenyl-2'-(N,N-dimethyl-amino)biphenyl (0.018 g, 0.046 mmol) is added 1 M LiHMDS (1.9 mL, 1.91 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-30% EtOAc gradient), dissolved in Et_2O (20 mL) and extracted with 1 M HCl (2 x 30 mL). The aqueous layer is washed with Et_2O (20 mL), made basic with 5 M NaOH (15 mL), extracted with EtOAc (2 x 20 mL), the combined organic layers washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.047 g, 0.12 mmol, 16%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.01 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 2.99-3.05 (m, 4H), 3.28-3.37 (m, 1H), 3.84-3.88 (m, 4H), 6.65 (s, 1H), 6.71 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{30}N_4OS$ $(M+H)^+$: 399.2; found: 399.2.

Example 228.

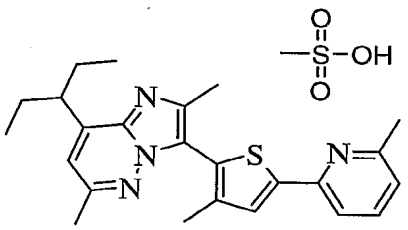
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 2-bromothiazole (Aldrich, freshly distilled, 75.0 μL, 0.84 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 0.52 mL, 0.83 mmol). After 15 minutes at -78 °C, the mixture is treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 1.8 mL, 0.90 mmol). The resulting mixture is warmed to room temperature then treated with a THF slurry (1 mL) containing 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (60.1 mg, 0.16 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 22 mg, 0.027 mmol). The mixture is heated overnight at 60 °C, then poured into sat'd NH_4Cl and extracted with diethyl ether. The organic extract is washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (45.8 mg, 75% yield) as an oil. ES-MS (m/z): calc'd for $C_{21}H_{24}N_4OS$: 380.17; found 381.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.83 (d, J = 3.5 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 7.20 (s, 1H), 6.68 (br s, 1H), 3.35 (br s, 1H), 2.53 (s, 3H), 2.49 (s, 3H), 2.40 (s, 3H), 1.90-1.76 (m, 4H), 0.88 (t, J = 7.5 Hz, 6H).

Example 229.

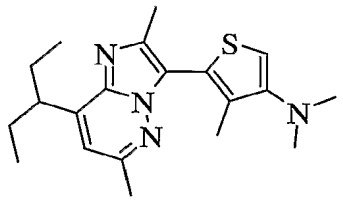
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine; compound with methanesulfonic acid.



To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36 mmol) and MeOH (6 mL) is added methane sulfonic acid (0.088 mL, 1.36 mmol). After one hour the solution is concentrated and the solution is treated with Darco-60® for 1 hour, filtered and concentrated to furnish the title compound (0.68 g, 1.36 mmol, >99%). ^{1}H NMR ($CDCl_3$: CD_3OD 95:5) δ 0.85 (t, J = 7.4 Hz, 6H), 1.67-1.91 (m, 4H), 1.96 (s, 3H), 1.97 (s, 3H), 2.20 (s, 3H), 2.61 (s, 3H), 2.90 (s, 3H), 3.17-3.29 (m, 1H), 7.33 (s, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 8.34 (t, J = 7.9 Hz, 1H), 9.95 (bs, 1H). LC/MS (m/z): calcd. for $C_{25}H_{32}N_4O_2S_2$ $(M+H)^+$: 405.6; found: 405.6.

Example 230.

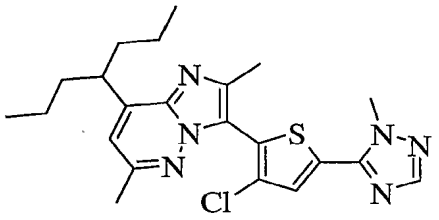
Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-3-yl}-dimethyl-amine.



To a –78 °C solution of dimethyl-(4-methyl-thiophen-3-yl)-amine (0.43 g, 3.06 mmol) and THF (5 mL) is added 1.6 M *n*-BuLi (1.91 mL, 3.06 mmol). The solution is stirred for 1 hour, then 0.5 M $ZnCl_2$ (6.1 mL, 3.06 mmol) is added and the solution warmed to ambient temperature. After 30 minutes 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.70 g, 2.04 mmol) and $PdCl_2$(dppf) (0.075 g, 0.10 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -30% EtOAc gradient) furnish the title compound (0.13 g, 0.36 mmol, 18%). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.03 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 2.77 (s, 6H), 3.28-3.37 (m, 1H), 6.63 (s, 1H), 6.65 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{28}N_4S$ $(M+H)^+$: 357.2; found: 357.2

Example 231.

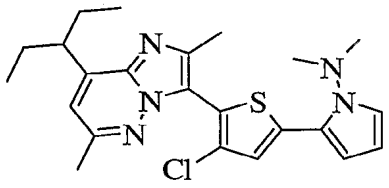
Preparation of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



A slurry of 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine (below) (0.30 g, 1.22 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-[1,2,4]triazole (below) (0.41 g, 1.47 mmol), KOAc (0.60 g, 6.11 mmol), TBABr (0.39 g, 1.22 mmol), and NMP (3 mL) is de-gassed with N_2 for 30 minutes. $Pd(OAc)_2$ (0.014 g, 0.061 mmol) and TDBPP (0.040 g, 0.061 mmol) are added and the solution heated at 125 °C for 2.5 hours. The solution is diluted with EtOAc (50 mL), washed with water (3 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) furnish the title compound (0.30 g, 0.68 mmol, 56%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.14-1.39 (m, 4H), 1.76 (q, J = 16.3, 7.7 Hz, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.41-3.50 (m, 1H), 4.15 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6S$ $(M+H)^+$: 443.2; found: 443.3.

Example 232.

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

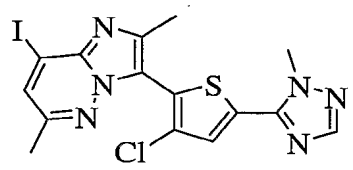


Using a procedure analogous to Example 27, 1-(dimethylamino)-pyrrole (0.20 mL, 1.65 mmol), THF (4 mL), 1.6 M *n*-BuLi (1.10 mL, 1.73 mmol), 0.5 M $ZnCl_2$ (3.46 mL, 1.73 mmol), 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.34 g, 0.82 mmol) and $PdCl_2$(dppf) (0.030 g, 0.041 mmol),

furnish the title compound (0.17 g, 0.38 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 6H), 2.84 (s, 6H), 3.28-3.39 (m, 1H), 6.21 (dd, J = 4.1, 3.2 Hz, 1H), 6.38 (dd, J = 4.1, 1.8 Hz, 1H), 6.68 (s, 1H), 7.02 (dd, J = 3.2, 1.8 Hz, 1H), 7.29 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}ClN_5S$ $(M+H)^+$: 442.2; found: 442.3.

Example 233.

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



A. 4-Chloro-thiophene-2-carbonitrile.

A 22-L reaction flask is equipped with a cooling bath, air stirrer, gas addition tube, and thermometer probe. The flask is purged with nitrogen, then charged $AlCl_3$ (1025 g, 7.69 moles) and $CHCl_3$(6.6 L, 16.5 vol.). After cooling the mixture to 0-5 °C, it is charged with 2-thiophene carbonitrile (400 g, 3.66 moles) dropwise via an addition funnel over 10-15 minutes while maintaining the temperature at ≤ 10 °C. The mixture is charged with Cl_2 gas (300g, 4.23 moles, 1.16 EQ) subsurface at ≤ 10 °C over 1.25 hours. The progress of the reaction is monitored by GC, wherein the GC sampling method is quenching an aliquot of the reaction mixture into 6N HCl, extracting with EtOAc, drying over Na_2SO_4, filtering, and injecting the filtrate.

When the reaction is deemed complete by GC analysis [the reaction was deemed complete when the ratio of (sm : prod : dichloro) was approximately (1 : 5.8 : 1) by area % GC.], 6N HCl (8.0 L) is added dropwise via addition funnel over 1.5 hours, while maintaining the temperature at ≤ 20 °C [The HCl addition is extremely exothermic and evolves gas]. The reaction is transferred to a separatory funnel and the layers are separated. After extracting the aqueous layer with $CHCl_3$ (4.0 L), the chloroform layers are combined and washed with de-ionized H_2O (6.0L). The organic layer is dried over Na_2SO_4, filtered and concentrated under vacuum to give a pale yellow semi solid 575g, 109.3%). GC (60°C to 280°C temperature gradient) Area-% analysis shows ~68%

product (t_{ret} = 6.5 min) with major impurities being the unreacted starting material (t_{ret} = 5.1 min) and the dichlorinated product (t_{ret} = 7.4 min). GC Method: Column: DB1; $T_{injecyt}$ = 300 °C ; $T_{initial}$ = 60 °C, t = 2.0 min; T_{final} = 280 °C, rate = 18 °C/min.

B. 4-Chloro-2-thiophene carboxamide.

A 12-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with KOH (288.6 g, 5.143 moles) and De-ionized H_2O (6.04 L) to form a solution that exotherms to ~31 °C. After allowing the solution to cool to ~28.0 °C, th mixture is charged with 4-chloro-2-thiophene carbonitrile (671.3 g, 4.675 moles)[1] followed by EtOH (675 mL). A gradual exotherm occurs upon the addition of EtOH and continues over 1-1.5 hours to ~38 °C. The reaction is stirred at ambient temperature overnight.

The reaction mixture is filtered under vacuum, washed with de-ionized H_2O and dried to give crude product. The solids are dissolved in EtOAc (10.0 L) treated with Na_2SO_4 and Darco for 1-2 hours; then, filtered and washed with EtOAc. The filtrate is concentrated on the Büchi until solids began to precipitate out at 45 °C at which time the vacuum is released, and the temperature is increased to 60-65 °C to redissolve the solids. With stirring at 60 °C, heptane (3.5 L) is added slowly to precipitate solids. After stirring for 15-20 minutes at 60 °C, the mixture is cooled to 30-40 °C and filtered. The solids are washed with heptane (2 x 0.75 L), and dried to give the title compound (t_{ret} = 9.9 min) as a white solid (235.4 g, 31.2 % 96.4 area % by GC analysis). A second crop is obtained from the filtrate to give 67.8 g, 9.0 %; 94.5% area-% by GC analysis). The Overall yield is 303.2 g, 40.1 %.

C. 4-Chloro-N-dimethylaminomethylene-2-thiophene carboxamide.

A 5-L reaction flask equipped with a heating mantle, air stirrer, Dean-Stark apparatus, and thermometer probe is charged with 4-chloro-2-thiophene carboxamide. (300 g, 1.856 moles) and dimethylformamide dimethylacetal (872 mL) to form a slurry that endotherms 1-2 °C from 22-20 °C. The mixture is heated gradually to 96 °C while collecting the distillate (mostly MeOH). The heating mantle is removed, and the mixture is cooled to $\leq$ 25 °C. De-ionized H_2O (3.0 L) is added via an addition funnel and the

[1] A small amount of solids were undissolved at this point.

temperature is maintained at $\leq$35 °C. The reaction mixture is extracted with EtOAc (1 x 3.0 L, 1 x 1.5 L), then combined the organics are washed with de-ionized H_2O (1.5 L). The organic phase is dried over Na_2SO_4, filtered, and concentrated under vacuum to give crude product (400 g).

The crude product is dissolved in EtOAc (320 mL, 0.8 Vol) at 50-60 °C; then, heptane (1700 mL, 4.25 Vol) is added slowly while gradually increasing the temperature to 70 °C. A seed crystal (Lot: PP6-H00086-075-1) is added to the cloudy solution to initiate precipitation. The resulting mixture is stirred to room temperature overnight, then filtered and washed with heptane. The solids are dried to give the title compound (t_{ret} = 13.0 min) as a white solid (329.8 g, 82%; 98.2 % area-% by GC analysis).

D. 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide. (155 g, 0.715 moles) and HOAc (1500 mL) to form a solution. Using an ice-water cooling bath to maintain the temperature at $\leq$ 30 °C, methylhydrazine (33.2 g, 0.721 moles) is added dropwise via an addition funnel over 15-20 minutes to form a light yellow slurry. Gradually, the reaction is heated to 90 °C and held at 90 °C for 30 minutes. After analysis of the mixture by GC, the reaction is cooled to ~70 °C; then, concentrated to a thick oil/slurry. De-ionized H_2O (1.67 L) is slowly added to precipitate solids; then, the mixture is cooled to < 30 °C, filtered and washed with de-ionized H_2O (1.67 L). The wet solids (125.8 g) are re-dissolved in warm MTBE (1.64 L), dried over Na_2SO_4, filtered and concentrated to dryness giving the title compound as a pale yellow solid (85.8 g, 60.1% 91.9 % area % by GC).

E. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole (105.3 g, 0.527 moles), ACN (1053 mL) and HOAc (105 mL) to form a solution. NBS

(103.2 g, 0.580 moles) is added portion-wise over 30-60 minutes while maintaining the temperature at ≤ 31 °C. After stirring for 1 hour[2], GC analysis indicated reaction completion. The reaction mixture is poured into de-ionized H_2O (2.1 L, 20vol), stirred for 30 minutes, filtered, and washed with de-ionized H_2O (2 x 1 L). The product is dried in a vacuum oven at 45 °C overnight to give the title compound as a pale yellow solid (123.0 g, 83.8 %; 96.6 % area-% by GC).

F. 2,6-Dimethyl-imidazo[1,2-*b*]pyridazine.

A 3 neck 1L round bottom flask is charged with 6-methyl-pyridazin-3-ylamine (20 g, 0.18 moles), ethanol 2B (200 mL), and chloroacetone (23.7 g, 20.4 mL, 0.256 moles, 1.4 equiv). The reaction mixture is heated at 70 °C overnight. NaHCO3 (23.2 g, 0.276 moles, 1.5 equiv) is added portion wise. After most of bubbling subsides, the reaction is heated at 100 °C overnight. The solvents are removed in vacuo and the residue is taken up in dichloromethane and filtered through a filter paper. The solvent is again removed in vacuo. The residue is purified using silica gel chromatography with a hexanes:ethyl acetate gradient to obtain the title compound (15.5 g, 57%). ^{1}H-NMR (DMSO-d6), δ 2.34 (s, 3H), 2.47 (s, 3H), 7.03, (d, J = 10 Hz, 1H), 7.85 (d, J = 10 Hz, 1H), 7.91 (s, 1H) ppm. MS (APCI): 148 (M+1).

G. 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g, 2..17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}*H*-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_3 (0.057 g, 0.22 mmol) are added and the solution is heated at 135°C for 4 hours. The solution is diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC/MS (m/z): calcd. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

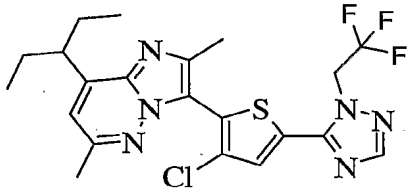
[2] The reaction temperature decreased after 1 hour to 26.7 °C

H. 3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a –78 °C solution of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.50 g, 4.35 mmol) and THF (50 mL) is added I_2 (1.21 g, 4.78 mmol). After 10 minutes 2 M LDA (5.44 mL, 10.87 mmol) is added. The solution is stirred for 30 minutes, quenched with water, diluted with EtOAc (100 mL), washed with water (100 mL), sat. $Na_2S_2O_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (100% EtOAc) furnish the title compound (0.61 g, 1.30 mmol, 30%). ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.55 (s, 3H), 4.14 (s, 3H), 7.47 (s, 1H), 7.51 (s, 1H), 7.89 (s, 1H),. LC/MS (m/z): calcd. for $C_{15}H_{12}ClIN_6S$ $(M+H)^+$: 471.0; found: 471.0.

Example 234.

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



A. 5-(4-Chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-^{1}*H*-[1,2,4]triazole.

To a solution of 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (1.00 g, 4.62 mmol) and AcOH (1. mL) is added 70 % aqueous 2,2,2-trifluoroethyl-hydrazine (0.79 mL, 4.85 mmol). The solution is heated at 90 °C for 45 minutes, concentrated, dissolved in Et_2O (40 mL), washed with water (30 mL), sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.24 g, 4.62 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 4.88 (q, J = 16.8, 7.8 Hz, 2H), 7.28 (d, J = 0.9 Hz, 1H), 7.31-7.33 (m, 1H), 7.94 (s, 1H). LC/MS (m/z): calcd. for $C_8H_5ClF_3N_3S$ $(M+H)^+$: 268.0; found: 268.0.

B. 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-^{1}*H*-[1,2,4]triazole.

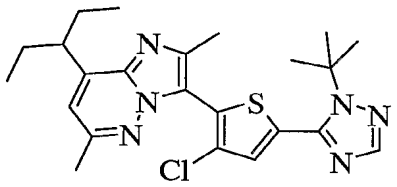
To a solution of 5-(4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (1.13 g, 4.22 mmol) and AcOH (10 mL) in a sealed tube, is added Br_2 (0.23 mL, 4.43 mmol). The solution is heated at 120 °C for 2 hours, and 140 °C for 5 hours. The solution is concentrated, diluted with Et_2O (150 mL), washed with sat $NaHCO_3$ (75 mL), sat. $Na_2S_2O_3$ (75 mL), brine (75 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (5%-15% EtOAc gradient) furnish the title compound (1.04 g, 3.00 mmol, 71%). ^{1}H NMR ($CDCl_3$) δ 4.88 (q, J = 16.0, 7.9 Hz, 2H), 7.22 (s, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_8H_4BrClF_3N_3S$ $(M+H)^+$: 345.9; found: 346.0.

C. 3-{3-Chloro-5-[2-(2,2,2-trifluoro-ethyl)-*2H*-[1,2,4]triazol-3-yl]-thiophen-2-yl}-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure analogous to Example 231, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 1.14 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (0.47 g, 1.37 mmol), KOAc (0.56 g, 5.60 mmol), TBABr (0.37 g, 1.14 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.013 g, 0.057 mmol) and TDBPP (0.037 g, 0.057 mmol) furnish the title compound (0.43 g, 0.89 mmol, 78%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 4.98 (q, J = 15.7, 7.9 Hz, 2H), 6.74 (s, 1H), 7.45 (s, 1H), 8.03 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClF_3N_6S$ $(M+H)^+$: 483.1; found: 483.2.

Example 235.

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



A. 1-*tert*-Butyl-5-(4-chloro-thiophen-2-yl)-*1H*-[1,2,4]triazole.

Using a procedure analogous to Example 234A, 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (5.00 g, 23.07 mmol) and AcOH (50.

mL), *tert*-butylhydrazine hydrochloride (3.16 g, 25.38 mmol) furnish the title compound (0.20 g, 0.83 mmol, 3.6%). ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 9H), 7.07 (d, J = 1.3 Hz, 1H), 7.51 (d, J = 1.3 Hz,1H), 8.08 (s, 1H).

B. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole.

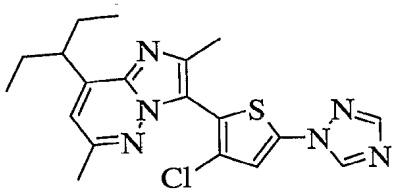
Using a procedure analogous to Example 249B, 1-*tert*-butyl-5-(4-chloro-thiophen-2-yl)-*1H*-[1,2,4]triazole (0.20 g, 0.83 mmol), AcOH (3 mL) and Br_2 (0.051 mL, 0.99 mmol) furnish the title compound (0.27 g, 0.83 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9H), 7.42 (s, 1H), 8.08 (s, 1H). LC/MS (m/z): calcd. for $C_{10}H_{11}BrClN_3S$ $(M+H)^+$: 320.0; found: 320.0.

C. 3-[5-(2-tert-Butyl-*2H*-[1,2,4]triazol-3-yl)-3-chloro-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure analogous to Example 231, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 g, 0.68 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (0.20 g, 0.82 mmol), KOAc (0.34 g, 3.42 mmol), TBABr (0.22 g, 0.68 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.0077 g, 0.034 mmol) and TDBPP (0.022 g, 0.034 mmol) furnish the title compound (0.039 g, 0.085 mmol, 13%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.65 (s, 9H), 1.73-1.91 (m, 4H), 2.51 (s, 6H), 3.26-3.37 (m, 1H), 6.69 (s, 1H), 7.65 (s, 1H), 8.11 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{29}ClN_6S$ $(M+H)^+$: 457.2; found: 457.3.

Example 236.

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



A. 3-(3-Chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

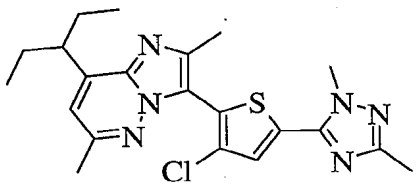
To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (2 g, 6 mmol) in 10 mL of anhydrous CH_3CN under nitrogen was added portionwise NIS (1.6 g, 7.2 mmol). The reaction mixture is stirred at reflux for 14 hours. After cooling, the solvent is concentrated under vacuum, the residue is disolved in EtOAc and washed with H_2O, 5% solution of sodium bisulfite, H_2O and brine. The organic layer is dried over magnesium sulfate, filtered and concentrated under vacuum. The crude residue is purified by silica gel chromatography using hex/EtOAc 8:2 as eluent mixture, to obtain 2.4 g (90%) of the title compound; mass spectrum 460 (M+1); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.24 (s, 1H), 6.71 (s, 1H), 3.32 (q, 1H, J = 7.2 Hz), 2.52 (s, 3H), 2.49 (s, 3H), 1.84 (q, 4H, J = 7.2 Hz); 0.88 (t, 6H, J = 7.2 Hz) ppm.

B. 3-(3-Chloro-5-[1,2,4]triazol-1-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(3-chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.65 mmol), *1H*-triazole (0.047 g, 0.69 mmol), CuI (0.0062, 0.033 mmol), Cs_2CO_3 (0.45 g, 1.37 mmol) and DMF (3 mL) is added (*1S, 2S*)-(+)-*N,N'*- dimethylcyclohexane-1,2-diamine (0.014 mL, 0.098 mmol). The solution is heated at 112 °C overnight, diluted with CH_2Cl_2 (10 mL) and filtered thru Celite® and concentrated. The residue is purified by ISCO flash chromatography (30%-40% EtOAc gradient furnish the title compound (0.028 g, 0.070 mmol, 11%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.35 (m, 1H), 6.72 (s, 1H), 7.22 (s, 1H), 8.10 (s, 1H), 8.50 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{21}ClN_6S$ $(M+H)^+$: 401.1; found: 401.2.

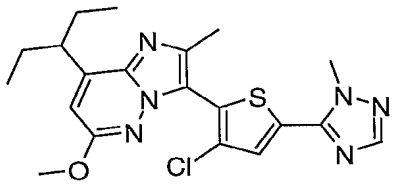
Example 237.

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



To a –78 °C solution of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.72 mmol) and THF (5 mL) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 15 minutes MeI (0.052 mL, 0.83 mmol) is added and the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The solution is recrystalized from acetone: hexane furnish the title compound (0.13 g, 0.30 mmol, 42%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.36 (s, 3H), 2.51 (s, 6H), 3.27-3.39(m, 1H), 3.40 (s, 3H), 6.72 (s, 1H), 8.02 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{25}ClN_6S$ $(M+H)^+$: 429.2; found: 429.2.

Example 238.Preparation of 3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. N-(6-Methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide.

3-Chloro-6-methoxy-pyridazine (10.0 g, 69. 18 mmol) is mixed with 2,2-dimethyl-propionamide (8.40 g, 83.01 mmol), BINAP (2.15 g, 3.46 mmol), Cs_2CO_3 (33.8 g, 103.77 mmol) in 1,4-dioxane (150 mL). It is degassed by passing N_2 through for 10 min at rt. $Pd_2(dba)_3$ (3.16 g, 3.46 mmol) is added and the resulting mixture is refluxed overnight. The mixture is cooled to rt, diluted with EtoAc (150 mL); filtered through silica gel; washed with EtOAc (2 x 150 mL). The filtrate is washed with H2O (2 x 300 mL); dried with $MgSO_4$; filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (6.59 g, 31.53 mmol, 46%). 1H NMR (CDCl3): δ. 1.35 (s, 9H), 4.08 (s, 3H), 7.01 (d, J = 9.7 Hz, 1H), 8.41 (d, J = 9.7 Hz, 1H), 8.44 (bs, 1H). ES-MS (m/z): calcd for $C_{10}H_{15}N_3O_2$ $(M+H)^+$: 210.3; found : 210.1.

B. N-[4-(1-Ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide.

Using a procedure analogous to Example 6a, from N-(6-methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide (6.09 g, 29.14 mmol) and a Grignard reagent prepared from 3-pentyl bromide (18.1 mL, 160.3 mmol) and Mg (3.84 g, 160.26 mmol) gives the title

compound (5.32 g, 19.08 mmol, 65%). 1H NMR (CDCl3): δ. 0.84 (t, J = 7.5 Hz, 6H), 1.36 (s, 9H), 1.50-1.72 (m, 4H), 3.50-3.70 (m, 1H), 4.07 (s, 3H), 6.96 (s, 1H). ES-MS (m/z): calcd for $C_{15}H_{25}N_3O_2$ $(M+H)^+$: 280.4; found : 280.2.

C. 4-(1-Ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[1,2-b]pyridazine.

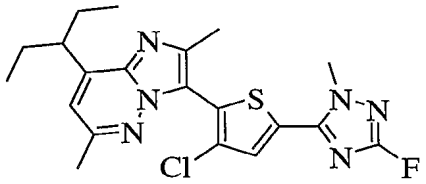
A solution of N-[4-(1-ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide (5.32 g, 19.08 mmol) in EtOH (250 mL) is treated with $ZnCl_2$ (26.0 g, 190.8 mmol) and refluxed for 48 h. The reaction is cooled to rt and concentrated. The residue is taken up with EtOAc (250 mL), and H_2O (100 mL). It is washed with H_2O (2 x 100 mL); dried with Na_2SO_4; filtered and concentrated. The residue is then dissolved in EtOAc (80 mL), reacted with chloroacetone (1.6 mL, 20.03 mmoL) at reflux overnight. While it is hot, $NaHCO_3$ (8.10 g) is added and the reaction is refluxed for 1 h. It is cooled to rt and filtered through silica gel washed with EtOAc and concentrated. Purification of the crude material by chromatography gives the title compound (0.48 g, 2.07 mmol, 11%). 1H NMR (CDCl3): δ. 0.84 (t, J = 7.5 Hz, 6H), 1.69-1.869 (m, 4H), 2.45 (s, 3H), 3.19-3.30 (m, 1H), 3.94 (s, 3H), 6.39 (s, 1H), 7.49 (s, 1H). ES-MS (m/z): calcd for $C_{14}H_{20}N_2O$ $(M+H)^+$: 233.3; found : 234.1.

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

A solution of 4-(1-ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[*1,2-b*]pyridazine (74.8 mg, 0.32 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^1H-[1,2,4]triazole (107.5 mg, 0.38 mmol), TDBPP (10.4 mg, 0.016 mmol), tetrabutylammonium bromide (103.0 mg, 0.32 mmol), KOAc (158 mg, 1.61 mmol) in NMP (15 mL) is purged with N2 for 5 min. Pd(OAc)2 (3.6 mg, 0.016 mmol) is added and the resulting mixture is stirred at 125 °C for 6 h. The reaction is cooled to rt, and diluted with EtOAc (10 mL); filtered through silica gel; washed with EtOAc (3 x 30 mL). The filtrate is washed with H2O (3 x 30 m); dried with Na2SO4, filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (0.1062 g, 0.2469 mmol, 77%). 1H NMR (CDCl3): δ. 0.89 (t, J = 7.6 Hz, 6H), 1.75-1.90 (m, 4H), 2.52 (s, 3H), 3.22-3.38 (m, 1H), 3.93 (s, 3H), 4.15 (s, 3H), 6.52 (s, 1H), 7.48 (s, 1H), 7.91 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{23}ClN_6OS$ $(M+H)^+$: 431.9; found: 431.3.

Example 239.

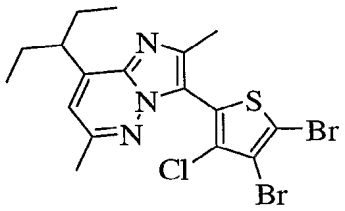
Preparation of 3-[3-chloro-5-(5-fluoro-2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.72 mmol) and THF (8 mL) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 30 minutes the solution is transferred via a cannula into a solution of N-fluorobenzenesulfonamide (0.40 g, 1.25 mmol) and THF. After 30 minutes the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The solution is purified by ISCO (20%-30% EtOAc gradient) furnish the title compound (0.068 g, 0.16 mmol, 16%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.71-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.26-3.36 (m, 1H), 4.08 (d J = 2.7 Hz, 3H), 6.75 (s, 1H), 7.97 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{22}ClFN_6S$ $(M+H)^+$: 433.2; found: 433.2.

Example 240.

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

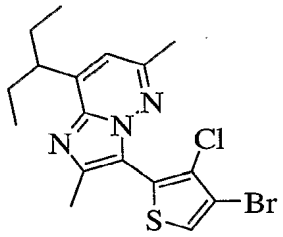


To a solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (5.92 g, 14.34 mmol) and triflouroacetic acid (40 mL) and 98% H_2SO_4 (10 ml) is added NBS (3.83 g, 21.15 mmol). After 10 minutes the solution is poured into ice, and made basic with 5M NaOH. The slurry is extracted with

EtOAc (3 x 100 mL), the combined organic layers washed with water (2 x 400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (6.61 g, 13.44 mmol, 94%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.47 (s, 3H), 2.52 (s, 3H), 3.25-3.34 (m, 1H), 6.72 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{18}Br_2ClN_3S$ $(M+H)^+$: 489.9; found: 490.0.

Example 241.

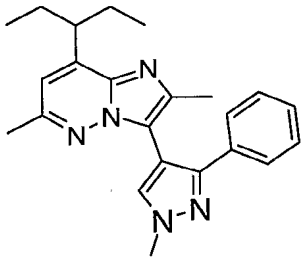
Preparation of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 76, 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.83 g, 3.72 mmol), 1.6 M *n*-BuLi (2.56 mL, 4.09 mmol), and THF (30 mL) furnish the title compound (1.05 g, 2.54 mmol, 68%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.48 (s, 3H), 2.51 (s, 3H), 3.27-3.36 (m, 1H), 6.71 (s, 1H), 7.55 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.0; found: 412.1.

Example 242.

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



A. 1-methyl-3-phenyl-^{1}*H*-pyrazole and 1-methyl-5-phenyl-^{1}*H*-pyrazole.

Sodium hydride (60% dispersion in mineral oil, 0.83 g, 20.8 mmol) is suspended in THF (45 ml) and stirred under a nitrogen atmosphere. 3-Phenyl pyrazole (2.5 g, 17.3 mmol dissolved in THF, 15 ml) is added slowly, stirred for 30 minutes then iodomethane (1.3 ml, 20..8 mmol) added and stirred for 3 hrs. The reaction is added to water and extracted twice with ethyl acetate. The combined organic extracts are ished with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 40% ethyl acetate in hexane) to elute the title compound. Obtained is a mixture of 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (2.6g, 95% yield).

B. 4-Bromo-1-methyl-3-phenyl-*1H*-pyrazole and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole.

The mixture of isomers, 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (1.0g, 6.3 mmol) and NBS (1.1g, 6.3 mmol) are combined in acetonitrile (25 ml), stirred and heated to 70 °C for 1 hr. The solution is concentrated and the crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 25% ethyl acetate in hexane) to elute 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (504 mg, 34% yield) and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole (295 mg, 20% yield), respectively:

^{1}H NMR: (400 mHz, DMSO): δ 8.01 (s, 1H), 7.95 (d, 2H), 7.41 (t, 2H), 7.38 (d, 1H), 3.85 (s, 3H).
^{1}H NMR: (400 mHz, DMSO): δ 7.63 (s, 1H), 7.50 (m, 5H) 3.77 (s, 3H).

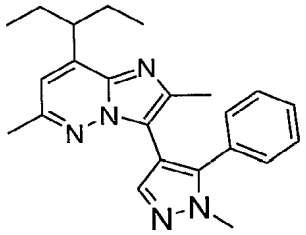
C. 3-(1-Methyl-3-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (250 mg, 1.1 mmol) and cesium carbonate (490 mg, 1.50 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (15mg) is added and the mixture is heated to 130°C overnight. The mixture is added to water and extracted twice with ethyl acetate. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude

product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50% ethyl acetate in hexane) to elute the title compound (17.5 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.68 (s, 1H), 7.37 (m, 2H), 7.20 (m, 3H), 6.59 (s, 1H), 4.04 (s, 3H), 3.36 (m, 1H), 2.38 (s, 3H), 2.15 (s, 3H), 1.82 (m, 4H), 0.86 (t, 6H).

Example 243.

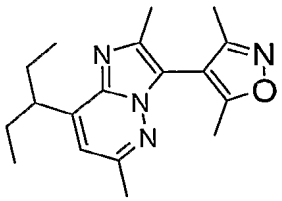
Preparation of 3-(1-methyl-5-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-5-phenyl-^1H-pyrazole (250 mg, 1.1 mmol), cesium carbonate (490 mg, 1.50 mmol) and $PdCl_2(PPh_3)_2$ (15 mg) in DMF (5 ml) gives the title compound (18 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.85 (s, 1H), 7.32 (m, 3H), 7.23 (m, 2H), 6.55 (s, 1H), 3.94 (s, 3H), 3.27 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.76 (m, 4H), 0.83 (t, 6H).

Example 244.

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

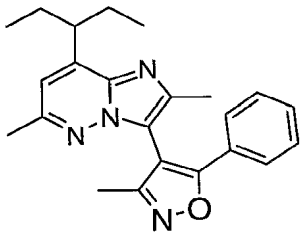


Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3,5-dimethyl

isoxazole (Alfa, 320 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml), heated at 130 for 4 hrs, then overnight at ambient temperature gives the title compound (65 mg, 23% yield). ES-MS (m/z): calc'd for $C_{18}H_{24}N_4O$: 312.4; found 313.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.68 (s, 1H), 3.32 (m, 1H), 2.50 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 1.82 (m, 4H), 0.87 (m, 6H).

Example 245.

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



A. 4-Bromo-3-methyl-5-phenyl isoxazole.

3-Methyl-5-phenyl isoxazole (Synthesis, **1997**, 439-442) (1.0g, 6.3 mmol) and N-bromosuccinimide (1.2 g, 6.9 mmol) are combined together in acetic acid (30 ml) and heated to reflux with stirring for 2 hrs. The solution is added to water and extracted twice with ethyl acetate. The combined organic extracts are washed with sodium bicarbonate (sat'd) and sat. NaCl then dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (1.5 g, 100% yield). ^1H NMR (400 mHz, $CDCl_3$): δ 8.02 (m, 2H), 7.49 (m, 3H), 6.34, 2.35 (s, 3H).

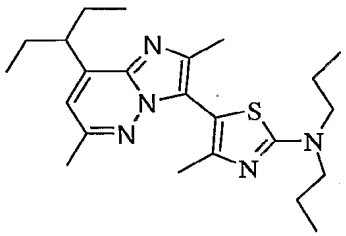
B. 3-(3-Methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using the procedure analogous to Example 257, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3-methyl-5-phenyl isoxazole (430 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml) are combined and heated at 130 °C. for 5 hrs to give the title compound (65

mg, 23% yield). ES-MS (m/z): calc'd for $C_{23}H_{26}N_4O$: 374.5; found 375.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.50 (d, 2H), 7.31 (m, 3H), 6.69 (s, 1H), 3.39 (m, 1H), 2.48 (s, 3H), 2.20 (s, 6H), 2.33 (s, 3H), 1.84 (m, 4H), 0.88 (m, 6H).

Example 246.

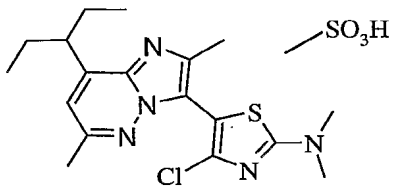
{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dipropyl-amine.



35 mg of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.09mmol) and 45 mg of di-n-propylamine (0.44 mmol) and 57 mg of cesium carbonate(0.18 mmol) are place into 4 ml reaction vial with 3 ml of dry THF and the vial is capped with a Teflon cap. The reaction vial is heated at 100°C for 4h. The reaction mixture is transferred into microwave reaction vessel and sealed. The reaction mixture is heated at 160°C for 30 min by microwave. The mixture is concentrated and applied onto silica-gel chromatography column (Hexane:AcOEt=3:1) to give the title compound. 5.3 mg (14%); mass spectrum(m/e): 414; ^1H-NMR($CDCl_3$):5.59(s, 1H), 3.45(m, 4H), 3.36(m, 1H), 2.57(s, 3H), 2.47(s, 3H), 2.17(s, 3H), 1.80(m, 8H), 0.99(t, 6H, J=7.5Hz), 0.89(t, 6H, J=9.4Hz).

Example 247.

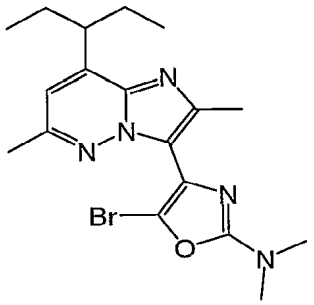
N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine, mesylate salt.



89 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine (0.236 mmol) is dissolved in 2.0 ml of ethylacetate and 0.236ml of 1M methanesulfonic acid in ethylacetate (0.236 mmol) is added. The solvents are removed under N_2 gas and precipitated crystals are collected, washed with Et2O and dried. 92mg (83%); mass spectrum(m/e): 378(M+1); ^{1}H-NMR($CDCl_3$): 7.30(s, 1H), 3.67(m, 1H), 3.22(s, 6H), 2.93(s, 3H), 2.78(s, 3H), 2.78(s, 3H), 2.71(s, 3H), 1.95(m, 2H), 1.82(m, 2H), 0.96(t, 6H, J=7.3Hz).

Example 248.

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



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

500 mg of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.46 mmol) , 622 mg of oxazole (9.0mmol), 79 mg of triphenylphosphine (0.3 mmol) and 989 mg of cesium carbonate (3.03 mmol) are placed into reaction vial with 7 ml of dry DMF. N_2 gas is bubbled into the mixture for 30 min and 67 mg of Pd_2dba_3 (0.07 mmol) is added. The reaction vial is capped with a Teflon cap and stirred at 130°C for 3 days. The reaction mixture is diluted with dichloromethane, washed with sat NaCl, dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give the title compound 172 mg (42%); mass spectrum(m/e): 285; ^{1}H-NMR($CDCl_3$): 8.04(s, 1H), 7.97(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.80(s, 3H), 2.65(s, 3H), 1.86(m, 4H), 0.88(t, 6H).

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

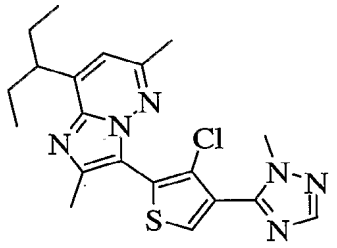
172 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo[*1,2-b*]pyridazine (0.60 mmol) and 270 mg of NBS (1.51 mmol) are dissolved in 8.0 ml of dichloromethane and stirred at room temperature overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give 70 mg of the title compound (26%); mass spectrum(m/e): 442; ^{1}H-NMR($CDCl_3$): 6.82(s, 1H), 3.32(m, 1H), 2.59(s, 3H), 2.54(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.4Hz).

C. {5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine.

67 mg of 3-(2,5-Dibromo-oxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 mmol), 146 mg of cesium carbonate (0.45 mmol) and 3.0 ml of dimethylamine 2.0M in THF (6 mmol) are placed into a 4 ml of reaction vial and the vial is capped with a Teflon cap. The reaction vial is heated at 130°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:AcOE t = 3:1) to give 53 mg of the title compound (87%); mass spectrum(m/e): 406; ^{1}H-NMR($CDCl_3$): 6.72(s, 1H), 3.37(m, 1H), 3.15(s, 6H), 2.58(s, 3H), 2.53(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.2Hz).

Example 249.

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

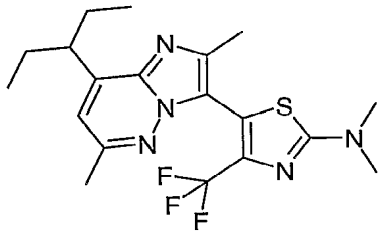


To a flask of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) is added 0.5 g/ mL Reike® Zn (1.3 mL, 0.97 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the solution transferred to a flask containing 5-bromo-1-methyl-*1H*-[1,2,4]triazole (0.12 g, 0.73 mmol) and PdCl2(dppf) (0.018 g, 0.024 mmol). The

solution is heated at 65 °C overnight, diluted with EtOAc (20 mL), washed with sat. NH_4Cl (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-50% EtOAc gradient) furnish the title compound (0.018 g, 0.043 mmol, 9%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.95 (s, 3H), 6.72 (s, 1H), 7.82 (s, 1H), 8.01 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.3.

Example 250.

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



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

Iodoimidazopiridazine (6.75 g, 19.7 mmol), triphenylphosphine (1.03 g, 3.94 mmol), Cs_2CO_3 (12.84 g, 39.4 mmol) and $Pd_2(dba)_3$ (900 mg, 0.98 mmol) are put into a sealed tube with 65 mL of dry DMF and N_2 gas is bubbled into the mixture for 5 minutes. Thiazole (8.36 g, 6.7 mL, 98.4 mmol) is added, and the mixture is heated at 130°C overnight. The mixture is cooled to r.t. and quenched by addition of NH_4Cl saturated solution (200 mL). The mixture is extracted with Et_2O (3 x 100 mL) and the organic layers washed with water (2 x 100 mL) and sat. NaCl (100 mL), dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent; hexane:EtOAc= 4:1) to give 3.80 g of the title compound (Yield: 64%). ESIMS: m/z 301 $[M+H]^+$.

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

To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine. (3.80 g, 12.6 mmol) in CH_3CN (55 mL) at room temperature is added NBS (5.18 g, 29.1 mmol), and the mixture is stirred at room temperature for 3 hours. A white precipitate is formed that is filtered in vacuo, to give 4.86 g of the title compound (Yield: 84%). ESIMS: m/z 459, 461 $[M+H]^+$.

C. 3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.86 g, 10.6 mmol) in THF (150 mL) under N_2 atmosphere at –78°C, BuLi (6.63 mL 1.6 M in hexane, 10.6 mmol) is added dropwise for a period of 10 minutes. The mixture is stirred at –78°C for 30 minutes. Water is added, and the mixture is extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$ and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to give 3.28 g of the title compound (Yield: 82%). ESIMS: m/z 379, 381 $[M+H]^+$.

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

To a solution of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.45 g, 6.5 mmol) in NMP (35 mL) in a sealed tube is added $FSO_2CF_2CO_2Me$ (2.5 g, 1.65 mL, 13 mmol) and CuI (2.48 g, 13 mmol). N_2 gas is bubbled into the mixture for 5 minutes, and the mixture is heated at 120°C for 9 hours. After cooling to room temperature, water (100 mL) and NaCl saturated solution (100 mL) are added to the mixture. The mixture is extracted with Et_2O (5 x 80 mL); washed with water (2 x 100 mL), and dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to obtain 960 mg of the title compound (Yield: 40%). ESIMS: m/z 369 $[M+H]^+$.

E. 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

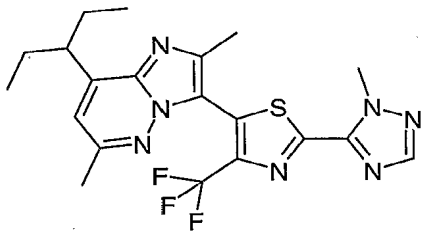
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine (915 mg, 2.48 mmol) in 40 mL of THF under N_2 atmosphere al –78°C, BuLi (1.86 mL 1.6 M in hexane, 2.98 mmol) is slowly added. The mixture is stirred at –78°C for 30 minutes. Then, a solution of CBr_4 (989 mg, 2.98 mmol) in 3 mL of THF is added, and the mixture is stirred at –78°C for 45 minutes. The reaction is quenched by addition of NH_4Cl saturated solution (50 mL), extracted with Et_2O (2 x 50 mL), dried over $MgSO_4$, and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent CH_2Cl_2) to obtain 685 mg of the title compound (Yield: 62%). ^{1}H NMR ($CDCl_3$): δ0.86 (t, J = 7.5 Hz, 6H), 1.82 (m, 4H), 2.45 (s, 3H), 2.51 (s, 3H), 3.27 (m, 1H), 6.74 (s, 1H). ESIMS: m/z 447, 449 $[M+H]^+$.

F. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine.

100 mg of 3-(2-Bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol) and 218 mg of cesium carbonate (0.66 mmol) are placed in 4 ml reaction vial and 3 ml of dimethylamine 2 M in THF is added. The reaction vial is capped with a Teflon cap and heated at 120°C overnight. The reaction mixture is filtered and concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt =3:1) to give 85 mg of the title compound. Yield 94%. mass spectrum (m/e) : 412 (M+1).

Example 251.

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

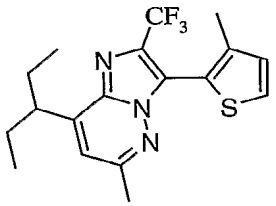


164 mg of 1-Methyl-1,2,4-triazole (1.96 mmol) is dissolved in 2 ml of THF and cooled to –78 °C. 0.8 ml of 2.5M n-butyllithium in hexane (1.96 mmol) is added slowly and stirred at –78 °C, warmed up to room temperature and stirred at r.t. for 15min and

cooled to –78 °C. 3.96 ml of 0.5 M $ZnCl_2$ in THF (1.98 mmol) is added and stirred at room temperature for 15 min. 180 mg of 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 54 mg of PdCl2(pddf) (0.06 mmol) are added. The vial is capped with a Teflon cap and heated at 80 °C overnight. NH_4Cl aq. is added to quench the reaction and the mixture is extracted by CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto silica-gel chromatography column (Hexane :AcOEt=3:1) to give 119 mg of the title compound. Yield 58%. mass spectrum (m/e) : 449(M+1).

Example 252.

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



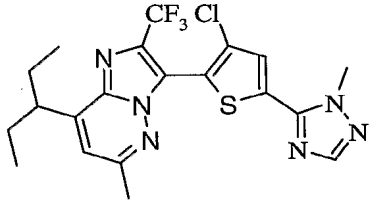
A. 8-(1-Ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

α-Bromotrifluoroacetone (402 mg, 2.93 mmol) is added to a dry 10 mL microwave reaction tube containing 4-(1-ethyl-propyl)-6-methyl-pyridazin-3-ylamine (500 mg, 2.79 mmol) in EtOH (2.0 mL). The resulting mixture is heated at 110 °C in the microwave for 1 hour. $NaHCO_3$ (246.5 mg, 2.93 mmol) is added, and the reaction is mixed well for 5 minutes. Then, the reaction is heated at 110 °C in the microwave for 1 hour. The solvent is removed via reduced pressure, and the reaction is diluted with ethyl acetate (30 mL). The organic layer is washed with H_2O (3 X 10 mL), and the combined aqueous layers are extracted with ethyl acetate (2 X 20 mL). The combined organic extracts are dried over Na_2SO_4, filtered, and purified by silica gel chromatography to give the title compound (29.5 mg, 0.068 mmol, 9.8 %). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, J = 7.6 Hz, 6H), 1.86 (m, 4H), 2.60 (s, 3H), 3.30 (m, 1H), 6.80 (s, 1H), 8.14 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{13}H_{16}F_3N_3$ $(M+H)^+$: 271.29; found: 272.2

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

To a dry 10 ml round bottom flask with reflux condenser containing 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (300 mg, 1.11 mmol), 2-bromo-3-methyl-thiophene (216 mg, 1.22 mmol), and Cs_2CO_3 (760 mg, 2.33 mmol) is added NMP (1.7 ml). The mixture is degassed with bubbling N_2 for 15 min and $Pd_2(dba)_3$ (50.8 mg, 0.055 mmol) and PPh_3 (58.2 mg, 0.222 mmol) are added. The reaction mixture is stirred at 130°C overnight. The mixture is cooled to rt, diluted with H_2O; and extracted with EtOAc (3 x 20 ml). The organic layers are dried (Na_2SO_4), filtered and purified by HPLC to give title compound (32 mg, 0.087 mmol, 8%). ^{1}H-NMR ($CDCl_3$), δ 0.93 (t, J = 7.2 Hz, 6H), 1.91 (m, 4H), 2.15 (s, 3H), 2.58 (s, 3H), 3.36 (m, 1H), 6.91 (s, 1H), 7.08 (d, J = 5.3 Hz, 1H), 7.55 (d, J = 5.5 Hz, 1H) ppm. ES-MS (m/z): calcd for $C_{18}H_{20}F_3N_3S$ $(M+H)^+$: 367.44; found: 368.1.

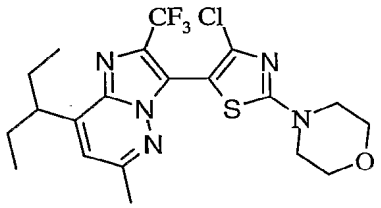
Example 253.Preparation of 3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (182 mg, 0.671 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-*1H*-[1,2,4]triazole (225 mg, 0.805 mmol), KOAc (330.2 mg, 3.36 mmol), and TBAB (217 mg, 0.671 mmol) are dissolved in NMP (3 mL). The mixture is degassed with bubbling nitrogen for 20 minutes. Then, $Pd(OAc)_2$ (8 mg, 0.034 mmol) and TDBPP (20.4 g, 0.34 moles) are added. The reaction mixture is heated to 125 °C for 3 hours to give the title compound (125 mg, 0.267 mmol, 40%). ^{1}H-NMR ($CDCl_3$), δ 0.88 (t, J = 7.2 Hz, 6H), 1.87 (m, 4H), 2.537 (s, 3H), 3.32 (m, 1H), 4.16 (s, 3H), 6.86 (s, 1H), 7.51 (s, 1H), 7.91 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{20}H_{20}ClF_3N_6S$ $(M+H)^+$: 468.93; found: 469.2.

Example 254.

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



A. 8-(1-Ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (460 mg, 1.70 mmol) are dissolved in dry THF (3.5 mL) and cooled to -78°C. A solution of 2.5 M *n*-butyllithium in hexanes (748 µL, 1.87 mmol) is added dropwise. The reaction mixture is stirred for 20 minutes at -78 °C, then warmed to 0 °C for 15 minutes. A solution of I_2 (453 mg, 1.79 moles) in THF (2.0 mL) is added dropwise. The reaction is stirred for 15 minutes at 0 °C, and then warmed to room temp. The reaction is stirred overnight, and the solvent is removed via reduced pressure. The reaction mixture is redissolved in ethyl acetate (50 mL) and washed with a 1 N solution of $Na_2S_2O_3$ (2 X 20 mL). The aqueous layer is extracted with ethyl acetate (2 X 40 mL). The combined organic extracts are dried with Na_2SO_4, filtered, and purified via silica gel chromatography to give the title compound (595 mg, 1.50 mmol, 88%). ^{1}H-NMR ($CDCl_3$), δ 0.82 (t, J = 8.0 Hz, 6H), 1.83 (m, 4H), 2.64 (s, 3H), 3.27 (m, 1H), 6.82 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_{13}H_{15}F_3IN_3$ $(M+H)^+$: 397.18; found: 398.3.

B. 2,4-Dichloro-thiazole.

In a 250 mL round bottom flask, 2.4-thiazolidine dione (12.5 g, 107 mmol) is dissolved in phosphorousoxychloride (70 mL) and pyridine (8.5 mL). The mixture is stirred under reflux for 3 hours and cooled to room temp. The reaction mixture is poured into ice water slowly and extracted with dichloromethane. The combined organic extracts are dried with Na_2SO_4, filtered, and concentrated. The residue is purified via silica gel

chromatography to give title compound (9.18 g, 59.6 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 7.01 (s, 1H) ppm.

C. 4-(4-Chloro-thiazol-2-yl)-morpholine.

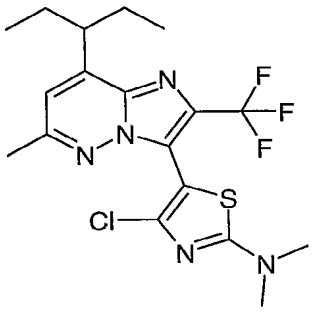
In a 75 mL dry pressure vessel, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and morpholine (560 μL, 6.4 mmol) are dissolved in dry THF (2.0 mL). Cs_2CO_3 (1.56 g, 4.8 mmol) is added, and the reaction vessel is sealed. The reaction mixture is heated to 110 °C overnight. Solvent is removed via reduced pressure, and the crude reaction mixture is purified via silica gel chromatography to give the title compound (597 mg, 2.92 mmol, 91%). ^{1}H-NMR ($CDCl_3$), δ 3.45 (m, 4H), 3.79 (m, 4H), 6.31 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_7H_9ClN_2OS$ $(M+H)^+$: 204.68; found: 205.2.

D. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (250 mg, 0.630 mmol), 4-(4-chloro-thiazol-2-yl)-morpholine (194 mg, 0.945 mmol), and Cs_2CO_3 (410 mg, 1.26 mmol) are dissolved in DMF. The mixture is degassed with bubbling nitrogen for 15 minutes. Then, $Pd_2(dba)_3$ (18 mg, 0.032 mmol) and PPh_3 (33 mg, 0.126 mmol) are added. The reaction mixture is heated to 130 °C overnight. The reaction is cooled to room temp., quenched with a solution of NH_4Cl sat? (20 mL), and extracted with Et_2O (3 X 50 mL). The combined organic extracts are washed with brine (30 mL), dried with Na_2SO_4, filtered and concentrated. The residue is purified via reverse phase HPLC with a 30-80% gradient of CH_3CN in 10mM NH_4HCO_3/H_2O/5%CH_3CN (pH 10.0)to give the title compound (11 mg, 0.023 mmol, 4%). ^{1}H-NMR ($CDCl_3$), δ 0.86 (t, J = 7.3 Hz, 6H), 1.84 (m, 4H), 2.55 (s, 3H), 3.31 (m, 1H), 3.54 (dd, J = 5.2, 4H), 3.84 (dd, J = 5.2 Hz, 4H), 6.82 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_{20}H_{23}ClF_3N_5OS$ $(M+H)^+$: 473.95; found: 474.2.

Example 255.

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



A. (4-Chloro-thiazol-2-yl)-dimethyl-amine.

Using a procedure analogous to Example 254C, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and dimethylamine (a 2.0 M solution in THF, 3 mL, 6.4 mmol) are reacted to give the title compound (60 mg, 0.152 mmol, 15%). ^{1}H-NMR ($CDCl_3$), δ 3.09 (s, 6H), 6.22 (s, 1H) ppm. ES-MS (m/z): calcd for $C_5H_7ClN_2S$ $(M+H)^+$: 162.64; found: 163.2.

B. {4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine.

Using a procedure analogous to Example 254D, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (250 mg, 0.630 mmol) is coupled with (4-chloro-thiazol-2-yl)-dimethyl-amine (154 mg, 0.945 mmol) to provide desired product. ^{1}H-NMR ($CDCl_3$), δ 0.85 (t, J = 7.4 Hz, 6H), 1.83 (m, 4H), 2.55 (s, 3H), 3.16 (s, 6H), 3.31 (m, 1H), 6.81 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{18}H_{21}ClF_3N_5S$ $(M+H)^+$: 431.91; found: 432.2.

Example A

In Vivo Potency Assessment Using Ex Vivo Binding

To assess in vivo potency, a compound of the present invention is evaluated using ex vivo binding. Using the procedures as provided in D. R. Gehlert *et al.*, *EJP* 509: 145-153 (2005), a compound is administered to a rat via the oral route. The binding of ^{125}I-

sauvagine to the cerebellum is then assessed ex vivo as described in Gehlert *et al.* For example, Example 199 provides an ED_{50} result of 1.3 mg/kg.

Example B

CRF1 Filter Binding Assay

The limitations of plasmid-based human CRF1 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF1 cell line is used to prepare membranes and binding reactions (200 µl) are set up as follows: 50 µl of ^{125}I-sauvagine (0.2 nM final), 50 µl compound and 100 µl CRF1 membrane (25 µg/reaction). The reactions are incubated at room temperature for 2 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are wash twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 µl Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 µM non-labeled sauvagine. Triplicate determinations are typically run and the median data points plotted by Graph Pad Prism.

Using this assay, the claimed exemplified compounds of the present invention inhibit the binding of ^{125}I-Sauvagine (4 nM) in roller/adherent cells with a Ki (inhibition constant) below 1 µM. For example, Examples 102 and 199 exhibit a Ki of 4.92 ± 0.57 nM and 9.98 ± 0.72 nM, respectively.

Example C

CRF2 Filter Binding Assay

The limitations of plasmid-based human CRF2 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF2 cell line is used to prepare membranes and binding reactions (200 µl) are set up as follows: 50 ul of ^{125}I-sauvagine (0.2 nM final concentration), 50 µl compound and 100 µl CRF2 membrane (25 µg/reaction). The reactions are incubated at room temperature for 2 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are washed twice with ice-cold

assay buffer (50 mM tris, 12.5 mM NaCl, 1mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 µl Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 µM non-labeled sauvagine. Alternatively, compounds are evaluated using a Scintillation Proximity assay. This assay is set up as follows: 50ul of ^{125}I-Sauvagine (0.2 nM final concentration), 50 µl compound or non-labelled sauvagine (NSB) and 100 µl containing 250 µg wheat germ agglutinin (WGA) SPA beads and CRF2 membrane (1.5 µg/reaction). Plates are incubated for 4-5 hours at room temperature and then centrifuged at 200 X g for 10 minutes. Bound radioactivity is assessed using a Wallac Trilux scintillation counter. Binding is assessed typically using triplicate determinations and the median data points plotted by Graph Pad Prism. Compounds are initially screened at a fixed concentration and, if sufficient activity is noted, subsequent concentration-response curves are generated.

Compounds of the present invention are tested in the CRF2 binding assay and exhibit weak affinity for the CRF2 receptor. For example, Examples 102 and 199 exhibit a percent inhibition at 50 µM of 9.0 ± 2.6 and 16.9 ± 1.9, respectively. These results suggest that the compounds of the present invention are highly selective for the CRF1 receptor.

Example D

Bioavailability and Pharmacokinetic Properties

The compounds of Formula I are antagonists of CRF1, and possess surprisingly useful properties related to their pharmacokinetics and bioavailability.

The volume of distribution (Vdist) relates the amount of the drug in the body to the concentration of the drug in the blood or plasma. The volume of distribution refers to the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as in the blood or plasma: Vdist = amount of drug in the body/ concentration of drug in blood or plasma (Goodman and Gillman's). For a 10 mg dose and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which the drug is present in the extravascular tissue. A large volume of distribution reflects the tendency of a compound to bind to the tissue components compared with plasma protein binding. In a clinical

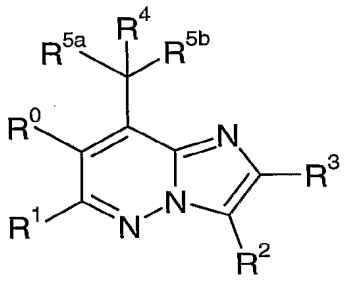
setting, Vdist can be used to determine a loading dose achieve a steady state concentration.

To test for volume of distribution, Male Sprague Dawley rats (N=3) are administered a single 3 mg/kg intravenous dose of compound. Multiple plasma samples are collected at time points from 0.08 to 24 hours post-dose. The plasma samples are analyzed by LC/MS/MS to determine the plasma concentrations. Plasma pharmacokinetic calculations are performed to determine the pharmacokinetic parameters including Vdist and plasma clearance (Clp).

An overwhelming majority of commercial CNS and cardiovascular drugs exhibit a human Vdist of <10 L/Kg. In comparison with CRF antagonists CP154526 (Schulz et al., *Proc. Natl. Acad. Sci. (USA)*, 93:10477 (1996)) and NBI30775 (Chen et al., *Drug Development Research*, 65:216 (2005)) which exhibit a rat Vdist of 114 L/Kg and 76 L/Kg, respectively, following a single intravenous dose, thiazole Examples 48 and 199 of the present invention exhibits a rat Vdist of only 9 and 2 L/Kg, respectively. Furthermore, thiophene Examples 88 and 39 of the present invention exhibit a rat Vdist of only 44 and 17 L/kg, respectively.

WE CLAIM:

1. A compound of Formula I



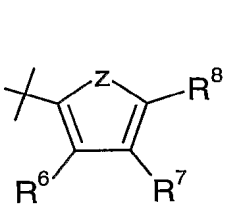
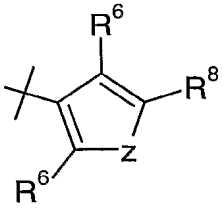
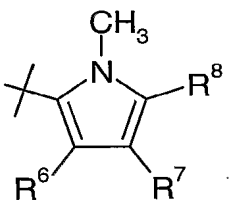
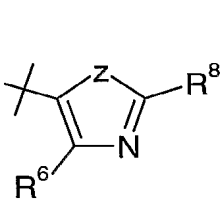
Formula I

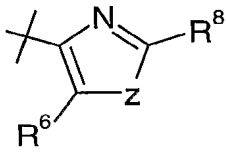
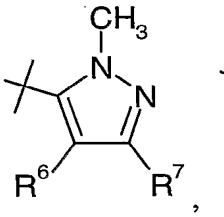
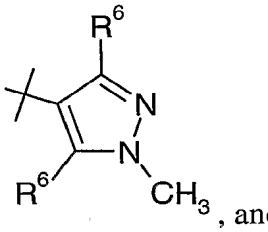
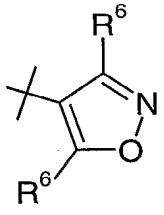
wherein:

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

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

R^2 is selected from the group consisting of:

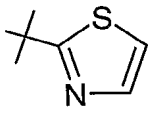
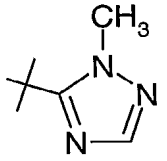
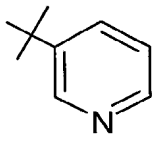
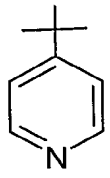
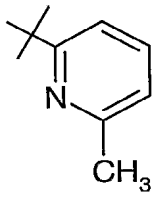
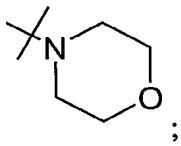
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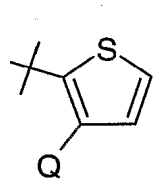
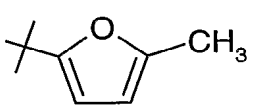
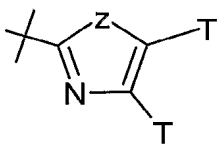
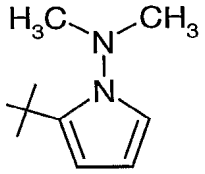
R^4 is hydrogen, halo, or hydroxy;

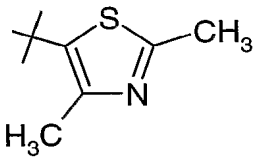
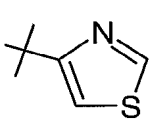
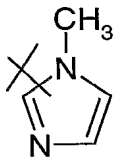
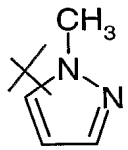
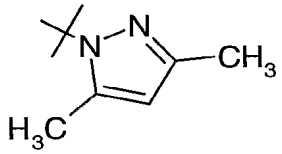
R^{5a} and R^{5b} are independently ethyl or n-propyl;

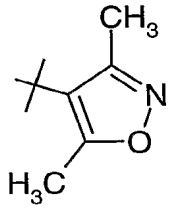
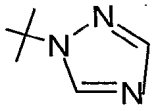
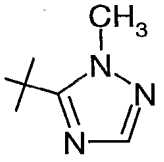
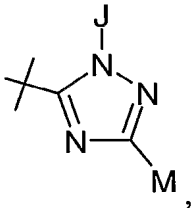
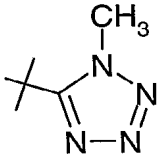
R^6 at each occurrence is independently hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, methoxy, or phenyl;

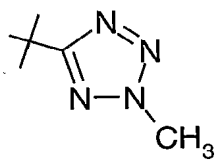
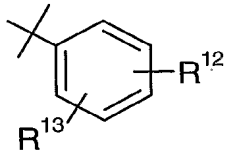
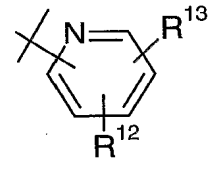
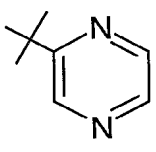
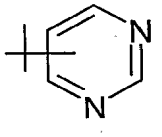
R^7 is hydrogen, halo, methyl, methoxy, dimethylamino,  ,  ,  ,  ,  , or  ;

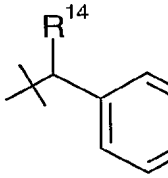
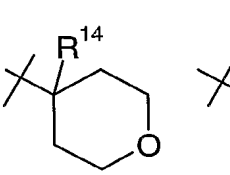
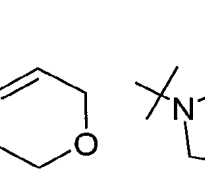
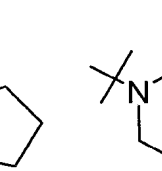
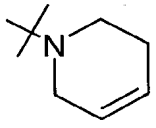
R^8 is selected from the group consisting of hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, R^aR^bN-, carbamyl, $(C_1\text{-}C_2)$alkoxy$(C_1\text{-}C_2)$alkyl, R^{11}-C(O)-,

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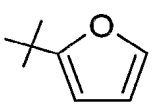
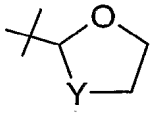
 ,  ,  ,  , or  ;

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

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

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

R^{14} is hydrogen or hydroxy;

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

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

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

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

Y is $-CH_2-$ or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

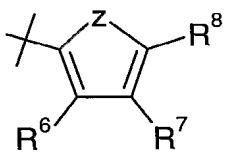
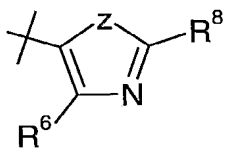
T is hydrogen or methyl;

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

M is methyl or halo;

and pharmaceutically acceptable salts thereof.

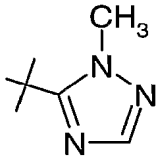
2. The compound of Claim 1 wherein R^0 and R^4 are hydrogen, R^1 and R^3 are methyl, and R^{5a} and R^{5b} are ethyl.

3. The compound according to any one of claims 1 to 2, wherein R^2 is selected from the group consisting of  or  and where z is S.

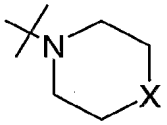
4. The compound according to any one of claims 1 to 3, wherein R^7 is hydrogen.

5. The compound according to any one of claims 1 to 4, wherein R^6 is halo or methyl.

6. The compound according to any one of claims 1 to 5, wherein R^8 is



or



and where X is O.

7. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

8. A compound according to any one of Claims 1 to 6 for use as a medicament.

9. Use of a compound according to any one of Claims 1 to 6 for the manufacture of a medicament for treating anxiety, depression, major depressive disorder, alcohol withdrawal symptoms, or irritable bowel syndrome in a mammal.

10. Use of a compound according to Claim 9 wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009942

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P25/20

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 364 952 A (EISAI CO., LTD) 26 November 2003 (2003-11-26) examples	1-10
A	WO 97/29109 A (JANSSEN PHARMACEUTICA N.V; NEUROCRINE BIOSCIENCES INC; CHEN, CHEN; WEB) 14 August 1997 (1997-08-14) examples	1-10
A	EP 1 466 527 A (SUMITOMO CHEMICAL TAKEDA AGRO COMPANY, LIMITED) 13 October 2004 (2004-10-13) examples	1-10

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2006	16/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menegaki, F

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

4038

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009942

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOREAU S ET AL: "Synthesis and anticonvulsant Properties of Triazolo- and Imidazopyridazinyl Carboxamides and Carboxylic Acids" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 6, no. 7, July 1998 (1998-07), pages 983-991, XP002991062 ISSN: 0968-0896 compounds 9,10,11 _____	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/009942

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 1364952 A	26-11-2003	WO	02062800 A1	15-08-2002
		US	2004082781 A1	29-04-2004
WO 9729109 A	14-08-1997	AU	713673 B2	09-12-1999
		AU	1599197 A	28-08-1997
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		BR	9707391 A	20-07-1999
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		DE	880523 T1	04-07-2002
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EP 1466527 A	13-10-2004	BR	0306810 A	26-10-2004
		CN	1617666 A	18-05-2005
		WO	03061388 A1	31-07-2003
		US	2005032650 A1	10-02-2005

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 October 2013 (31.10.2013)

WIPO | PCT

(10) International Publication Number
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(51) **International Patent Classification**:
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(21) **International Application Number**:
PCT/EP2013/058413

(22) **International Filing Date**:
23 April 2013 (23.04.2013)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
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12165231.7 23 April 2012 (23.04.2012) EP

(71) **Applicant**: **HOLSBOERMASCHMEYER NEUROCHEMIE GMBH** [DE/DE]; Maximilianstrasse 13, 80539 Munich (DE).

(72) **Inventor**: **HOLSBOER, Florian**; Rohmederstrasse 12, 80805 Munich (DE).

(74) **Agent**: **HUENGES, Martin**; Maiwald Patentanwalts GmbH, Postfach 33 05 23, 80065 Munich (DE).

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

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2013/160317 A2

(54) **Title**: CRHR1 ANTAGONISTS FOR USE IN THE TREATMENT OF PATIENTS HAVING CRH OVERACTIVITY

(57) **Abstract**: The present invention relates to a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in a novel group of patients, i.e. patients having corticotropin releasing hormone (CRH) overactivity.

CRHR1 antagonists for use in the treatment of patients having CRH overactivity

Field of the Invention

The present invention relates to a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity.

Background of the Invention

While current antidepressant drugs are effective treatments of depression and anxiety symptoms in a number of psychiatric disorders, a large fraction of patients only show partial remission of symptoms or do not respond at all (Trivedi *et al.*, Am J Psychiatry, 2006). This may be due to the fact that these drugs do not target the inherent pathophysiologic disturbances leading to clinical condition in these patients. A number of novel antidepressant strategies, derived from both animal studies and human studies have been tested, but so far with little success. One of these approaches is the use of corticotropin releasing hormone receptor type 1 (CRHR1) antagonists. A wealth of data ranging from molecular studies in experimental animals to open label studies in human patients indicate that CRHR1 antagonists are a promising novel approach in the treatment of depression and anxiety (Ising *et al.*, Exp Clin Psychopharmacol, 2007; Holsboer *et al.*, CNS Spectr, 2001; Paez-Pereda *et al.*, Expert Opin Invest Drugs, 2011). However, so far all randomized clinical trials have failed to demonstrate the superiority of this drug to placebo (Coric *et al.*, Depress Anxiety, 2010; Binneman *et al.*, Am J Psychiatry, 2008).

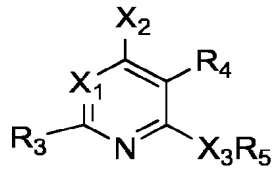
Hence, there is still a need for antidepressant drugs effective in the treatment of depression and/or anxiety symptoms in a number of psychiatric disorders.

It has now been found that despite the so far unsuccessful clinical trials, a specific group of patients, i.e. patients suffering from central corticotropin releasing hormone (CRH) overactivity, profits from the treatment with CRHR1 antagonists.

Summary of the Invention

One aspect of the invention relates to a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity.

In an embodiment of the invention, the CRHR1 antagonist is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

X_1 is $-CR_6$ or N;

X_2 is $-NR_1R_2$, $-CR_1R_2R_9$, $-C(=CR_2R_{10})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{10}$, $-CHR_2SR_{10}$, $-C(S)R_2$ or $-C(O)R_2$;

X_3 is NH, O, S, $-N(C_1\text{-}C_2$ alkyl) or $-C(R_{11}R_{12})$, wherein R_{11} and R_{12} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{11} and R_{12} is cyano and the other is hydrogen or methyl, or
X_3 is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5;

R_1 is $C_1\text{-}C_6$ alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, $C_3\text{-}C_8$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $-O\text{-}CO\text{-}(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}NH(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $-NH(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}$

C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, C_1-C_{12} alkoxyalkyl, aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or –(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl;

and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 or –$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OCF_3, CF_3,

amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, -NHCOCH$_3$ -NHCONHCH$_3$, -SO$_n$(C_1-C_4 alkyl) wherein n is 0, 1 or 2, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH$_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl,

wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, -NHCH$_3$, -N(CH_3)$_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO$_2$NH(C_1-C_4 alkyl), -SO$_2$N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO$_2$NH$_2$, -NHSO$_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO$_2$(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, 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$_2$OH, -CH$_2$OCH$_3$ or -CH$_2$OCH$_2$CH$_3$;

R_9 is hydrogen, hydroxy, fluoro, or methoxy;

R_{10} is hydrogen or C_1-C_4 alkyl.

Further, CRHR1 antagonists of the invention encompass compounds of formula (I) as defined above, wherein X_1 is –CR_6. Optionally, in the CRHR1 antagonists of the invention X_1 is -CR_6, wherein R_6 is hydrogen.

In a further embodiment of the CRHR1 antagonists of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ of the compound of formula (I) as defined above is substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring, which may be saturated or may contain one to three double bonds and in which one carbon atom may be replaced by CO or SO_2 and one to four carbon atoms may optionally be replaced by nitrogen.

In a specific embodiment of the CRHR1 antagonists of the invention, X_2 of the compound of formula (I) as defined above is $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

Optionally, in the compounds of formula (I) as defined above $-NHCHR_1R_2$ is $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$,, $-NHCH(CH_2CH_2OCH_3)_2$ or $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, or $-NR_1R_2$ is $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$, or $-OCHR_1R_2$ is $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$.

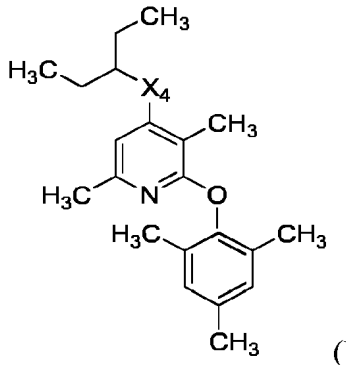
In another embodiment of the CRHR1 antagonists of the invention, R_3 and R_4 of the compound of formula (I) as defined above are methyl.

In a further embodiment of the CRHR1 antagonists of the invention, X_3 of the compound of formula (I) as defined above is O.

Another embodiment of the invention relates to the CRHR1 antagonists of formula (I) as defined above, wherein R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3.

A specific embodiment of the invention relates CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having

corticotropin releasing hormone (CRH) overactivity, wherein the CRHR1 antagonist is a compound of the formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein
X_4 is O or NH.

In another specific embodiment, the CRHR1 antagonist of the invention is a class I or class II CRHR1 antagonist.

Another specific embodiment of the invention relates to a CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity, wherein the CRHR1 antagonist is selected from the group consisting of CP154,526, Antalarmin, CRA 5626, Emicerfont, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, Pexacerfont, R121919, NBI30545, PD-171729, Verucerfont, NBI34041, NBI35965, SN003, CRA0450, SSR125543A, CP-316,311, CP-376,395, NBI-27914, ONO-2333Ms, NBI-34101, PF-572778, GSK561579 and GSK586529.

In an exemplary embodiment of the present invention, the CRHR1 antagonist is DMP-696.

In an exemplary embodiment of the present invention, the CRHR1 antagonist is CP 316,311.

In an exemplary embodiment of the present invention, the CRHR1 antagonist is SSR125543A.

Brief Description of the Drawings

Figure 1: Graph of the phenotypic distribution of ln(AAUC) at in-patient admission. The X-axis shows the ln of the AUC of the ACTH response and the Y-axis the frequency in total N/bin. The dashed vertical indicates the cut-off for being classified as a low vs. high responder. AAUC is the area under the curve of the ACTH response.

Figure 2: Increased REMS activity in CRH-COE^{CNS} mice is suppressed by DMP696 (50mg/kg/d) application via drinking water. Treatment day one, light grey; treatment day 2, dark grey; treatment day three, black. Symbols indicate significant differences between baseline and treatment day one (+), two (#) or three (*). Light and dark bar on the x-axis indicate light and dark period, respectively.

Figure 3: Increased activity of REMS in CRH-COE^{CNS} is suppressed by application of the CRH-R1 antagonist SSR125543 (50mg/kg/d) via drinking water. Baseline day, white; treatment day two, dark grey; treatment day three, black. Symbols indicate significant differences between baseline and treatment day two (#) or three (*). Light and dark bar on the x-axis indicate light and dark period, respectively.

Figure 4: REMS activity in Cor26 CRH mice is suppressed by application of the CRH-R1 antagonist CP-316311 (50mg/kg/d) via drinking water. Baseline day, white; treatment day two, dark grey; treatment day three, black.

Definitions

Where the term "comprise" or "comprising" is used in the present description and claims, it does not exclude other elements or steps. For the purpose of the present invention, the term "consisting of" is considered to be an optional embodiment of the

term "comprising of". If hereinafter a group is defined to comprise at least a certain number of embodiments, this is also to be understood to disclose a group which optionally consists only of these embodiments.

Where an indefinite or a definite article is used when referring to a singular noun such as "a" or "an" or "the", this includes a plural form of that noun unless specifically stated. Vice versa, when the plural form of a noun is used it refers also to the singular form. For example, when SNPs are mentioned, this is also to be understood as a single SNP.

Furthermore, the terms first, second, third or (a), (b), (c) and the like in the description and in the claims are used for distinguishing between similar elements and not necessarily for describing a sequential or chronological order. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other sequences than described or illustrated herein.

The term "corticotropin releasing hormone receptor 1" of "CRHR1" of "CRF_1" refers to the receptor which binds to corticotropin-releasing hormone.

The term "CRHR1 antagonist" refers to a compound capable of binding directly or indirectly to a CRH receptor 1 so as to modulate the receptor mediated activity. CRHR1 antagonists are well known in the literature and are e.g. described in WO 94/13676, EP 0 773 023, WO 2004/047866, WO 2004/094420, WO 98/03510, WO 97/029109, WO 2006/044958, WO 2001/005776 and WO 95/033750. Exemplary CRHR1 antagonists comprise NBI30775/R121919 (Neurocrine), CP316.311 (Pfizer), CP154,526 (Pfizer), Emicerfont (Glaxo), ONO-2333Ms (Ono Pharmaceutical), Pexacerfont (Bristol-Myers-Squibb), SSR125543 (Sanofi-Aventis), NBI-34101 (Neurocrine) and TAI041 (Taisho).

Most of the non-peptidic CRHR1 antagonists can be described by or adhere to a pharmacophore model that comprises or features a lipophilic top group, a

heterocyclic core containing an invariable hydrogen bond acceptor, which is almost always a heterocyclic nitrogen, and a lipophilic, usually aromatic, bottom group.

Class I CRHR1 antagonists as used herein may be characterized in that the heterocyclic hydrogen bond acceptor and the bottom group are connected by a two-atom linker as exemplified by CRHR1 antagonists R-121919, NBI-30545, CP-154526, DMP696, pexacerfont (BMS-562086), emicerfont (GW876008), or verucerfont (GSK561679). Class II CRF1R antagonists as used herein may be characterized by a two-atom linker between hydrogen bond acceptor and the bottom group as present in CRHR1 antagonist SSR125543A.

"Downstream target" or "molecule which is downstream of the CRHR1 receptor" as used herein may denote a molecule such as an endogenous molecule (e.g. peptide, protein, lipid, nucleic acid or oligonucleotide) that is regulated by CRHR1 directly or indirectly. The direct or indirect regulation may comprise direct or indirect modulation of the activity and/or expression level and/or localization, degradation, stability of the downstream target.

The term "normal CRH activity" refers to a range of CRH activity which can be found in human beings who are not affected by a condition which is associated with an increase of CRH activity (such as depression). A value indicative for normal CRH activity is usually considered to be indicative or predictive for a patient not responding to a treatment with a CRHR1 antagonist.

Further definitions of the terms will be given below in the context of which the terms are used.

Detailed Description of the Invention

While so far all randomized clinical trials have failed to demonstrate the superiority of CRHR1 antagonist to placebo in the treatment of depression and anxiety, it has now been found that a certain patient group, i.e. patients with corticotropin releasing

hormone (CRH) overactivity, is responsive to the treatment with corticotropin releasing hormone receptor type 1 (CRHR1) antagonists.

Hence, the present invention relates to CRHR1 antagonists for use in the treatment of depressive symptoms and/or anxiety symptoms in said novel patient group, i.e. patients having CRH overactivity.

The terms "CRH overactivity", "CRH system overactivity", "CRH hyperactivity", "CRH hyperdrive" or "central CRH hyperdrive" are used herein interchangeable. An indication for CRH overactivity may be an increase in activity or concentration of CRH or of one or several molecules downstream of the CRHR1 receptor, that are activated or whose concentration is increased based on the activation of CRHR1 receptor upon CRH binding. A further indication for CRH overactivity may be a decrease in activity or concentration of one or several molecules downstream of the CRHR1 receptor, that are inactivated or whose concentration is decreased based on the activation of CRHR1 receptor upon CRH binding. A value indicative for CRH overactivity is usually considered to be indicative or predictive for a patient responding to a treatment with a CRHR1 antagonist. CRH activity vs. CRH overactivity may be defined relatively to the whole group, e.g. by using a median split of the area under the curve of the ACTH response in the dex/CRH test. Responses in the upper median may be categorized as being predictive of CRH overactivity, while responses in the lower median are indicative of normal CRH activity.

A "value indicative for CRH activity", a "value indicative for CRH overactivity" and/or a "value indicative for normal CRH activity" can be obtained by determining the concentration or activity of CRH and/or of a downstream target of the CRHR1 receptor. The analysis is usually set up in a way that it can be excluded that the modulation of activity or concentration of a downstream target of the CRHR1 receptor is due to another disturbance than CRH activity. For instance, the concentrations or activities of adrenocorticotrophin (ACTH) and/or cortisol are useful biomarkers for determining a value indicative for CRH overactivity.

Typically, the CRH overactivity in each patient may be determined by measuring the ACTH and/or cortisol level response to a combined dexamethasone suppression/CRH stimulation test as described in Heuser *et al.* (J Psychiatr Res., 1994).

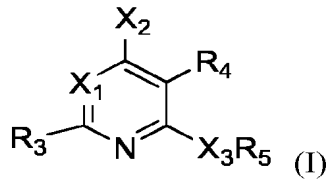
The neuroendocrine response to the dex/CRH test may be analyzed using the total area under the curve (AUC) of the ACTH response. Patients suffering from depression normally show an increased release of cortisol and of adrenocorticotropic hormone (ACTH) in response to the combined treatment with dexamethasone and CRH as performed during the test, thus indicating a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Patients with a high HPA axis dysregulation show AUC values of cortisol of between 3000 and 18000 AUC units (ng/ml x 75 min) and/or AUC values of ACTH of between 1000 and 6500 AUC units (pg/ml x 75 min). Patients having a low HPA axis dysregulation show AUC values of cortisol of between 300 and 2500 AUC units (ng/ml x 75 min) and/or AUC values of ACTH of between 250 and 1000 AUC units (pg/ml x 75 min) Various antidepressants lead to a reduction of these increased cortisol and ACTH levels in a combined dex/CRH test performed after the treatment with the antidepressants. Treatment response to antidepressants can thus be determined by performing a second dex/CRH test after treatment with the antidepressant and comparing the neuroendocrine response to the one shown in a combined dex/CRH test performed prior to treatment with the antidepressant.

In one embodiment of a combined dexamethasone suppression CRH stimulation test, subjects are pre-treated with dexamethasone and blood is drawn in certain intervals. Further, human CRH is administered after the first pretreatment with dexamethasone. Plasma ACTH and/or cortisol concentrations are then determined. The neuroendocrine response to the dex/CRH test may be analyzed using the total area under the curve (AUC) of the ACTH response. Details of an exemplary dex/CRH test are also described in Example 1 below.

Depressive symptoms comprise *inter alia* low mood, low self-esteem, loss of interest or pleasure, psychosis, poor concentration and memory, social isolation, psychomotor agitation/retardation, thoughts of death or suicide, significant weight change (loss/gain), fatigue, and feeling of worthlessness. The depressive disorders can last for weeks to lifelong disorder with periodic reoccurring depressive episodes. For the diagnosis of the depression mode (e.g. moderate or severe depression) the Hamilton Depression Rating Scale (HAM-D) (Hamilton, J Neurol Neurosurg Psychiatry, 1960) may be used. The depression mode may be also, in addition or alternatively, rated by alternative scales as the Beck Depression Inventory (BDI), the Montgomery-Åsberg Depression Scale (MADRS), the Geriatric Depression Scale (GDS), and/or the Zung Self-Rating Depression Scale (ZSRDS).

Anxiety symptoms comprise *inter alia* panic disorders, generalized anxiety disorder, phobias and posttraumatic stress disorder. Typical symptoms of anxiety are or include avoidance behavior which may lead to social isolation, physical ailments like tachycardia, dizziness and sweating, mental apprehension, stress and/or tensions. The strength of these symptoms ranges from nervousness and discomfort to panic and terror in humans or animals. Most anxiety disorders may last for weeks or even months, some of them even for years and worsen if not suitably treated. For measuring the severity of anxiety symptoms, the Hamilton Anxiety Rating Scale (HAM-A) and/or the State-Trait Anxiety Rating Scale (STAI) can be used.

A CRHR1 antagonist which may be used according to the invention in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

X_1 is -CR_6 or N;

X_2 is -NR_1R_2, -$CR_1R_2R_9$, -$C(=CR_2R_{10})R_1$, -$NHCHR_1R_2$, -$OCHR_1R_2$, -$SCHR_1R_2$, -CHR_2OR_{10}, -CHR_2SR_{10}, -$C(S)R_2$ or -$C(O)R_2$;

X_3 is NH, O, S, -N(C_1-C_2 alkyl) or -$C(R_{11}R_{12})$, wherein R_{11} and R_{12} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{11} and R_{12} is cyano and the other is hydrogen or methyl, or
X_3 is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, C_1-C_{12} alkoxyalkyl, aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or –(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl;

and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2,

-SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 or –$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OCF_3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -$N(CH_3)_2$, -$NHCOCH_3$ -$NHCONHCH_3$, -SO_n(C_1-C_4 alkyl) wherein n is 0, 1 or 2, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl,

wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO_2(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, 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, -CH_2OCH_3 or -$CH_2OCH_2CH_3$;

R_9 is hydrogen, hydroxy, fluoro, or methoxy;

R_{10} is hydrogen or C_1-C_4 alkyl.

In an embodiment of the invention, the CRHR1 antagonist of the present invention is a compound of formula (I) as defined above, wherein X_1 is –CR_6.

Alternatively, the CRHR1 antagonists of the invention encompass compound of formula (I) as defined above, wherein X_1 is N.

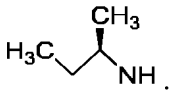
If X_1 is –CR_6, R_6 may be selected from the group consisting of hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C_1-C_4 alkyl), -C(O)(C_1-C_4 alkyl), -C(O)O(C_1-C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3 or -$CH_2OCH_2CH_3$. In a specific embodiment of the CRHR1 antagonists of the invention R_6 is hydrogen.

A further embodiment of the invention relates to a CRHR1 antagonist of formula (I) as defined above, wherein X_2 is selected from the group consisting of –$NHCHR_1R_2$, -$OCHR_1R_2$ or -NR_1R_2.

In a specific embodiment, X_2 is –$NHCHR_1R_2$. In another specific embodiment, X_2 is –$OCHR_1R_2$. In a further specific embodiment, X_2 is –NR_1R_2.

If X_2 is –$NHCHR_1R_2$, it is optionally selected from the group consisting of -$NHCH(CH_2OCH_3)_2$, -$NHCH(CH_2OCH_3)(CH_2CH_3)$, -$NHCH(CH_2CH_3)_2$, -$NHCH(CH_2CH_2OCH_3)_2$, -$NHCH(CH_3)(CH_2CH_3)$ or -$NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically X_2 is -$NHCH(CH_2CH_3)_2$. Alternatively, X_2 is -$NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is -$NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is –

$NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is $-NR_1R_2$, it is optionally selected from the group consisting of -$N(CH_2CH_3)(CH_3)$, -$N(CH_2CH_2CH_3)_2$, -$N(CH_2CH_2CH_3)$(CH_2-cyclopropyl), -$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, -$N(CH_2CH_2OCH_3)_2$, or-$N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, X_2 is $-N(CH_2CH_2OCH_3)_2$.

If X_2 is -$OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, -$OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (I) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (I) is C_1 alkyl. In a further embodiment of the invention R_1 of formula (I) is C_2 alkyl. In a further embodiment of the invention, R_1 of formula (I) is C_3 alkyl. In a further embodiment of the invention, R_1 of formula (I) is C_4 alkyl. In a further embodiment, of the invention, R_1 of formula (I) is C_5 alkyl. In a further embodiment of the invention, R_1 of formula (I) is C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and the

(C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of $-CH_2OCH_3$, $-CH_2CH_2OCH_3$ and $-CH_2$-cyclopropyl.

In another embodiment of the invention, R_2 of formula (I) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (I) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl. In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively, each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and

-SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is –$NHCHR_1R_2$, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is –$NHCR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

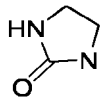
In another embodiment of the invention X_2 is -NR_1R_2 which forms a 5- to 8-membered ring. In a further embodiment of the invention X_2 is –$CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by -NR_1R_2 or –$CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

In a specific embodiment, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur

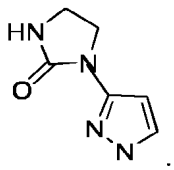
atom. Optionally, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by –NR_1R_2 is a pyrazol-1-yl. Alternatively, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by –NR_1R_2 or –$CR_1R_2R_9$ may be substituted with at least one substituent. In one embodiment of the invention, the 5- to 8-membered ring formed by –NR_1R_2 or –$CR_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by –NR_1R_2 or –$CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by –NR_1R_2 or –$CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by –NR_1R_2 or –$CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by –NR_1R_2 is substituted with



Optionally, X_2 is



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5 membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

A further embodiment of the invention encompasses CRHR1 antagonists of formula (I) as defined above, wherein X_3 is NH, O, NCH_3, or N, whereby, if X_3 is N, X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5. Specifically, X_3 of formula (I) as defined above is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with

R_5. More specifically, X_3 of formula (I) as defined above is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5 wherein X_3 and R_4 form a group –N-CH_2CH_2-. Alternatively, X_3 is O or NH, more specifically X_3 is O.

The CRHR1 antagonist of the invention further encompasses a compound of formula (I) as defined above, wherein R_3 is methyl. In a further embodiment of the invention, R_4 of formula (I) as defined above is C_1-C_4 alkyl. Optionally R_4 of formula (I) as defined above is methyl. Alternatively, R_4 of formula (I) as defined above is ethyl. The present invention also encompasses CRHR1 antagonists wherein both R_3 and R_4 are methyl.

In another embodiment of the invention, the CRHR1 antagonist is a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO_2(C_1-C_6 alkyl). The C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl.

In an embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In a specific embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with one substituent independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with two substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3. In another embodiment of the invention,

the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with three substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3.

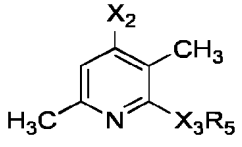
In a specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with two substituents, wherein the two substituents are CH_3 and OCH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with three substituents, wherein the three substituents are CH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, the three substituents of said phenyl are independently selected from CH_3 and Cl.

Specifically, R_5 is 2-chloro-4-methoxy-5-methyl-phenyl, 2,4,6-trimethyl-phenyl, 2,4,6-trichloro-phenyl, 4-methoxy-2-methyl-phenyl, 2,4-dichloro-phenyl, 4-chloro-2,6-dimethyl-phenyl, 2,4-dimethyl-phenyl, or 2,4-dimethoxy-phenyl. More specifically R_5 is 2,4,6-trimethyl-phenyl or 4-chloro-2,6-dimethyl-phenyl. Even more specifically, R_5 is 4-chloro-2,6-dimethyl-phenyl.

In a specific embodiment of the invention, the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (II)



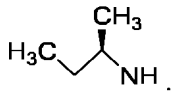
(II),

wherein X_2, X_3, R_1, R_2 und R_5-R_{12} are as defined above for formula (I).

A further embodiment of the invention relates to a CRHR1 antagonist of formula (II) as defined above, wherein X_2 is selected from the group consisting of $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

In a specific embodiment, X_2 is $-NHCHR_1R_2$. In another specific embodiment, X_2 is $-OCHR_1R_2$. In a further specific embodiment, X_2 is $-NR_1R_2$.

If X_2 is $-NHCHR_1R_2$, it is optionally selected from the group consisting of $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $-NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH_3)(CH_2CH_3)$ or $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, X_2 is $-NHCH(CH_2CH_3)_2$. Alternatively, X_2 is $-NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is $-NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is $-NR_1R_2$, it is optionally selected from the group consisting of $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, X_2 is $-N(CH_2CH_2OCH_3)_2$.

If X_2 is $-OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (II) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (II) is a C_1 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_2 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_3 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_4 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_5 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and/or the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of –CH_2OCH_3, -$CH_2CH_2OCH_3$ and –CH_2-cyclopropyl.

In another embodiment of the invention, R_2 of formula (II) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (II) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl. In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl,

benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively, each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is –NHCHR_1R_2, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-

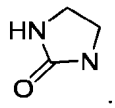
C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is $-NHCR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is $-NR_1R_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention, X_2 is $-CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

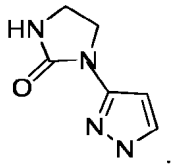
In a specific embodiment, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by $-NR_1R_2$ is a pyrazol-1-yl. Alternatively, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ may be substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring. In one embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



Optionally, X_2 is



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5-membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

A further embodiment of the invention encompasses CRHR1 antagonists of formula (II) as defined above, wherein X_3 is NH, O, NCH_3, or N, whereby if X_3 is N, X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5. Specifically, X_3 of formula (II) as defined above is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5. More specifically, X_3 of formula (II) as defined above is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5, wherein X_3 and R_4 form a group $-N\text{-}CH_2CH_2-$. Alternatively, X_3 is O or NH, more specifically X_3 is O.

In another embodiment of the invention, the CRHR1 antagonist is a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, $-NHCH_3$, $-N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl), $-SO_2N$(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO_2(C_1-C_6 alkyl). The C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl.

In an embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl,

F, CF_3. In a specific embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with one substituent independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with two substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with three substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3.

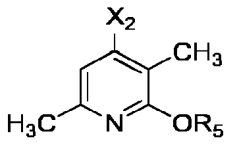
In a specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with two substituents, wherein the two substituents are CH_3 and OCH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with three substituents, wherein the three substituents are CH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, the three substituents of said phenyl are independently selected from CH_3 and Cl.

Specifically, R_5 is 2-chloro-4-methoxy-5-methyl-phenyl, 2,4,6-trimethyl-phenyl, 2,4,6-trichloro-phenyl, 4-methoxy-2-methyl-phenyl, 2,4-dichloro-phenyl, 4-chloro-2,6-dimethyl-phenyl, 2,4-dimethyl-phenyl, or 2,4-dimethoxy-phenyl. More specifically R_5 is 2,4,6-trimethyl-phenyl or 4-chloro-2,6-dimethyl-phenyl. Even more specifically, R_5 is 4-chloro-2,6-dimethyl-phenyl.

In another specific embodiment of the invention the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (III)

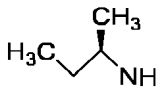

(III),

wherein X_2, R_1, R_2 und R_5-R_{10} are as defined for formulas (I) and (II) above.

A further embodiment of the invention relates to a CRHR1 antagonist of formula (III) as defined above, wherein X_2 is selected from the group consisting of –$NHCHR_1R_2$, -$OCHR_1R_2$ or -NR_1R_2.

In a specific embodiment, X_2 is –$NHCHR_1R_2$. In another specific embodiment, X_2 is –$OCHR_1R_2$. In a further specific embodiment, X_2 is –NR_1R_2.

If X_2 is –$NHCHR_1R_2$, it is optionally selected from the group consisting of -$NHCH(CH_2OCH_3)_2$, -$NHCH(CH_2OCH_3)(CH_2CH_3)$, -$NHCH(CH_2CH_3)_2$, -$NHCH(CH_2CH_2OCH_3)_2$, -$NHCH(CH_3)(CH_2CH_3)$ or -$NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, X_2 is -$NHCH(CH_2CH_3)_2$. Alternatively, X_2 is -$NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is –$NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is –$NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is –$NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is –NR_1R_2, it is optionally selected from the group consisting of -$N(CH_2CH_3)(CH_3)$, -$N(CH_2CH_2CH_3)_2$, -$N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), -$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, -$N(CH_2CH_2OCH_3)_2$, or -$N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. More specifically, X_2 is –$N(CH_2OCH_3)_2$. Alternatively, X_2 is -$N(CH_2CH_2OCH_3)_2$.

If X_2 is -$OCHR_1R_2$, it is optionally selected from –$OCH(CH_2CH_3)_2$, –$OCH(CH_2CH_3)CH_3$, –$OCH(CH_2CH_3)(CH_2CH_2CH_3)$, or –$OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is –$OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention may encompass compounds of formula (III) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (III) is a C_1 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_2 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_3 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_4 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_5 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of –CH_2OCH_3, -$CH_2CH_2OCH_3$ and –CH_2-cyclopropyl.

In another embodiment of the invention, R_2 of formula (III) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (III) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl.

In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl, said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively, each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is –$NHCHR_1R_2$, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7

independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is –NHCR_1R_2, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is -NR_1R_2 which forms a 5- to 8-membered ring. In a further embodiment of the invention, X_2 is –C$R_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by -NR_1R_2 or –C$R_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

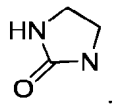
In a specific embodiment, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by –NR_1R_2 is a pyrazol-1-yl. Alternatively, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by –NR_1R_2 or –C$R_1R_2R_9$ may be substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring.

In one embodiment of the invention, the 5- to 8-membered ring formed by –NR_1R_2 or –C$R_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8

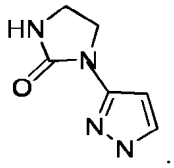
membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



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Optionally, X_2 is



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In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one

carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5-membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the ring carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

In another embodiment of the invention, the CRHR1 antagonist is a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, $-NHCH_3$, $-N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl), $-SO_2N$(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO_2(C_1-C_6 alkyl). The C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl.

In an embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In a specific embodiment of the invention, the CRHR1 antagonist

encompasses a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with one substituent independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with two substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with three substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3.

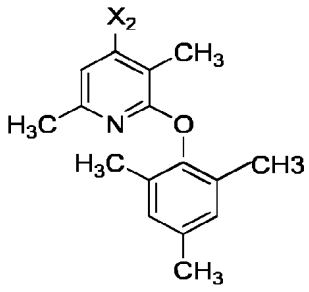
In a specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with two substituents, wherein the two substituents are CH_3 and OCH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with three substituents, wherein the three substituents are CH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, the three substituents of said phenyl are independently selected from CH_3 and Cl.

Specifically, R_5 is 2-chloro-4-methoxy-5-methyl-phenyl, 2,4,6-trimethyl-phenyl, 2,4,6-trichloro-phenyl, 4-methoxy-2-methyl-phenyl, 2,4-dichloro-phenyl, 4-chloro-2,6-dimethyl-phenyl, 2,4-dimethyl-phenyl or, 2,4-dimethoxy-phenyl. More specifically, R_5 is 2,4,6-trimethyl-phenyl or 4-chloro-2,6-dimethyl-phenyl. Even more specifically, R_5 is 4-chloro-2,6-dimethyl-phenyl.

Another specific embodiment of the invention relates to a CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity, wherein the CRHR1 antagonist is a compound of formula (IV)



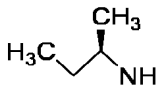
(IV),

wherein X_2, R_1, R_2, R_7, R_8, R_9 and R_{10} are as defined above for formulas (I) to (III).

A further embodiment of the invention relates to a CRHR1 antagonist of formula (IV) as defined above, wherein X_2 is selected from the group consisting of –$NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

In a specific embodiment, X_2 is $–NHCHR_1R_2$. In another specific embodiment, X_2 is $–OCHR_1R_2$. In a further specific embodiment, X_2 is $–NR_1R_2$.

If X_2 is $–NHCHR_1R_2$, it is optionally selected from the group consisting of -$NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH)_3(CH_2CH_3)$ or $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, X_2 is $-NHCH(CH_2CH_3)_2$. Alternatively, X_2 is $-NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is $-NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is $–NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is $–NR_1R_2$, it is optionally selected from the group consisting of -$N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), -

$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, X_2 is $-N(CH_2CH_2OCH_3)_2$.

If X_2 is $-OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$ or $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (IV) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (IV) is a C_1 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_2 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_3 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_4 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_5 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of $-CH_2OCH_3$, $-CH_2CH_2OCH_3$ and $-CH_2$-cyclopropyl.

In another embodiment of the invention, R_2 of formula (IV) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (IV) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl. In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively, each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is –NHCHR$_1$R$_2$, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and/or the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is –NHCR$_1$R$_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

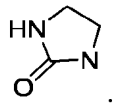
In another embodiment of the invention, X_2 is -NR$_1$R$_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention, X_2 is –CR$_1$R$_2$R$_9$ which forms a saturated 5- to 8-membered ring. The ring formed by -NR$_1$R$_2$ or –CR$_1$R$_2$R$_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

In a specific embodiment, -NR$_1$R$_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, -NR$_1$R$_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by –NR$_1$R$_2$ is a pyrazol-1-yl. Alternatively, -NR$_1$R$_2$ forms a 5-membered ring containing two double bonds, wherein one of the ring carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by –NR$_1$R$_2$ or –CR$_1$R$_2$R$_9$ may be substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring. In one embodiment of the invention, the 5- to 8-membered ring

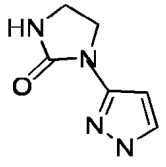
formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



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Optionally, X_2 is



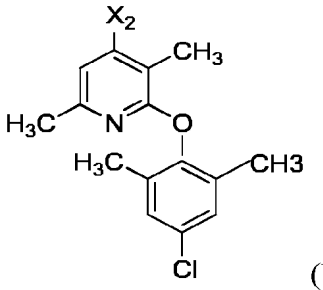
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In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally,

one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5-membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$,containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$,containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

In another specific embodiment of the invention, the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (V)



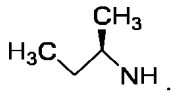
(V)

or a pharmaceutically acceptable salt thereof, wherein X_2, R_1, R_2, R_7, R_8, R_9 and R_{10} are as defined for formulas (I)-(IV) above.

A further embodiment of the invention relates to a CRHR1 antagonist of formula (V) as defined above, wherein X_2 is selected from the group consisting of $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

In a specific embodiment, X_2 is $-NHCHR_1R_2$. In another specific embodiment, X_2 is $-OCHR_1R_2$. In a further specific embodiment, X_2 is $-NR_1R_2$.

If X_2 is $-NHCHR_1R_2$, it is optionally selected from the group consisting of $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH_3)(CH_2CH_3)$ or $-NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, X_2 is $-NHCH(CH_2CH_3)_2$. Alternatively, X_2 is $-NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is $-NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is $-NR_1R_2$, it is optionally selected from the group consisting of $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, X_2 is $-N(CH_2CH_2OCH_3)_2$.

If X_2 is $-OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$ or $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (V) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (V) is a C_1 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_2 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_3 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_4 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_5 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of –CH_2OCH_3, -$CH_2CH_2OCH_3$ and –CH_2-cyclopropyl.

In another embodiment of the invention, R_2 of formula (V) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (V) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl. In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl, said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl,

benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is –NHCHR_1R_2, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and/or the

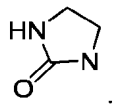
(C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is $-NR_1R_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention, X_2 is $-CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

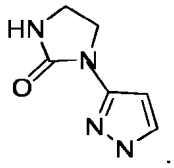
In a specific embodiment, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by $-NR_1R_2$ is a pyrazol-1-yl. Alternatively, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ may be substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring. In one embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



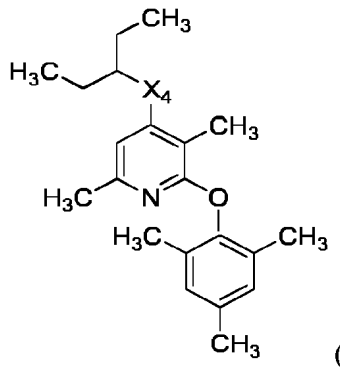
Optionally, X_2 is



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5 membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$ containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$ containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$ containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-Dialkylpyrazol-1-yl, more specifically 3,5-Diethylpyrazol-1-yl.

In another specific embodiment of the invention the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein
X_4 is O or NH.

In another embodiment of the invention, the CRHR1 antagonist is selected from the group consisting of CP154,526, Antalarmin, CRA 5626, Emicerfont, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, Pexacerfont, R121919, NBI30545, PD-171729, Verucerfont, NBI34041, NBI35965, SN003, CRA0450, SSR125543A, CP-316,311, CP-376,395, NBI-27914, ONO-2333Ms, NBI-34101, PF-572778, GSK561579 and GSK586529.

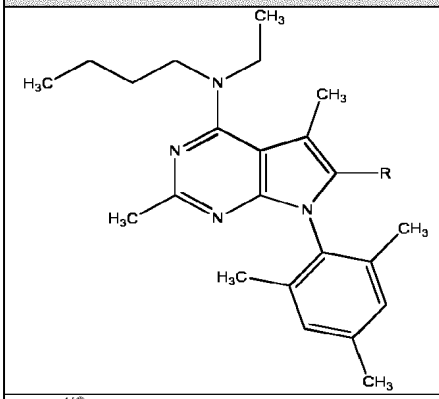
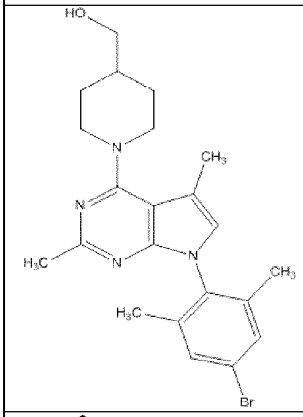
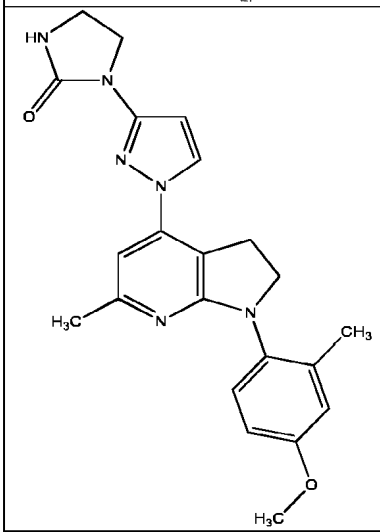
In a particular embodiment of the invention, the CRHR1 antagonist is DMP-696.

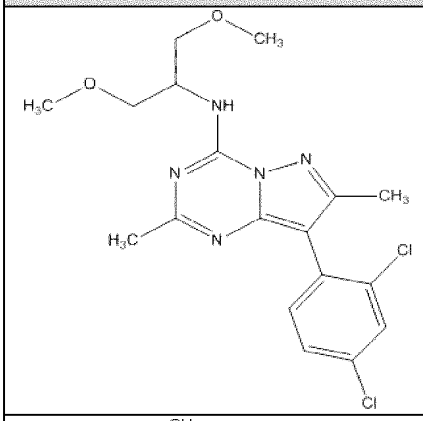
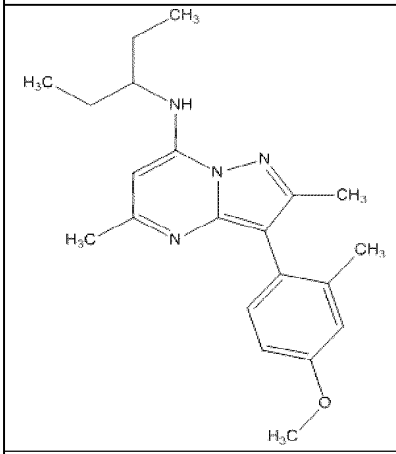
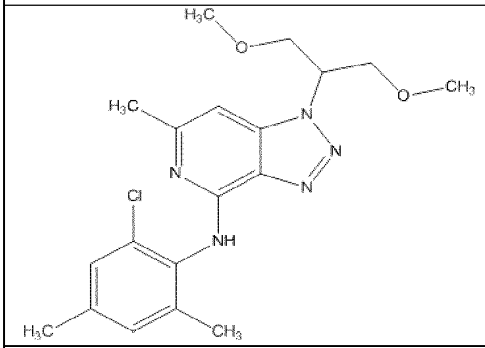
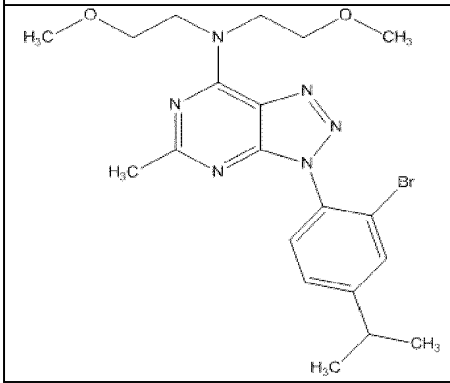
In a particular embodiment of the invention, the CRHR1 antagonist is CP-316,311.

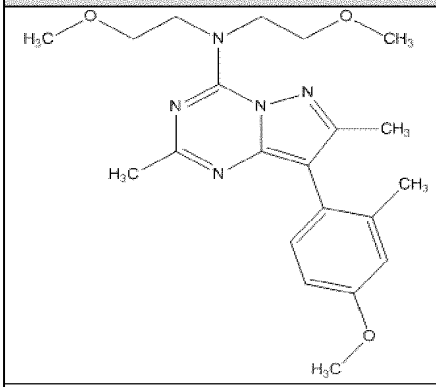
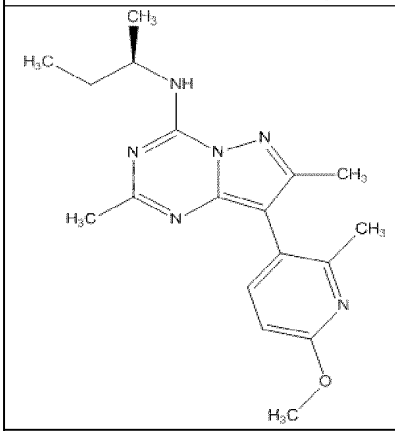
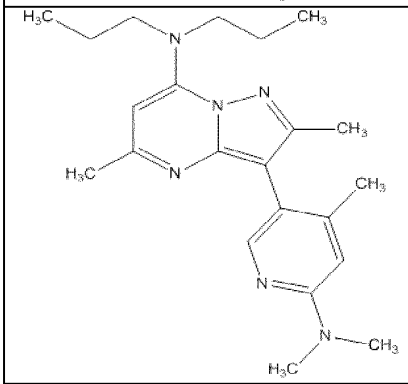
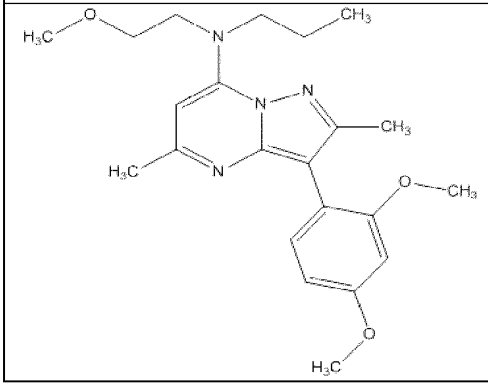
In a particular embodiment of the invention, the CRHR1 antagonist is SSR125543A

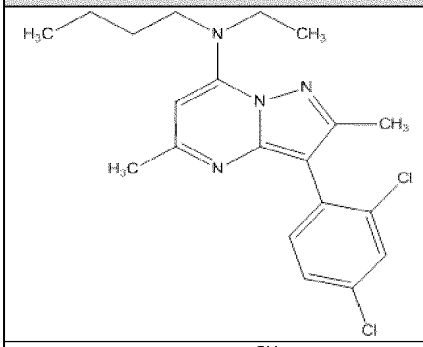
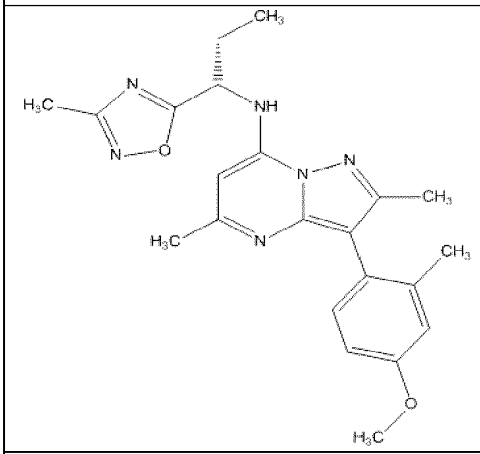
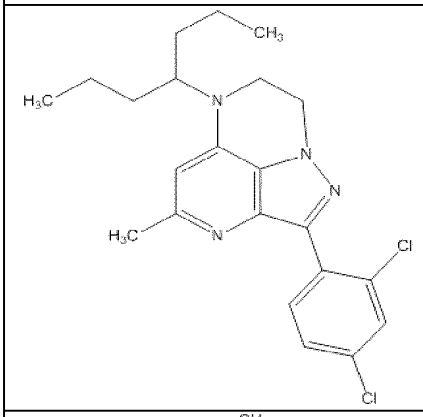
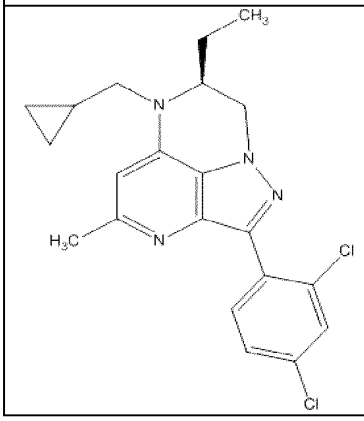
The corresponding structural formulas of some of the above-mentioned CRHR1 antagonists for use in the present invention are set out in Table 1 below:

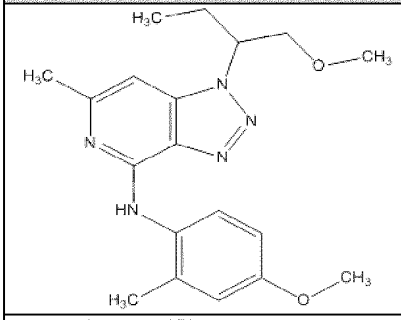
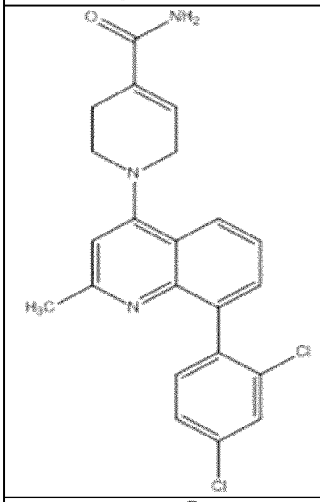
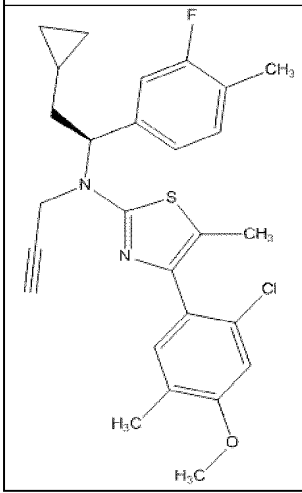
Table 1

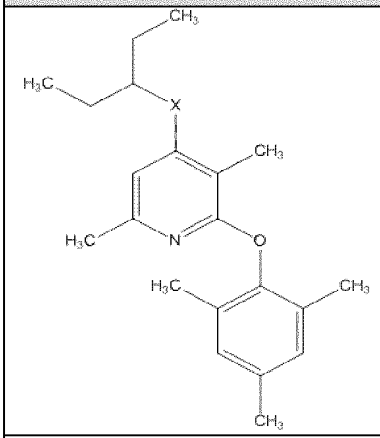
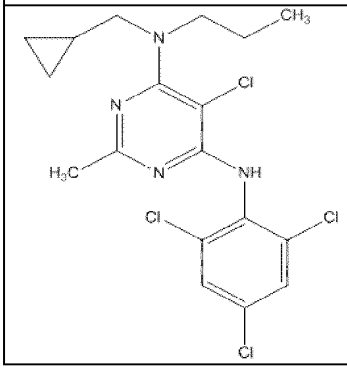
Structural formula	CRHR1 antagonist (name)
	R = H **CP154,526** R = CH_3 **Antalarmin**
	**CRA5626 / R317573 / JNJ19567470 / TAI-041**
	**GW876008 /Emicerfont**

Structural formula	CRHR1 antagonist (name)
	**DMP-696**
	**DMP-904**
	**DMP-695**
	**SC-241 / LWH-234**

Structural formula	CRHR1 antagonist (name)
	**BMS-561388**
	**BMS-562086 / Pexacerfont**
	**R121919 / NBI30775**
	**NBI30545**

Structural formula	CRHR1 antagonist (name)
	**PD-171729**
	**GSK561679 / NBI-77860 / Verucerfont**
	**SB-723620 / NBI34041**
	**NBI35965**

Structural formula	CRHR1 antagonist (name)
	**SN003**
	**CRA0450 / R278995**
	**SSR125543A**

Structural formula	CRHR1 antagonist (name)
	X = O **CP-316,311** X = NH **CP-376,395**
	**NBI-27914**

ONO-2333Ms, NBI 34101, PF-572778, GSK561579 and GSK586529 are described by Zorilla and Koob (Drug Discovery Today, 2010, 371-383) as corticotropin releasing factor receptor antagonists (corticotropin releasing factor is a synonym for CRHR1 antagonists) tested in clinical trials.

In another aspect of the invention, the above-described CRHR1 antagonists are for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity, wherein CRH overactivity is detected by determining the status of a marker indicative for CRH overactivity.

In one embodiment, the marker indicative for CRH overactivity is selected from the group consisting of a biomarker, a set of biomarkers and a clinical marker.

The one or more biomarkers may be obtained by a genome-wide screening for single nucleotide polymorphisms in patients with depressive and/or anxiety symptoms.

For example, the biomarker or set of biomarkers constituting a marker for CRH activity may be selected from one or more biomarkers of the group comprising:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,

- SNP rs11025990,
- SNP rs3758562,
- SNP rs10156056.

In particular, the biomarker or set of biomarkers constituting a marker for CRH activity may be selected from one or more biomarkers of the group comprising:

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

- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

In a specific embodiment, the set of biomarkers comprises at least 15, at least 20, at least 25 or all of the following biomarkers:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,

- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,
- SNP rs11025990,
- SNP rs3758562,
- SNP rs10156056.

In another specific embodiment, the set of biomarkers comprises at least 15, at least 20, at least 25 or all of the following biomarkers:

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

- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,

- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,

- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

For example, the set of biomarkers consists of the following biomarkers:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,

- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,
- SNP rs11025990,
- SNP rs3758562,
- SNP rs10156056.

In another example, the set of biomarkers consists of the following biomarkers:

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

- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,

- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

The status of a marker indicative for CRH overactivity may be determined by a method comprising determining the status of a marker as defined herein in a nucleic acid isolated from a patient's sample, wherein the presence of indicator nucleotides as defined herein is indicative for CRH overactivity.

The term "biomarker", as used herein, relates to any nucleic acid sequence of any length, or a derivative thereof, which comprises a polymorphic variant as defined in:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,

- SNP rs11025990,
- SNP rs3758562, and/or
- SNP rs10156056.

A biomarker may, for instance, be represented by a nucleic acid molecule of a length of e.g. 1 nt, 2 nt, 3 nt, 4 nt, 5 nt, 10 nt, 15 nt, 20 nt, 25 nt, 30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 60 nt, 70 nt, 80 nt, 90 nt, 100 nt, 200 nt, 300 nt, 400 nt, 500 nt, 1000 nt, 2000 nt, or more or any length in between these lengths. The representing nucleic acid may be any suitable nucleic acid molecule, e.g. a DNA molecule, e.g. a genomic DNA molecule or a cDNA molecule, or a RNA molecule, or a derivative thereof. The biomarker may further be represented by translated forms of the nucleic acid, e.g. a peptide or protein as long as the polymorphic modification leads to a corresponding modification of the peptide or protein. Corresponding information may be readily available to the skilled person from databases such as the NCBI SNP repository and NCBI Genbank.

The SNPs as described herein may be present on the Watson or the Crick strand, with presence of the corresponding base. I.e. if, for example, a polymorphism is present on the Watson strand as A, it is present on the Crick strand as T, if the polymorphism is present on the Watson strand as T, it is present on the Crick strand as A, if the polymorphism is present on the Watson strand as G, it is present on the Crick strand as C, and if the polymorphism is present on the Watson strand as C, it is present on the Crick strand as G, and vice versa. Also the insertion or deletion of bases may be detected on the Watson and/or the Crick strand, with correspondence as defined above. For analytic purposes the strand identity may be defined, or fixed, or may be choose at will, e.g. in dependence on factors such the availability of binding elements, GC- content etc. Furthermore, for the sake of accuracy, the SNP may be defined on both strands (Crick and Watson) at the same time, and accordingly be analyzed.

A "polymorphic site" or “polymorphic variant” as used herein relates to the position of a polymorphism or SNP as described herein within the genome or portion of a

genome of a subject, or within a genetic element derived from the genome or portion of a genome of a subject.

The term "wildtype sequence" as used herein refers to the sequence of an allele, which does not show the CRH overactivity phenotype according to the present invention. The term may further refer to the sequence of the non phenotype-associated allele with the highest prevalence within a population, e.g. within a Caucasian population.

The term "indicator sequence" as used herein refers to the sequence of an allele, which shows an association with a CRH overactivity phenotype according to the present invention. The term "indicator nucleotide" as used herein refers to the identity of the nucleotide at the position of a SNP or polymorphic site as defined herein, associated with a CRH overactivity phenotype according to the present invention. The term may refer to a non-wildtype nucleotide at positions of SEQ ID NO: 1 to 30 as described below:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs9542951 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

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

The term "determining the status of a biomarker" or determining the status of a marker" as used herein refers to any suitable method or technique of detecting the identity of an SNP, e.g. at the positions of the biomarkers described herein. The determination method may be a sequencing technique or a technique based on complementary nucleic acid binding. The context of the indicated positions, as well as the strand may differ, e.g. from patient to patient, or from sample to sample etc.

The term "allele" or "allelic sequence" as used herein refers to a particular form of a gene or a particular nucleotide, e.g. a DNA sequence at a specific chromosomal location or locus. In certain embodiments of the present invention a SNP as defined herein may be found at or on one of two alleles in the human genome of a single subject. In further, specific embodiments, a SNP as defined herein may also be found

at or on both alleles in the human genome of a single subject. The presence of an indicator nucleotide or an indicator triplet as defined herein on both alleles may have a higher predictive value than the presence of an indicator nucleotide or an indicator triplet on one allele only, the other allele comprising a wildtype genotype. The presence or absence of indicator nucleotides or indicator triplets on one or two alleles may be connected or linked with an algorithm for predicting the a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms as described herein.

A person skilled in the art would be able to derive the exact position, nucleotide sequence, and indicator sequence from the above identified rs-nomenclature, e.g. from suitable database entries and associated information systems, e.g. the Single Nucleotide Polymorphism database (dbSNP) which is incorporated herein by reference. The information may also be retrievable in case of changes to the nomenclature, or to the surrounding sequence elements, e.g. based on history functions of a suitable database.

The term "isolated nucleic acid molecule" a used herein refers to a nucleic acid entity, e.g. DNA, RNA etc, wherein the entity is substantially free of other biological molecules, such as, proteins, lipids, carbohydrates, other nucleic acids or other material, such as cellular debris and growth media. Generally, the term "isolated" is not intended to refer to the complete absence of such material, or to the absence of water, buffers, or salts, unless they are present in amounts which substantially interfere with the methods of the present invention.

In another embodiment, the biomarker constituting a marker for CRH overactivity is REM density.

Such a marker or set of markers or combination of markers as described above may be used for predicting a treatment response to CRH antagonists in patients with depressive and/anxiety symptoms.

Exemplary embodiments for determining the status of a marker indicative for CRH overactivity are described below.

In particular, it has been found that a treatment response to CRH antagonists in patients with depressive symptoms and/or anxiety symptoms can be reliably predicted by using a machine-learning based prediction algorithm derived from the association of SNPs with values indicative for CRH overactivity.

The term "treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms" in the sense of the invention refers to a response in a patient with depressive symptoms and/or anxiety symptoms during and/or after the treatment with one or more CRHR1 antagonists compared to before the treatment. The response may range from a partial alleviation of the symptoms to a complete remission of the symptoms, indicated by the change of symptoms strength and/or frequency of relapse of individual symptoms and/or the mean change on a depression scale, e.g. as described herein. The response can occur shortly after treatment or after a certain time period. A decrease in symptom severity from pre-treatment of 25% or more is usually considered a partial alleviation of symptoms. Remission may be defined as achieving a value of 8 or less on the Hamilton Depression Rating Scale (HAM-D) or equivalent values on other rating scales named below.

A further aspect concerns the provision of an algorithm for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms. The method may comprise the following steps:

(a) performing a single nucleotide polymorphism (SNP) genotyping analysis in a group of patients with depressive symptoms and/or anxiety symptoms;

(b) determining a value indicative for CRH activity in each patient of the group, wherein a value indicative for CRH overactivity is indicative or predictive for a patient responding to a treatment with a CRH1 antagonist;

(c) identifying at least one SNP associated with a value indicative for CRH overactivity as determined in step (b);

(d) determining the algorithm by machine-learning from the association of the at least one SNP identified in step (c) with the value indicative for CRH overactivity.

In a step (a), a single nucleotide polymorphism (SNP) genotyping analysis in a group of patients with depressive symptoms and/or anxiety symptoms is performed.

A "group of patients" as used herein comprises at least two patients, such as at least 10 patients, or at least 100 patients, or at least 150 patients. Patients included in the analysis of step (a) may exhibit at least a moderate to severe depressive mode. The group of patients may comprise patients with CRH overactivity and/or patients with normal CRH activity.

The term "polymorphism" as used herein refers to a variation in the genome of individuals, including, insertions, deletions, point mutations and translocations.

The term "single nucleotide polymorphism" is well understood by the skilled person and refers to a point mutation at a certain position in the nucleotide sequence. In other words, only one nucleotide differs in a certain region.

The nucleotide, that is present in the majority of the population, is also referred to as wild-type allele or major allele. As used herein, this state is defined as "absence of a SNP".

The specific nucleotide that is present in the minority of the population is also referred as the point mutation, mutated nucleotide or minor allele. As used herein this state is defined as "presence of a SNP".

In theory, the wild-type allele could be mutated to three different nucleotides. However, the event of a mutation to a first nucleotide in the reproductive cells of an individual that gets established in a population occurs very rarely. The event that the same position is mutated to a second nucleotide and established in the population virtually never occurs and can be therefore neglected. Therefore, as used herein, a

certain nucleotide position in the genome of an individual can have two states, the wild-type state (absence of a SNP) and the mutated state (presence of a SNP).

The term "single nucleotide polymorphism (SNP) genotyping analysis" as used herein refers to a test of determining in one or several patients the presence or absence of at least one SNP, typically several SNPs, and in some embodiments all (known) SNPs the human genome, including endogenous and exogenous regions. In particular, a SNP genotyping analysis as used herein may not be limited to the CRHR1 gene or to genes of the CRH pathway. In other words, an SNP genotyping analysis as used herein can be a genome-wide screening for SNPs.

SNP genotyping analysis can be performed by methods known in the art such as microarray analysis or sequencing analysis or PCR related methods or mass spectrometry or 5'-nuclease assays or allele specific hybridization or high-throughput variants of these techniques or combinations thereof. These and other methods are known in the art. See for example Rampal, DNA Arrays: Methods and Protocols (Methods in Molecular Biology) 2010; Graham & Hill, DNA Sequencing Protocols (Methods in Molecular Biology) 2001; Schuster, Nat. Methods, 2008 and Brenner, Nat. Biotech., 2000; Mardis, Annu Rev Genomics Hum Genet., 2008. Genomewide arrays can be purchased from different suppliers such as Illumia and Affymetix.

For example, the determination of the nucleotide sequence and/or molecular structure may be carried out through allele-specific oligonucleotide (ASO)-dot blot analysis, primer extension assays, iPLEX SNP genotyping, Dynamic allele-specific hybridization (DASH) genotyping, the use of molecular beacons, tetra primer ARMS PCR, a flap endonuclease invader assay, an oligonucleotide ligase assay, PCR-single strand conformation polymorphism (SSCP) analysis, quantitative real-time PCR assay, SNP microarray based analysis, restriction enzyme fragment length polymorphism (RFLP) analysis, targeted resequencing analysis and/or whole genome sequencing analysis.

In some embodiments, any of the methods described herein comprises the determination of the haplotype for two copies of the chromosome comprising the SNPs identified herein.

A "subject's sample" as used herein may be any sample derived from any suitable part or portion of a subject's body. In some embodiments, blood or saliva samples are used. The sample used in the context of the present invention should be collected in a clinically acceptable manner, in particular in a way that nucleic acids and/or proteins are preserved.

The term "primer" may denote an oligonucleotide that acts as an initiation point of nucleotide synthesis under conditions in which synthesis of a primer extension product complementary to a nucleic acid strand is induced.

The term "probe" may denote an oligonucleotide that selectively hybridizes to a target nucleic acid under suitable conditions.

The primers and probes may be generated such that they are able to discriminate between wild-type allele or mutated allele of the position of a SNP to be analyzed. Methods for the design of sequence specific primers and probes are known in the art (see e.g. William B. Coleman, Gregory J. Tsongalis, Molecular Diagnostics: For the Clinical Laboratorian, 2007; Weiner *et al.* Genetic Variation: A Laboratory Manual, 2010).

Typically, a SNP is considered in the genotyping analysis if it occurs in a certain percentage in the population, for example in at least 5 % or at least 10% of the population. In other words, the minor allele frequency (MAF) is larger than 0.05 or 0.10 (MAF > 0.05 or MAF > 0.10).

For the SNP genotyping analysis a nucleic acid or DNA sample from a subject or patient may be used. The nucleic acid or DNA sample can be a blood sample, a hair sample, a skin sample or a salvia sample of the patient. Any other sample obtainable

from the patient and containing patient nucleic acid or DNA can also be used. The sample can be collected from the patient by any method known in the art. For example, a blood sample can be taken from a patient by use of a sterile needle. The collection of salvia out of the mouth and throat of the patient can be performed by use of a sterile cotton bud or by flushing said area and collecting the flushing solution.

Usually, the nucleic acid or DNA is extracted or isolated or purified from the sample prior to SNP genotyping analysis. Any method known in the art may be used for DNA extraction or purification. Suitable methods comprise *inter alia* steps such as centrifugation steps, precipitation steps, chromatography steps, dialyzing steps, heating steps, cooling steps and/or denaturation steps. For some embodiments, a certain nucleic acid or DNA content in the sample may be reached. Nucleic acid or DNA content can be measured for example via UV spectrometry as described in the literature. However, in alternative embodiments SNP genotyping analysis may also be performed by using a non-extracted or non-purified sample.

DNA amplification may also be useful prior to the SNP analysis step. Any method known in the art can be used for DNA amplification. The sample can thus be provided in a concentration and solution appropriate for the SNP analysis.

The analyzed SNPs may be represented by values 0, 1 or 2. The value "0" may indicate that the SNP is present on none of the two homologous chromosomes. The value "1" may indicate that the SNP is present on one of the two homologous chromosomes. The value "2" may indicate that the SNP is present on both homologous chromosomes. Homologous chromosomes correspond to each other in terms of chromosome length, gene loci and staining pattern. One is inherited from the mother, the other is inherited from the father.

In a step (b) of the method for providing a prediction algorithm, a value indicative for CRH activity in each patient is determined.

Steps (c) and (d) of the method for providing a prediction algorithm may analyze the association of the analyzed SNPs with the value indicative for CRH overactivity and/or normal CRH activity and generate an algorithm for predicting the treatment response to CRHR1 antagonists.

In an exemplary embodiment, the group of patients may be split into two sets of similar size and similar values for descriptors such as demographic descriptors or clinical descriptors. These two sets are hereinafter also referred to as "training set" and "test set".

In step (c) of the method of this exemplary embodiment, at least one SNP associated with the value indicative for CRH overactivity as determined in step (b) is identified in the training set.

Further, there can be at least two alternatives for the result provided by the prediction algorithm. First, the result may be a categorical answer whether the patient responds to CRHR1 antagonist treatment or not. Second, the prediction algorithm may provide the answer to which degree the patient responds or does not respond to the treatment. Depending on the desired result provided by the prediction algorithm the way of determining the algorithm may differ.

In the alternative that the prediction algorithm will analyze whether a patient responds or does not respond to CRHR1 antagonist treatment, the values indicative for CRH activity may be provided as logic data variable (Boolean type; 0 vs. 1; true vs. false, high vs. low responder). Therefore, if the test performed to determine values indicative for CRH overactivity provides a data range, the patients may be dichotomized by a threshold into high vs. low responders.

In the alternative that the test will analyze to which degree the patient responds or does not respond to the CRHR1 antagonist treatment, the values indicative for CRH activity may be provided as numerical values.

Typically, SNPs that are modified in a significant percentage of the population are used in the method for providing a prediction algorithm. For example, only SNPs with a minor allele frequency (MAF) greater than 0.05 or 0.10 may be selected for further analysis. This means that only SNPs that are modified in at least 5 % or 10% of the population are selected for further analysis.

Association for all SNPs with the value indicative for CRH activity is tested by an association analysis testing the likelihood for a patient to be CRH overactive vs. CRH non-overactive in dependence of the genotype of said patient. Said association analysis may be conducted for example by an additive genetic model and/or by a logistic regression. A SNP is e.g. identified to be associated with a value indicative for CRH overactivity if the corresponding p-value is at least 1 x 10^{-3} or at least 1 x 10^{-4} or at least 1 x 10^{-5}. The lower the p-value the more the SNP is associated with a value indicative for CRH overactivity. Accordingly, a SNP is e.g. identified to be associated with a value indicative for normal CRH activity if the corresponding p-value is at least 1 x 10^{-3} or at least 1 x 10^{-4} or at least 1 x 10^{-5}.

In the step (d) of this exemplary embodiment, the algorithm for predicting a treatment response to CRHR1 antagonists may be determined by the use of SNPs in the test set by a machine learning method.

The term "algorithm for predicting" as used herein may refer to a classification function (also known as binary classification test).

The term "machine-learning" as used herein may refer to a method known to the person skilled in the art of machine learning. In particular, machine learning is concerned with the design and development of algorithms that allow computers to evolve behaviors based on empirical data, such as from sensor data or databases. It may be selected from the group consisting of artificial neural network learning, decision tree learning, support vector machine learning, Bayesian network learning, clustering, and regression analysis.

The term "reliable prediction of the treatment response to CRHR1 antagonists" as used herein may refer to a high performance of the prediction algorithm. The evaluation of the performance of the prediction algorithm may depend on the problem the algorithm is applied for. If the algorithm is used to identify patients that are likely to response to the treatment with CRHR1 antagonists the performance is usually expressed by a high accuracy and/or sensitivity and/or precision. If patients should be identified which are likely not to respond to the treatment with CRHR1 antagonists, specificity and/or negative predictive value are typical statistical measures to describe the performance of the prediction algorithm.

For optimizing the prediction performance of the algorithm, the step of determining the algorithm by a machine-learning method in a first subset of the test set and testing the prediction performance in an second independent subset of the test set may be repeated based on different numbers and groups of SNPs, until the desired prediction performance is reached.

Accuracy, sensitivity, precision, specificity and negative predictive value are exemplary statistical measure of the performance of the prediction algorithm. In the following, examples are given for determining the performance of the prediction algorithm.

As used herein, accuracy may be calculated as (number of true positives + number of true negatives) / (number of true positives + number of false positives + number of true negatives + number of false negatives), e.g. (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist + number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). The accuracy of prediction may e.g. be at least 60%, at least 70%, at least 80% or at least 90%.

A used herein, sensitivity may be calculated as (true positives) / (true positives + false negatives), e.g.: (number of patients correctly diagnosed as responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). The sensitivity of prediction may be at least 60%, at least 70%, at least 80% or at least 90%.

As used herein, precision (also referred to as positive predictive value) may be calculated as (true positives) / (true positives + false positives), e.g.: (number of patients correctly diagnosed as responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist). The precision of prediction may be at least 60%, at least 70%, at least 80% or at least 90%.

As used herein, specificity is calculated as (true negatives) / (true negatives + false positives), e.g.: (number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist). The specificity of prediction may be at least 60%, at least 70%, at least 80% or at least 90%.

As used herein, negative predictive value is calculated as (true negatives) / (true negatives + false negatives), e.g.: (number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). The negative predictive value may be at least 60%, at least 70%, at least 80% or at least 90%.

Other statistical measures useful for describing the performance of the prediction algorithm are geometric mean of sensitivity and specificity, geometric mean of positive predictive value and negative predictive value, F-measure and area under ROC curve, and the positive and negative likelihood ratios, the false discovery rate

and Matthews correlation coefficient. These measures and method for their determination are well known in the art.

In general, a prediction algorithm with high sensitivity may have low specificity and vice versa. The decision to select an algorithm having certain statistical characteristics such as accuracy, sensitivity or specificity may also depend on the costs associated with a treatment with a CRHR1 antagonist should the prediction be positive and/or whether such a treatment is detrimental in cases where the result is a false positive.

For a prediction whether a patient likely responds to the treatment with CRHR1 antagonists the prediction algorithm may be based on a number of SNPs sufficient to achieve a prediction sensitivity and/or precision of at least 55%, optionally at least 80%.

For the prediction whether it is unlikely that a patient responds to the treatment with CRHR1 antagonists the prediction algorithm may be based on a number of SNPs sufficient to achieve a prediction specificity and/or negative predictive value of at least 55%, optionally at least 80%.

For a prediction whether a patient responds to a treatment with CRHR1 antagonists or not the prediction algorithm may be based on a number of SNPs sufficient to achieve sensitivity and/or precision and/or specificity and/or negative predictive value of at least 55%, optionally at least 80%.

In one embodiment, a number N of SNPs is associated with a value indicative for CRH overactivity or normal CRH activity in step (d) of the method for providing an algorithm and/or the presence or absence of a number N of SNPs is determined in step (a) of the method for predicting a treatment response, wherein N is sufficient to provide an accuracy of at least 80% and a sensitivity of at least 70% and a specificity of at least 70%. In another embodiment, a number N of SNPs is associated with a value indicative for CRH overactivity in step (d) of the method for providing an

algorithm and/or the presence or absence of a number N of SNPs is determined in step (a) of the method for predicting a treatment response, wherein N is sufficient to provide an accuracy of at least 85% and a sensitivity of at least 80% and a specificity of at least 80%.

Typically, at least 10, at least 20, at least 25 or at least 30 SNPs are used for determination of the algorithm in step (d) of the method for providing a prediction algorithm.

The skilled person in the art knows that the use of different machine-learning methods and adapting parameters used therein can be also used for improvement of the prediction reliability. The whole statistical work-flow can be automated by a computer.

Another aspect is a method for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms, wherein the method may comprise the following steps:

(a) determining in a nucleic acid sample obtained from a patient the presence or absence of at least one single nucleotide polymorphism (SNP) associated with a value indicative for CRH overactivity;

(b) predicting the treatment response to CRHR1 antagonists by linking the prediction algorithm provided by the method described above with the presence or absence of the at least one SNP determined in step (a).

"Linking an algorithm for predicting a treatment response to CRHR1 antagonists in patients having depressive symptoms and/or anxiety symptoms with the presence or absence of the at least one SNP" as used herein may refer to using such an algorithm to predict the treatment response based on the determined presence or absence of the at least one SNP, e.g. by integrating the at least one SNP determined in step (a) of the above method by the algorithm.

In one embodiment the method comprises a further step of obtaining a nucleic acid

sample from a patient preceding the step of SNP determination.

In one embodiment of the method for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms, step (a) comprises determining at least one of the SNPs, optionally all of the SNPs which were associated with a value indicative for CRH overactivity when determining the algorithm by machine-learning from this association.

Typically, a SNP is considered in the genotyping analysis of step (a) of the method of prediction if it occurs in a certain percentage in the population, for example in at least 5 % or at least 10% of the population. In other words, the minor allele frequency (MAF) is larger than 0.05 (MAF > 0.05) or 0.10 (MAF > 0.10).

For the SNP genotyping analysis of step (a) of the method of prediction, a nucleic acid or a DNA sample from a patient may be used. The nucleic acid or DNA sample can be a blood sample, a hair sample, a skin sample or a salvia sample of the patient. Any other sample of the patient containing nucleic acid or DNA can also be used. The sample can be collected from the patient by any method known in the art. For example, a blood sample can be taken from a patient by use of a sterile needle. The collection of salvia out of the mouth and throat of the patient can be performed by use of a sterile cotton bud or by flushing said area and collecting the flushing solution.

Usually, the nucleic acid or DNA is extracted or purified from the sample prior to SNP genotyping analysis. Any method known in the art may be used for DNA extraction or purification. Suitable methods comprise *inter alia* steps such as centrifugation steps, precipitation steps, chromatography steps, dialyzing steps, heating steps, cooling steps and/or denaturation steps. For some embodiments, a certain DNA content in the sample may be reached. Nucleic acid or DNA content can be measured for example via UV spectrometry as known in art. However, the SNP genotyping analysis may also be performed by using a non-extracted or non-purified sample.

Nucleic acid or DNA amplification may also be useful prior to the SNP analysis step. Any method known in the art can be used for DNA amplification. The sampled can thus be provided in a concentration and solution appropriate for the SNP analysis.

The analyzed SNPs may be represented by values 0, 1 or 2. The value "0" may indicate that the SNP is present on none of the two homologous chromosomes. The value "1" may indicate that the SNP is present on one of the two homologous chromosomes. The value "2" may indicate that the SNP is present on both homologous chromosomes. Homologous chromosomes correspond to each other in terms of chromosome length, gene loci and staining pattern. One is inherited from the mother, the other is inherited from the father.

In order to determine SNPs, SNP-specific primers and/or probes, a primer extension reaction, SNP microarrays, DNA-sequencing may be used. These reagents and methods are routinely used in the art (see for example Chen, PCR Cloning Protocols (Methods in Molecular Biology) 2002; Schuster, Nat. Methods, 2008, Rampal, DNA Arrays: Methods and Protocols (Methods in Molecular Biology) 2010; Brenner, Nat. Biotech., 2000; Mardis, Annu Rev Genomics Hum Genet., 2008). For example, MALDI-TOF (matrix-assisted laser desorption ionization time of flight) mass spectrometry on the Sequenom platform (San Diego, USA) may be used to genotype the selected variants. For primer selection, multiplexing and assay design, and the mass-extension for producing primer extension products the MassARRAY Assay Designer software may be used using the sequences presented in table 2 as input. The MassARRAY Typer 3.4 software may be used for genotype calling. Any other reagent or method known to the person skilled in the art may be used in order to detect the SNPs in an individual.

In one embodiment, at least one SNP determined in step (a) and used for the prediction algorithm of step (b) is a SNP selected from the group consisting of SNPs as shown in table 2 and an SNP in strong linkage disequilibrium with any of the SNPs shown in table 2.

Table 2: SNPs (together with flanking sequences) which may be used to predict the response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms. The position of the SNP is indicated in bold as **[wild-type allele/mutated allele]**.

SNP_ID	SEQUENCE
RS6437726 SEQ ID NO. 1	CAAGAAAGAGAGTAATAAAAATAACCACAATGAGGGCTCTCATTAATACT GGATCTTATGGAAACCAATTGTTCAGTCCCTCAACAAAAGACCAGATGG GCAGGAAGCTAAATATACACCATGCACTAAACATTATGAGTATCATAGTT TACAAGTCAAAGGGGGCTCTATTGAAGATAGTTCTATTTTCCCTCTATAT T**[A/G]**TCTGCTAGACAATACCTGATAACATTATCCAAGTAAATGACAACTT GATAAATAGTAATTTCCAATGGTGAACAGAGGTGACATTTCCTCATTACA AAAATATTTTCTTTGGCAGATGAGATTAACTGAATAAGAAATCCACTGAC ACTGAAATCACAGAGCCAAATTCCCTATCACAGCACTTATCACATTGCGT TAGG
RS1986684 SEQ ID NO. 2	TTCCTTGTAGCGGGGAGAGAGACTCAGGGAAGGCAGGGTGATACCTGA GTTGGGGCTTAAAGCAAGGTAGGGTGTGTGTGGTGATGGCAAAATAGG TAGGAAGACAGCACGGGCAAAGTCCTGGAGGCAAGGACAGAAAGAGGA AGTGGCAGGAAGTGAGGCTGGGGAAATGAGTAGGGGTCAATCATGATG TTTCTGGT**[A/G]**TAGGGAAGAGTTTGGAATGCATCCTCTAGGCCATACGC CATTGGGGGCTTTTAAGAAAGACAGTGATGTTGGTTTGATTTGCATTTTA TATAGACTTTTCTGGCAGCTGAGAGGAAGGTGGTTTTGAGAATCACAAA GCTGCGGGAAGATCAGTCAGGAGGGTTCTAGAATAATCCAGGCAAGAG CTGATGGGGACTGAG
RS7380830 SEQ ID NO. 3	ACAGGGGTGGCTACTCTTTCTCCAGAAATAGGTGTCCTGTGGGGCATTT TGAAGTAGAATGTTGATAGTTGCTTTCAATTTTAGACTGGTAAATAAGAAT TGGGCATTTGAATTTCAATATACTCACTGTGTAACTGTTATTGAGTATGCT TTAAGTGACCTATAATACTGCTTCATTTAACTTTATTGTCCTAATAACT**[C/T]**TCTTAGAGTGACAATAACTTAGGTTAGCCACTTGCCTAGGGTTCTGAA ACCAAGTAAATGGTGGAGCTGGAATTGC**T**GTTCTTGTCAGTCATTAGACT AGATCGGTTTTCTTCTTCCTACAAATTTTATATACTAAAAAATTTTGAAAAA AGACATTTT**T**CTTTGGGAAAAATAGGGAATGTCAGATCCCTTTGGAGATG
RS3903768 SEQ ID NO. 4	CTCGCAGCAACCAAGCCTGCCCAAGCCGGGGAAACCTGGGGAGCAAAC CTTCACCTGCACTGTACATCAGAGACCAGTTGGCCCTATTTTGGCTCCT GTGGACAGGTAAGTATCCCTTTTGACTCATCCCCCAAATATCAGGTGAG CCAGGAAAATAAGGCCTTTGGCTTAGACAGTCAATTCAAAGTCTGCCAT AGCAT**[A/C]**CCTAATTACATCCCTATTGCCCCTTTTCTAGGTCGTTTCTCC TCTAACACGATTTTATTTTTCTGTCAGCCATTTTATTTTATTTCTCACCTTG AAATATATGTTTTCTTTGCAGTTTTTGCTTTGGCTTCCTGCTAACTCTATT TGGGCAATTGTTTAAGGCTGAACACTTGGTTATGAGAGGTACCCTGTTG TGTTGA
RS7325978 SEQ ID NO. 5	TCATCAAGTCTCCTTTTTCTCTAGGAAAAATAACATTGTCAAGGTTATTAA CAGTCAATAAGCTGTCATAGGCTCAGCATGGATGGGGATATTGGGTTTC CTTGTGCTTATATGAAAGATGGGAAAATCCGAAGTTCTTTTCACCCTGAT ATGGAAAATACCCAACATGAGGAGAAGCAGCAGCTATATGATTCTGAGC A**[C/T]**AGAATGGGAGTAAGAATAGGGTCATGCTGTACTGATTATCTGCTA ATAAAATGCAAAAGTGTTAGGTAATTTCATCAATATCCAGTTAATACTAAT ATAGTTAATATTTCATGACTGGGTAATATTTTATAATGATAAATATTTTTAT AGATCTTAGCTCTTTTTATTCTCATATCAACTGTATGAAATCAGTGATTGG T

SNP_ID	SEQUENCE
RS13585 SEQ ID NO. 6	CTGGGGACCTCAGGGAGAGGTACGCAGGTTGCCATGGCTGCGTCTGCA GTCCACCTGCCTTTCCACGCCAGGGAGTCAGTGATGTGGAGCCCCCTG GGCCCCAGTGGAAGCAGCGATCAGACTATGTGTCCTTGAAATAATGTTT ATTCCACGCTGTCCCGACAGCCCCCTCTGCAGGTCCCCT**[C/T]**GGTGTA CTCTGAGGTGGGAAACCCTCCCTGGGGGCGGTGAAGGGGAACTCGGG CCACCCCACCAGCCAGCAGATGCTCCAGCAGCCAGAGCCCCAGCCTGG AGCTGAGGCTCTTCCTGGGGCTCGCCGGGCCCCTGCAGGCTTTTCGGA CCCTCAGCCAGCCCGGCTTCCTCTGCTTTGGGCAGCAGCAAGCTGGCC CTT
RS9368373 SEQ ID NO. 7	TTCCTGTGCCTCAGCTCCTCTGTAGAATGGTGCTGGCAATACAGTTTGC CTCATTGGGCTCTTGTAAGCTTTAAATAGGTTATTATACATAAAGAGCTA ATAGTGATGCCTGTAGCCGTTGTCTAAGTGCTAGCTCTGATGATGGTGA CAAAGAAGTAATAGCAATCAGTGGTTTAGATTAAACCATTTTAGGCATAA AC**[C/T]**GTTCTGCTAGAATCCAAGGGGAGATTTTTTCCCATCAAGGAGAC ATAGCTTGTTGGGAAGATAAGACATACCCAATTGCAGAAGTAATTAATTA ATTCTTTTTTTTTTTTTTTTTTTTTTTTTTTGCGATGGAGTTTCGCTCTTGTT GCCCAGGCTGGAGTGCAATAGCATGATCTCGGCTCACCACAACCTCTG CCTCCT
RS10935354 SEQ ID NO. 8	ATAGGCCCTATACAGCTCTCAATTTCTTTAATCAATCTTCCTAGCAGCCC GTGAGAAATATTACTGTCTTCAGCTTCCTAAAGGAGAAAACAGAGGCCT GGAGGGATTAAAAGACTTTTCTAAGATTTTAGAGGGCATGTTAGGGTTCA GGCCCAGGGCTGTCTAACCCAAGGCCTAATTCCTTCTATTACATCCATC AT**[A/G]**CATGAGTGAGCACTGGGCATGAGGATACGTCAGTGAAAGGGGC CCTGTAACATGGACCTTACATTTTGGCTGGGGGAGACAGGCAATGAATA CATAGGACCATGTTGGGAAGTGCTAAGTACTCTGATGATAACACAGCAG GGTGAGGTGACAGAGGTCTAGGGAGAGTGGTGTTCAGCAAAAACTTCT CTGGGGAGAGA
RS8095703 SEQ ID NO. 9	AAAATTTACCAGGTTTAAAAAAAAAAAAACTCAAATGATATTTCAGAAACC TACCCCTTTCAAAACAAGGAGGAGAAAAATCTTCTCCACAAAAGCACATA TTGAAAAAATATTTTGGGGGCAAGGCCTGAAAGGGTTGGCAGTGTGCAG TTCTGTTATTATTCCCGTGGCCATTTTATGGGCCTCAGCAAAACACTGGG **[A/G]**TCATTATCTGTCTTCTGGTTACTCCAGGAGAGCTAGCCATCACAAC CCAATGGAAGAGACTTCAGAGAAACCCACACAGGCACCAGAAGTCCTTC CCTTTCATCTGCCACTGTGGGGTTTTGTCCTCATCTATTACAATGTTGTC CAATCTCAGACTGCATTCAGAACAAAGGCTCTCAGACTGAGGATGAGTT CTTGGA
RS10206851 SEQ ID NO. 10	CCAAATAATTGTTATTGTTGTTTTAACATGGCAATCACGTTATTTGCCATA TGTGAAAAAGAATATTTAAAATGCTTTTTAAAACTATGTATGTAAAAGAAT GTTTAAATTGTTTTAAAAATATGTTATATCTACCTTGGCACCATCCTTGCT GTTGAGAAATGACTTTTACCTGCTTACTTAGAAGGAAATGTCAGAAG**[C/T]**AGAAGTACATTTGAATACGATTATTTGAAAGCTTCATCCATTTTTCAAAG AATGTATACAGTAACACTAAATAGAAAGCATAGTTTATCAACTCTTCACTA AGAACAGTCTAGCAAGTATATCAGAGTGGCTGTGGTTCCAGTTGGACTA ACCTAATCATTTATGAAAAGGTGATAATAAGCTTGGACCAAGAGCACCCA
RS9542977 SEQ ID NO. 11	CAGATGTTATGTGAAACTCTGGAGAAATAGTAGCAAGCAAGACTCACAT GCCTCCTGCCCTCACAGAGCTCCATGATCTGGTGAAAGTGCCAGATATT TAAACCCATGGATGTGTGCACACAAAATAACAATTCTCTCAAGCGTTGTG AAGAAAAGTCACAGAGCACTACAAAAGCATGTAAGAGTGAGGCAAAACC TAT**[C/T]**GTGTTAGGACAGGGAAGGCTTCTGTGAGCTAACCTGAAGGAT GAGTAGGGGTGAGCCAGATGAAAAGGCGAGAGAAAAACATTCTGAGCA GAGACTGCCACTGAGTGCATCCCAGTTTTCCCAACATCTTAACACTGTAT AATGACTACACTGGATTTTCTTCATCCTGGATCCATGGTTAGACATGTTA ATATGCCTTC

SNP_ID	SEQUENCE
RS4942879 SEQ ID NO. 12	CCCAGTCTGTGGTATTTTTTTATAGCAGCACAAACAGACTAACACAAGAG GTGGATAGGATTTGCGAGCATGGACCTTGGAGGTTTGTGGCCTCAATTT AAAGTGAGTACATTCACCCAGCTGGTGTTTTTCTCTTGCTGCTTGGGCA CAGAGATGGAGTAAATGGGTCTAATCAAGGATAAAGGGAGAGCCAAAGA GAT**[A/G]**GTAATATTTGAAAGGAAGTGTTTTTAATGATGTGCCATGTAATC TGAGCTGGGTCAGGAATGAAGTGAAAAACTAAGAGATGATGGATGATGA TAGGGGCTGTGAAAGGAAAACAAATCTTGGGGCCCCCAAATCACTAAGC TAAAGGAGAAAGTCAAGCTGGGAACTGTTTAGGGCAATCCTGCCTCCCA TTTTATTCA
RS9542954 SEQ ID NO. 13	TATTACTGCTGAGAAAACTGGGTTTGATAAACTAAAGATGCCCATGTATA TCAGTCATGCTCCTGGTGAGAACAGGTGGCTCACTGCATAATGAGAGGA ATATTCAATTAACTATTTACAAAGCTATGGATGACATGTAGGGAAGCCAC AGAGAGAGTACAGTATCTAGAGCTAGTAAGAGTAGAAGGCCATCACTGT CC**[A/C]**CAGGCCTAAAGGAGGTAGAGCAGTCAAAGGAAACAAGAGACAA GGGAGGCTGCGAGGACAGGGCCACCTGGCAGAGCCATAACCTTAAACT AGGTAGTCACTTCTTGGCAACTCTGCAGGTAGGGAGCCAACCTCACTTT TAACCCTCCCTCTGATGCCCAGCTGGTTTACCCCATTGGTGAAAATCAG TGGGTGAGGGA
RS1593478 SEQ ID NO. 14	CATGAAAAGATACTTAACATTGTAACATCTTTGCATTAGGGAACTGCAAA TCAAAATCATAACAAAATAGTACTGCATGCTCATTAGGATGACTATAATC CAAAAGAATAAAAAAGAAAATAACAGGTGTTGGTAGGGATACAGATATAG AGAAACTGGAGCTCTCATGCCTTGCTGGGGGGCATGTAAAATGATTCTG C**[C/T]**GCTTTGGAAAACAGTTTGGTGGTTCCTCAAAAAGTTAAACATATAA TCCAACAATTCCACCCAAAAGAATTGAAAGCAGGGTCTAGTACACCAAC GTTCATAGCAGCTTTATTCACATCAAGCCAAAGGTGGAAGCAGCCCAAA TGTCTACTGATGGATGAGTTGATACACAAAATGTGGTATATATATGCAAT GGAATA
RS9542951 SEQ ID NO. 15	GCCACTTGAATGCCCCAAAATGGAGAGA**T**GGGCGTGGGAAGAGAAAGA CACCTCAGCAACACAGAGCTGAGAAAACACTGTGAGTTTTATTTAATTCC TACTTACCGTTATTTTGCATAGTAAACAAAAGGGATATTTTTGAAAATCCC TTTGGATAATTTCTGCCACCTAAAATTCTGAGCATTTTGACTCACTGCCTT **[A/G]**TAAAAAGAATCAATTAATTGAATAAGAGAAGGGATTCTCCCCTGAT CTTTTCAAGAATCCTTAAAAGGCACATTTCTCACTAAGGATCTTGAAAGT GTATTTCTAGCCAATCCCAGGAGTCACTGCTCAGAGATTTACATTTCACA AATGTAATCAACAGCCTAAGCAGAATATTGACGTTTGGACTGCAGAGCT CTGCT
RS2188534 SEQ ID NO. 16	AGGGTCCCCAAATATTTCCATTTGAGATGACAAAGTGCTCTTCAGTCATT TAGCTTACTCTTCAGTTCAGATGACTTATCATCTTGATTTCAGAGAGTTCA TATATGTCTGTTTTAAAAAACTGGTTCAAAAAGTCTGAAGTTACGAAACTA AACCAAATATGCATTACTCTCATGTCAAATTACAAGCTCTTAGCTGC**[G/T]** GGGATTTTTTCACATGCAGCCTGGAGCCCTTGAAAACCTCTGTTTTCTGT TAGACTCTCCAGGGTACACAGAAGTTGCCTCATTATTTTAGTTAATGGTG ACTGCAAATAAGCCCCCCAAGTCATTTAACTATGTGCTTACCACTGCTTT AAAAGAACCCCAAGTTAGGTCCTCATGTAGGTAAAGGAGCTCCCTTCAC A
RS12524124 SEQ ID NO. 17	ACTTGGGCCCAAAGGCATTCAACTAGAAAGCTGGTAATAATAACAGCGA CAGTTTATTGAGTCTTAGTGTTTCTGAGAACTTTTCTAAGTACTTTACACA TATTAAATTTTTAAATCTTCACATTAGTCC**T**GTGAGGAAGGTACTATTGTT ATGTCTGTATTACCCATGGGGATACTGACGCACAAAGAAGTCAAGTAAT**[A/G]**TATTTAAGATTCTAGTAAGTGCAGAGCCCAGGTGCATGCAGTGCCT GGGCTCTGCCACCCATGCAGTGCTGACTAGGGCTTCCACCCATGGATTT TTTTTTTTTTTTTTTTTTTTTGAGACAGAGTTTCGCTCTTGTTGCCCAGGC TGGAGTGCAATGGCATGATCTCGGCTCACCACAACCTCCGCCTCTCGG GTTCAA

SNP_ID	SEQUENCE
RS4352629 SEQ ID NO. 18	CCCATAATAATGAAGGATTGGACCTGATAATCTATCAGGTACATTTTAGC CTGAAATTTATTTGTACACACGCACAAACACAGACATGTGCACACACACA TACACATATATATATAACATTTATAAATTTTAAAACATAAAGCTATACTAGA AATGAAAGCTTATATATTGAACTGCCCCACCTTTCTATTTGCAGCCAG**[C/** **T]**TACCACCCCAGTCTAATGTTTCACTTTATATAAATTCATTTATTCTTTTA CTCATTTCAAATATATGATGATGTAACTATAAAATCAACATTTAGTCACTC TGAATAACCCAAAATAGCAAATAATTTAAAAATCACTTCCACTTGACTTTA GAATCTATTACATGCATTGTTTTTCCAGAAAATTTACCTCATAATTAT
RS7448716 SEQ ID NO. 19	CTACTTATATGATTAGAGAACAAGAATACTAGGGGGAAAATCAGCATGCA TATAATCTAAGAAATTGTCATTATAATTTTAAAATCCTTTGCAAAATCAGTA AATATGAGTTTAACTTATATAATGATACACACACACACTGATATGATGCTT TATTGTCTAAACACTGGCTGCTTGTGGAGACGTATTCTGGTAACAAA**[A/G** **]**AATATAGCATCTTAAAATTGATGCTAGCATTGTATATCCAAATAGAGAGT AAATGCAACCAGAATATTTTTTATATGTTTAACATTGTAGTGTTGCTGACA TCATTATATATTTGGTTATGTTAATCTCAAAATGCACAATATAGCTGTATG ATCTGTATAATGCAAAAAAATGTAGAGCTTCATTTTGATATTTATTAT
RS11873533 SEQ ID NO. 20	CTGGAAGGGAACAATGGAAGAGGTGCATTAGTCACATTCCAAAATGCAG GAAGCAATAACATGTGGCACTATTGTCATTTATGTAGCACCCTAAATACT GGGACAAATGACATAGATGCCCTTCTGTGATTACTAAACTCCCCCACAG TGTCTCAGAAGGAAGAGCTTTTGACAGGAAATCATCAAGATCTGATGAC ATT**[A/C]**GAGAGCAATTAACATTCTCTTCAACCATGAACTAATTGCCTCAT TCACATTTTTCTAGCCATCCTAGGAAGCAGATAATAAGCAGCAATTGTCC TGCCCAGGAATTCTGACTTGTGTAATTTGTAAAGCTTTTCTTTGTATCTAT TTCTTTCCTGTGGCCATCTTTTTGTTTTTGGACTGTTTGGTAACAGTAAGT GGGT
RS10062658 SEQ ID NO. 21	ATCATTCAGTATTAAGAGAGAAATGAATACATTTTCAGATATACAAGAATT CAGTTTACCTCCCACAGAATCTCTGAAAAAAATATTAGATTACTATAGTTA AAAAGGAAAATAAAATAAGTCCTGTTAGAAATAATTGGTAAAAAAGCAAA GGTGATGAAAACTTATTGAAATATATTATTAAAGTAATTGTTAAAAAT**[A/G]** TACACTAAATCTAGAATATATAAATGTAGCAGTTGTTAAGGGGAAGGGGA AATAGAAGTGGAAGAAAATGAACATTAGAACAAATGTTTAGCAGTGGGAT TATTTTATTGGAAGTCTAATGTAAGAAGTATATTCTCCAGGGAGGTATTT CAAGGACATATGAATAGTAAAGGGATAATAAAACAACTCTATAAGGTAGT
RS12547917 SEQ ID NO. 22	CACACACAACGCTGGGCCCAGTAAATAAGTTTTGTTTTTTCCCAGGGAA AAGTTGAACAACAATGGTGAGACCAGGAAGGCTCTCCGTTCACAGGAAA TACTGTGTCACCGCTCGGCCGCAGGCTGTGTGAGGTCACGGGCGACGC TCGGGTCACGTGTGGCGGCTCCTGTTCACAGTGCCGTGTGTGATAAACT GGGAC**[C/**T**]**TTCTGGTGAGGGGAGACTGGCGGGGGGTGGGGAGGGCA AGGAGTGGGAAAGTCGCCTATAAATGTTTAACAAAAGATCCGCAATGGG AACAGGAACTTGCATTCTTTCTTTCAATGGACAAAGCTTCCACATCAAGA TACGCTTGTGTGCTGGGACCAAATGCCACAGTGCGGCGAAACTCGTGA GCACAAGTCCTGCGT
RS1038268 SEQ ID NO. 23	ACAACAGGGTATCCTAGCCCAGCAAAATTGACTCATAAATTTAATGATCA CGCAATTGGTAATTCTAAATCCAGTCAGAAGTCTACATTCTGTGTCCACA GTGTCATGTCTAGATGTTGGTCCAGTCTCCCATGGACTGTGCCTTGTTAT TTGTTTTCTCTTTGCTAAGCCACATCCCCTGAGGGCTCTGTTTATGCTCA**[** **C/T]**TGCAAAATCTTTGACTTTTTAACTTACTGGGCATATTGTCTTCCTACT TTTGTTCTCTTCTGTTATTTTATTTACTTGACTCTGACATGTCTCATTCCC

SNP_ID	SEQUENCE
RS2375811 SEQ ID NO. 24	TTTCAATGGGACTGGTTGGACAGTGGGTGCAGCCCATGAAGGGCAAGC CAAAGCAGGCCGGGGCATCACCTCACCCGGGAAGCACAAGGGGTCAG GCGATTTCTCTTTCCTAGTCAAGGGAAGCCATGGCAGACTGCACCTGGA AAAACGAGACACTTCCACCCAAATACTGCGTTTTTCGCAAGGTCTTAGCA ACTAAC**[A/G]**GACAAGGAGATTCTCTCCCGTGCCTGGCTCGGCTGGTCC CACACCCACGGTGACTTGTTCACTGCTAGCACAGCAGTTTGAGATCGAA CTACGAGGCAACAACCTGGCTAAGGGAGGGGCATCTGCCATTGCTGAG GCTTGAGTAGGTAAACAAAGTGGCCAGGAAGCTCGAACTGGGTGGAGC CCACTGCAGCTTAGCA
RS1352671 SEQ ID NO. 25	ACTTTAGGGACTTTGAGTGATGGACAACCCCCTATCAGATATCATCAGC CTGAAACATCCTTATCTTGGCATTAAATTAGAAGGAACCCCAGACCCTGC GTACCAGAATTGTTAGAATCACAGTCTCAGTAAAGAACCAACTCCTGATC ACTTCTCTAAAGGAAAGTTCTAGAAGTCTGCACACTCTGCAGTCACTTTC A**[A/C]**TTCTATCCAAGTGTACACTTAGAACTCTAGAAAACACTACGGACA GTCTTCAGCCAGGTAAAGCCTAAAACCAGCAAAGAACAGGGAGAGTGA GGGA
RS364331 SEQ ID NO. 26	CGGATTATCACAGTTCTCAAAAGAGGAGTATGCATTTGCTTGCTCCAATT CCTCTTCTTCTACACTCTCTTAAGCATTCCTCAACCAGTCTAATATCTCAT AGTTCCCCAAAACTGCTCTGTTCAAGACCATTAGTAAGATCTTTGATGTT AATCTGTGGACCGTATCTCTGTCCTTATTTTACTTGAAGCCCAACAGCA**[A/C]**ATAAAAAAGTTGTTCTCCTCTCCTCCCTGCTACACTTTCCTTATGTG GCTTGCTGGGCTCCTCAGTCCCCTGTGAAAAACTCTGACATGGAGATAC TGCAGACCAGTAGAAGGGCTGGGCAGACACTATACAGAAACAGTATGC CCTACATGCTCCTTGGCTAAATCTCTAGAATTTTTTTCAGAACTCATCCA CAAATT
RS1924949 SEQ ID NO. 27	ATTTTATCTCATTTACTTATTAAATCAAACCAATATTTTATGAAGTGATTCC AGTATTGGAATAAAAATGTAATTCTTTAATCATTAAAAAATCTTTATGAATA CCTTACATCAACTGTAGGGGACCAACCAGGGAAAAGCAGGGAGACTTG TAGAATCTACACCTCCAGAACAACCGACCTCCATCTTCTGGACAACTC**[A/ G]**TCTTCTAAAGTGCAGGACAGACTAGTTGGGGGAGAAAGGAGGAAATG AAAGAGATAGACTAAAAGGGAGGGAGAGAACAGATATTTTTTAAGTACC TGTTATGTTCTGGATACAGCACAGAGTACATTGTATCTATTATTATAAGG CATAAAGAAAGATTTCTCAGGTTTTTGGAGTCAGATTGCAATATAAAATA ATAG
RS11025990 SEQ ID NO. 28	TAACTTCAAATTGTTTTGCAAAATCTCTGTCATAAAAATGCTTACCAACAA ATACTGATACTAAATTTAGATGTGGGGGTATTAGTTATAATCCTGAAGTG GGAGGGGGAACTTCTTAATTCCAATTTAGTTCTAAGAGAAGGAAGAGTA TTTAGGCCCAGAGAAGGTTACGCTTAAAGGTCTGATAGTGTTTTCTTTGA **[A/G]**AAATATGTCTCAAACTAGAGAATAAAACTAATTATCTCATCTAAGTT ACCTAGAGACATTTATGCTCATCAGTTTGATAAAGGACTGCAAGTAGACA CAGAAGCTGTATTTTCAGTCTTGAACCCAGCAATAGTACATTAACAAGAT TGGGGCAAGGCAAAGGGACTTTTGTGGCACAAGATACAATATATGGATT GCGT
RS3758562 SEQ ID NO. 29	CTCTTCAAAGGCCTTTGCCCTTGGGTACCACAGGTTCTGAGACAAGAGG GCTATGGAGAGCCCCCATTATAGCTGGAGCCTCCTGCCCTGCCCAAAG GTGTGACTTGAAGGGTGGAATTTCAGGCAGCGTGGCTCGCCCCAGGGA GGCAAAGAGGCCAGGGGAATCTTCAAAGGCCCTGGGCTCATCCCAGCT AGGAGGC**[A/G]**GGCACAGTCATAACCCTAATCCAGTGAACTCAGCCCTC ATCCTGACTCTCATGGTATTCTGTCCCAGGGAGCCTCTTTCCAGCTTTCT TAGAAGCTTTAATGTCAGCACTTGCAGGGCCTTAGAAACTGCACGCTAC CTCTTCATTTCATACATGAGGAAACTGAGGCCCAGGGTGGACACAGGGC TGCCCAGCGAGTTA

SNP_ID	SEQUENCE
RS10156056 SEQ ID NO. 30	ATTATAAAGCAAAGCACTAACCTCATAGAATACCTGAGTCAAGTTCCCTG TGTTCTCATTTTCTAGCCTCTTCTACCAGACACTATGAAAAATAACAGCC CCATCTCTCCAGAAAATCTTAGGAGATATAGGCGTGCTGAATTTAAGGT GTCTGTGGCACATGCAAGTGGATCAGCCACTGGGCTGTCCAGAATGCA AGA**[C/G]**AGAACTCAGAGTTGGGGACATAAACTTGGCAGTCATCTGTGTA AAAGAGAAAAGGTAGGTAAAGTCCCACAAGGATGGGTTGGCCTACAGAA GGCACAGAGAGAAGAGAGCCTGGTTTAGCATGGGCTACGATCAGAGTC CCTGGGTTCAAATCTTGGCTCCACCCATTTCTATCTGGTTGCTCTAGGG CATGTTACCTA

Polymorphisms in linkage disequilibrium with a SNP of table 2 can be identified by by methods known in the art. For example, Develin and Risch (Genomics, 1995) provide guidance for determining the parameter delta (also referred to as the "r") as a standard measure of the disequilibrium. Gabriel *et al.* (Science, 2002) provides instructions for finding the maximal r^2 value in populations for disease gene mapping. Further, Carlson *et al.* (Am. J. Hum. Genet. (2003) disclose methods for selecting and analyzing polymorphisms based on linkage disequilibrium for disease gene association mapping. Stoyanovich and Pe'er (Bioinformatics, 2008) show that polymorphisms in linkage disequilibrium with indentified SNPs have virtually identical response profiles. Currently, several databases provide datasets that can be searched for polymorphisms in strong linkage disequilibrium, which can be accessed by the following addresses: http://1000.genomes.org, http://www.hapmap.org, http://www.broadinsitute.org/mpg/snap. An example workflow for determining SNPs linkage disequilibrium to a specific SNP is outlined in Uhr *et al.* (Neuron, 2008).

SNP in strong linkage disequilibrium as used herein means that the SNP is in linkage disequilibrium with an r^2 higher than 0.7 or higher than 0.8 in the tested population or an ethnically close reference population with the identified SNP.

In another embodiment, at least 20, optionally at least 25 or at least 30 SNPs selected from the group of table 2 are determined in step (a) and integrated by the prediction algorithm in step (b). For example, all intergenic SNPs of table 2 are determined in step (a) and integrated by the prediction algorithm in step (b). In another exemplary embodiment, all SNPs selected from the group of table 2 are determined in step (a)

and integrated by the prediction algorithm of step (b).

Typically, in step (a) of the method of predicting a treatment response to CRHR1 antagonists, the presence or absence of those SNPs is determined which were identified to be associated with values indicative for normal CRH activity or CRH overactivity and were thus considered when determining the prediction algorithm by machine-learning as described above.

In one embodiment of the method for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms, the method as described above may be accompanied by analyzing the rapid-eye-movement (REM) sleep, e.g. during night sleep of a patient in a sleep EEG.

In other embodiments, an increase in REM sleep may serve as a biomarker to identify patients who would benefit from treatment with a CRHR1 antagonist.

REM sleep typically comprises a characteristic coincidence of nearly complete muscle atonia, a waking-like pattern of brain oscillations and rapid eye movements (REMs). The amount of REMs during consecutive REM sleep episodes is usually increasing throughout the night. Single and short REMs with low amplitude can be characteristic for initial parts of REM sleep. The amount of REMs, in particular within the first REM sleep episode, can be of clinical relevance. Recent clinical and animal data supports the correlation of REM density with an increased CRH activity. For example, Kimura et al. (Mol. Psychiatry, 2010) showed that mice overexpressing CRH in the forebrain exhibit constantly increased rapid eye movement (REM) sleep compared to wildtype mice. In addition, it could be shown that treatment with the CRHR1 antagonist DMP696 could reverse the REM enhancement.

Further, the SNP analysis and REM density analysis as described herein may be combined for predicting the response of patients with depressive symptoms and/or anxiety symptoms to treatment with a CRHR1 antagonist. The REM analysis may be carried out before, concomitant or after the SNP analysis. For example, the REM

density analysis may be carried out on persons that where identified by the SNP analysis as CRH hyperdrive patients.

The recording of a "sleep-EEG" (also referred to "polysomatic recordings") may comprise electroencephalography (EEG), vertical and horizontal elecrooculography (EOG), electromyography (EMG) and/or electrocardiography (ECG). In EOG, muscle activities of right and left eye may be recorded by electrooculograms (one or typically two channels) in order to visualize the phasic components of REM sleep.

"REM analysis" or "analyzing the rapid-eye-movement (REM)" may refer to a method comprising recoding of muscle activities of right and left eye by EOG and then analyzing the electrooculogram. The recognition of REM in the electrooculogram may be done manually (for example by standard guidelines Rechtschaffen and Kales, 1968, Bethesda, MD: National Institute of Neurological Diseases and Blindness).

The invention is further described in the following example which is solely for the purpose of illustrating specific embodiments of the invention, and is also not to be construed as limiting the scope of the invention in any way.

Example 1

Methods:

Patients:

Patients with unipolar or bipolar depression admitted as in-patients to the Max Planck Institute of Psychiatry (MPI), Munich, Germany, for treatment of a depressive episode were included in the study. Patients were diagnosed by psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. Patients with bipolar disorder or depressive disorder due to a general medical or neurological condition were excluded, as were patients with a lifetime diagnosis of drug abuse and depressive symptoms secondary to alcohol or substance abuse or dependency. Ethnicity was recorded using a self-report sheet for

nationality, first language and ethnicity of the patient and of all four grandparents. All patients were Caucasian and part of the Munich-Antidepressant-Response-Signature (MARS) project (Hennings *et al.*, J Psychiatr Res., 2009) (www.mars-depression.de). They were treated with antidepressant medications according to doctor's choice. Severity of depressive symptoms was assessed at admission and at the time of the dex/CRH test by trained raters using the 17-item Hamilton Depression Rating Scale (HAM-D, Hamilton, J Neurol Neurosurg Psychiatry, 1960). 192 patients fulfilling the criteria for at least a moderate to severe depressive episode (HAM-D≥18) at both time points and who had been administered a dex/CRH test within 10 days of in-patients admission and had genome-wide SNP data were included in this analysis. The study was approved by the Ethics Committee of the Ludwig Maximilians University in Munich, Germany, and written informed consent was obtained from all subjects.

Dex/CRH test:

The dex/CRH test was administered as described in detail in Heuser *et al.* (J Psychiatr Res., 1994). In brief, subjects were pre-treated with 1.5 mg of dexamethasone per os at 11 pm. The following day, at 3 pm, 3.30 pm, 3.45 pm, 4 pm and 4.15 pm blood was drawn. An intravenous bolus of 100 µg of human CRH (Ferring, Kiel, Germany) was given at 3.02 pm. Plasma ACTH concentrations were assessed by an immunometric assay without extraction (Nichols Institute, San Juan Capistrano, California; USA). The neuroendocrine response to the dex/CRH test was analyzed using the total area under the curve (AUC) of the ACTH response.

SNP Genotyping:

After enrollment in the study 40 ml of EDTA blood was drawn from each patient. DNA was extracted from fresh blood using the Puregene® whole blood DNA-extraction kit (Gentra Systems Inc; MN). Genotyping was performed on Illumina Human 610k quad genotyping arrays (Illumina Inc., San Diego, USA) according to the manufacturer's standard protocols. The average call rate exceeded 99 %, with samples below 98 % being either retyped or excluded from the study. The reproducibility for samples genotyped twice was 99.99 % or better.

Data analysis:

To identify genetic predictors for the ACTH response to the dex/CRH test in patients with moderate to severe depression, the 192 patients were randomly split into a training (N = 96) and test set (N = 96). The demographic and clinical descriptors of these two samples are given in table 3.

Table 3:

Demographic and clinical description of the 192 patients in the trainings and test set.

	training set	test set	p-value
N	96	96	
% female	52,1	57,2	n.s.
% bipolar (1 or 2)	12,5	12,5	n.s.
% with psychotic symptoms	15,2	11,4	n.s.
age (mean years (SD))	47,2 (14,2)	51,3 (13,2)	0,038
BMI at admission (mean SD)	24,9 (4,1)	24,9 (4,3)	n.s.
age-on (mean years (SD))	34,72 (14,5)	36,6 (15,9)	n.s.
number of previous episodes (mean N (SD))	3,2 (4,0)	3,3 (4,7)	n.s.
depression severity at admission (mean HAMD-17 score (SD))	26,4 (4,4)	27,7 (4,8)	0,058
depression severity at dex-crh test (mean HAMD-17 score (SD))	26,9 (5,0)	28,5 (5,0)	0,029
Cortisol AUC (mean (SD))	3611,4 (3414)	3688,6 (3491)	n.s.
ACTH AUC (mean (SD))	1246 (910)	1482,8 (1319)	n.s.
days after admission when dex-CRH test was performed	6,1 (2,2)	5,9 (2,2)	n.s.

After natural log transformation of the AUC of the ACTH response in the dex/CRH test, patients were dichotomized into high vs. low responders. For the ACTH AUC the cut-off was ln ACTH AUC > 7.0. This placed 46.4% (89 out of a total of 192 individuals) in the high responder class. See the corresponding histogram in Figure 1.

Using an additive genetic model and a logistic regression with sex and age as covariates in PLINK (http://pngu.mgh.harvard.edu/purcell/plink/), the association of all SNPs with a MAF > 0.05 were tested on the 610k arrays with the dichotomized response for cortisol and ACTH in the dex/CRH test in the training set. The top 30 associated SNPs were then used to predict either ACTH or cortisol response status in the test set using a "Probabilistic Neural Network und General Regression Neural Network" approach (implementation DTREG 10.3.3 www.dtreg.com). All values were derived from a 20 fold cross validation.

Results:

The top 30 association with ACTH response status are given in table 4. Association p-values ranged from 5.0 e-5 to 2.3 e-4 for the ACTH response.

The genotypes for the 30 SNPs each were then used to predict ACTH response status in the second, independent test cohort (subgroup of the test set).

Table 4: List of 30 SNPs used to predict ACTH AUC in the second test cohort.

SNP	Chromosome	Coordinate_HG18	P-value training	GeneVariant	GeneName
rs6437726	chr3	108321446	5.037e-005	INTERGENIC	N/A
rs1986684	chr11	110629697	5.287e-005	UPSTREAM	N/A
rs7380830	chr5	66022641	5.459e-005	INTRONIC	ENSG0000019656
rs3903768	chr13	49294756	6.811e-005	INTERGENIC	N/A
rs7325978	chr13	71960761	8.206e-005	INTERGENIC	N/A
rs13585	chr22	45131843	0.0001016	REGULATORY_REGION,3PRIME_UTR	TRMU
rs9368373	chr6	22024631	0.0001063	INTERGENIC	N/A
rs10935354	chr3	141026326	0.0001073	INTERGENIC	N/A
rs8095703	chr18	11041081	0.0001183	INTERGENIC	N/A
rs10206851	chr2	5381477	0.0001267	INTERGENIC	N/A
rs9542977	chr13	71958236	0.0001499	INTERGENIC	N/A
rs4942879	chr13	49314940	0.0001537	INTERGENIC	N/A
rs9542954	chr13	71918308	0.0001643	INTERGENIC	N/A
rs1593478	chr18	2292023	0.0001663	INTERGENIC	N/A
rs9542951	chr13	71913959	0.0001664	INTERGENIC	N/A
rs2188534	chr7	111837550	0.0001823	INTERGENIC	N/A
rs12524124	chr6	22051921	0.000185	INTERGENIC	N/A
rs4352629	chr5	87792577	0.0001985	INTERGENIC	N/A
rs7448716	chr5	87788451	0.0001985	INTERGENIC	N/A
rs11873533	chr18	3732713	0.0002107	INTRONIC	DLGAP1
rs10062658	chr5	102881920	0.0002216	INTERGENIC	N/A
rs12547917	chr8	142306580	0.0002282	INTRONIC	SLC45A4
rs1038268	chr9	31967623	0.000229	INTERGENIC	N/A
rs2375811	chr9	31979998	0.000229	INTERGENIC	N/A
rs1352671	chr9	32033985	0.000229	INTERGENIC	N/A
rs364331	chr9	32039631	0.000229	INTERGENIC	N/A
rs1924949	chr13	71975473	0.0002323	INTERGENIC	N/A
rs11025990	chr11	21218608	0.0002323	INTRONIC	NELL1
rs3758562	chr10	72032086	0.0002369	INTRONIC	PRF1
rs10156056	chr7	22720613	0.0002394	INTERGENIC	N/A

The results of the prediction in the test set are summarized below:

For the prediction of the dichotomized ACTH response status in the dex/CRH the following prediction values were achieved:

ACTH:

Accuracy = 85.33%

Sensitivity = 87.18%

Specificity = 83.33%

Geometric mean of sensitivity and specificity = 85.23%

Positive Predictive Value (PPV) = 85.00%

Negative Predictive Value (NPV) = 85.71%

Geometric mean of PPV and NPV = 85.36%

Precision = 85.00%

Recall = 87.18%

F-Measure = 0.8608

Area under ROC curve (AUC) = 0.851852

Using genome-wide SNP association data for the ACTH response in the dex/CRH test, a subset of 30 SNPs could be identified that allowed an accurate, sensitive and specific prediction of these phenotypes in independent sets of patients. Increased ACTH secretion in this test has been linked to an increase in central CRH/CRHR1 function. Although environmental, pharmacological and disease state-dependent factors have previously been described to influence the endocrine response to this test in depressed patients (Ising *et al.*, Neuropsychopharmacol Biol Psychiatry, 2005; Heim *et al.* Biol Psychiatry, 2008; Kunzel *et al.* Neuropsychopharmacology, 2003), it has now been shown that genetic polymorphisms alone are strong predictors.

Patients with depression or anxiety disorders, classified into the high ACTH response group according to the genotypes of the presented 30 SNPs described in this example will be more likely to respond to CRHR1 antagonist treatment. This allows an

enrichment of such patients for CRHR1 antagonist treatment studies who will most likely respond to this specific treatment.

Example 2:

Sleep disturbances, such as decreased slow-wave sleep, increased sleep fragmentation and rapid-eye-movement sleep (REMS) disinhibition, are cardinal symptoms of major depression in humans. This study aims to identify those patients where a central CRH hyperdrive plays a causal role and which would therefore respond favourably to a CRHR1 antagonist. To test the relationship between a central CRH-overexpression and REM-disinhibition in particular, transgenic mouse models where CRH is overexpressed as a result of genetic engineering were employed.

Many animal models of depression share increases in REM-sleeps (REMS) as a common feature. Therefore, increased REMS in animals should reflect REMS-disinhibitions in humans. Mice with CNS-specific CRH-overexpression strikingly share the characteristic increases in REMS. As such, an increase in REMS indicates a central hypersecretion of CRH and may serve as a biomarker to identify those patients who would benefit from treatment with a CRHR1 antagonist.

Experiments were conducted with two different mouse lines of excessive central CRH secretion and their respective control littermates (CL). Mice of the CRH-COE^{CNS} line are characterised by CRH-overexpression within the whole CNS, whereas mice of the Cor26 CRH line display a CRH-overexpression specific to CRH-ergic neurons of the CNS. Three different CRHR1 antagonists were tested. While DMP-696 (bicyclic) and CP-316,311 (monocyclic) are class I CRH-R1 antagonists, SSR125543A (long off-rate, typical slow-tight binding inhibitor) belongs to class II CRH-R1 antagonists. DMP-696 and SSR125543A were applied to CRH-COE^{CNS} mice (n_{DMP696}= 6/6 COE/CL; $n_{SSR125543}$= 6/5 COE/CL), while CP-316,311 was tested in Cor26 CRH mice ($n_{CP316.311}$= 5/3 Cor26/CL). In all cases, animals were left to recover from EEG/EMG-electrode implantation for two weeks, after which two days of baseline recording were initiated. Treatment with CRH-R1

antagonist or respective vehicle control commenced thereafter for five consecutive days. Antagonists were applied through the drinking water at a daily dose of 50mg/kg body weight. EEG and EMG recordings were manually scored as wake, non-REMS (NREMS), and REMS in four second epochs by an experienced evaluator.

As previously shown, CRH-COE^{CNS} mice display significantly higher REMS activity under baseline condition as compared to controls. Chronic DMP-696 (50mg/kg/d DMP-696) treatment entails only a mild suppression of REMS in CL mice. However, DMP-696-treated CRH-COE^{CNS} mice show a significant decrease in REMS activity beginning with treatment day two ($P<0.05$). The strongest suppression of REMS activity in CRH-COE^{CNS} animals could be observed on treatment day three (Figure 2).

Comparable to DMP696 treatment, oral application of SSR125543A (50mg/kg/d) affected REMS levels in CRH-overexpressing mice. No effects of SSR125543 on REMS activity in control animals could be detected. In contrast, a significant suppression of REMS could be observed beginning with day two in CRH-overexpressing animals ($P\leq0.035$). Similar to DMP696 treatment, REMS suppression in CRH-COE^{CNS} mice never exceeded baseline REMS-levels of CL (Figure 3).

Application of CP-316,311 (Pfizer) in the Cor26 CRH mouse line showed no significant effect on REMS levels in CL animals (data not shown). Similarly, in CRH-overexpressing Cor26 CRH mice suppression in REMS apparently seemed weak. However, comparison of the area under the curve (AUC) within the light period of baseline and treatment day three showed a significant decrease ($P=0.006$) of REMS levels after CP-316,311 application (Figure 4).

CRH is one of the major drivers of the stress response in the brain. Hyperactivity of the CRH system seems to be responsible for cognitive impairments, emotional responses, and behavioural changes which are typical for depression. One of those

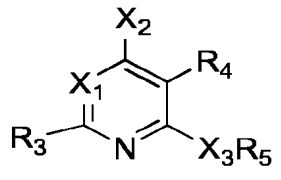
behavioural changes are sleep disturbances exemplified by REMS disinhibition. The link between CRH-overexpression and REMS level increases is evidenced by the mouse lines used in these experiments. Since CRH-overexpression in the Cor26 CRH mouse line is limited to CRH-ergic neurons, the net increase of CRH is lower when compared to the whole brain overexpression in CRH-COE^{CNS} mice. As a result, the phenotype of increased REMS levels was less profound in Cor26 CRH mice as compared to CRH-COE^{CNS} animals.

The main finding of this study is that the normalization of CRH-elicited sleep-EEG disturbances is striking when (1) different chemical classes of CRHR1 antagonists are used and (2) different animal models for CRH-induced sleep-EEG changes that are typical for human depression are employed. REMS disinhibition is indicative of a central CRH dysfuntion (i.e. hyperactivity) and as such may serve as a biomarker for the identification of depressed patients where depression is caused by central CRH-hyperdrive. Normalization of the sleep pattern by application of different CRHR1 antagonists could be shown in all of our experiments, employing different classes of CRHR1 receptors and different animal models overexpressing centrally CRH.

Claims

1. Corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity.

2. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

X_1 is $-CR_6$ or N;

X_2 is $-NR_1R_2$, $-CR_1R_2R_9$, $-C(=CR_2R_{10})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{10}$, $-CHR_2SR_{10}$, $-C(S)R_2$ or $-C(O)R_2$;

X_3 is NH, O, S, $-N(C_1\text{-}C_2$ alkyl) or $-C(R_{11}R_{12})$, wherein R_{11} and R_{12} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{11} and R_{12} is cyano and the other is hydrogen or methyl, or

X_3 is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5;

R_1 is $C_1\text{-}C_6$ alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, $C_3\text{-}C_8$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $-O\text{-}CO\text{-}(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}NH(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $-NH(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}C_2$ alkyl)$(C_1\text{-}C_4$ alkyl), $-S(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}C_4$ alkyl)$CO(C_1\text{-}C_4$ alkyl), $-NHCO(C_1\text{-}C_4$ alkyl), $-COO(C_1\text{-}C_4$ alkyl), $-CONH(C_1\text{-}C_4$ alkyl), $-CON(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), CN, NO_2, $-SO(C_1\text{-}C_4$ alkyl) and $-SO_2(C_1\text{-}C_4$ alkyl), and

wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, C_1-C_{12} alkoxyalkyl,
aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or –(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl;

and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 or –$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy,
-CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OCF3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -$N(CH_3)_2$, -$NHCOCH_3$ -$NHCONHCH_3$, -SO_n(C_1-C_4 alkyl) wherein n is 0, 1 or 2, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4

alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -$NH(C_1$-C_2 alkyl), -$N(C_1$-C_2 alkyl)$_2$, -$COO(C_1$-C_4 alkyl), -$CO(C_1$-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl,

wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -$COO(C_1$-C_4 alkyl), -$CO(C_1$-C_4 alkyl), -$SO_2NH(C_1$-C_4 alkyl), -$SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2(C_1$-C_4 alkyl), -$S(C_1$-C_6 alkyl) and $SO_2(C_1$-C_6 alkyl), and wherein the C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, 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, -CH_2OCH_3 or -$CH_2OCH_2CH_3$;

R_9 is hydrogen, hydroxy, fluoro, or methoxy;

R_{10} is hydrogen or C_1-C_4 alkyl.

3. CRHR1 antagonist for use according to claim 2, wherein
X_1 is $-CR_6$.

4. CRHR1 antagonist for use according to claim 3, wherein X_1 is CH.

5. CRHR1 antagonist for use according to any of claims 2 to 4, wherein the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with at least one substituent selected from C_1-C_4 alkyl or
with a 4-8 membered ring, which may be saturated or may contain one to three double bonds and in which one carbon atom may be replaced by CO or SO_2 and one to four carbon atoms may optionally be replaced by nitrogen.

6. CRHR1 antagonist for use according to any of claims 2 to 4, wherein
X_2 is $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

7. CRHR1 antagonist for use according to claim 6, wherein
$-NHCHR_1R_2$ is $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $-NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH_3)(CH_2CH_3)$ or $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl,
or
$-NR_1R_2$ is $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$
or
$-OCHR_1R_2$ is $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$.

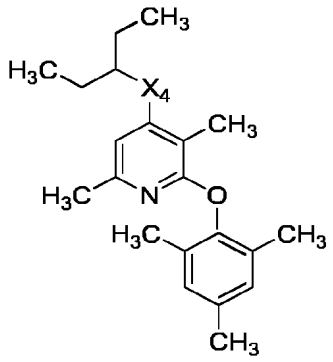
8. CRHR1 antagonist for use according to any of claims 2 to 7, wherein
R_3 and R_4 are methyl.

9. CRHR1 antagonist for use according to any of claims 2 to 8, wherein

X_3 is O.

10. CRHR1 antagonist for use according to any of claims 2 to 9, wherein
R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3.

11. CRHR1 antagonist for use according to any of claims 1 to 10, wherein the CRHR1 antagonist is a compound of the formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein
X_4 is O or NH.

12. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is a class I CRHR1 antagonist.

13. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is a class II CRHR1 antagonist.

14. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is selected from the group consisting of CP154,526, Antalarmin, CRA 5626, Emicerfont, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, Pexacerfont, R121919, NBI30545, PD-171729, Verucerfont, NBI34041, NBI35965,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

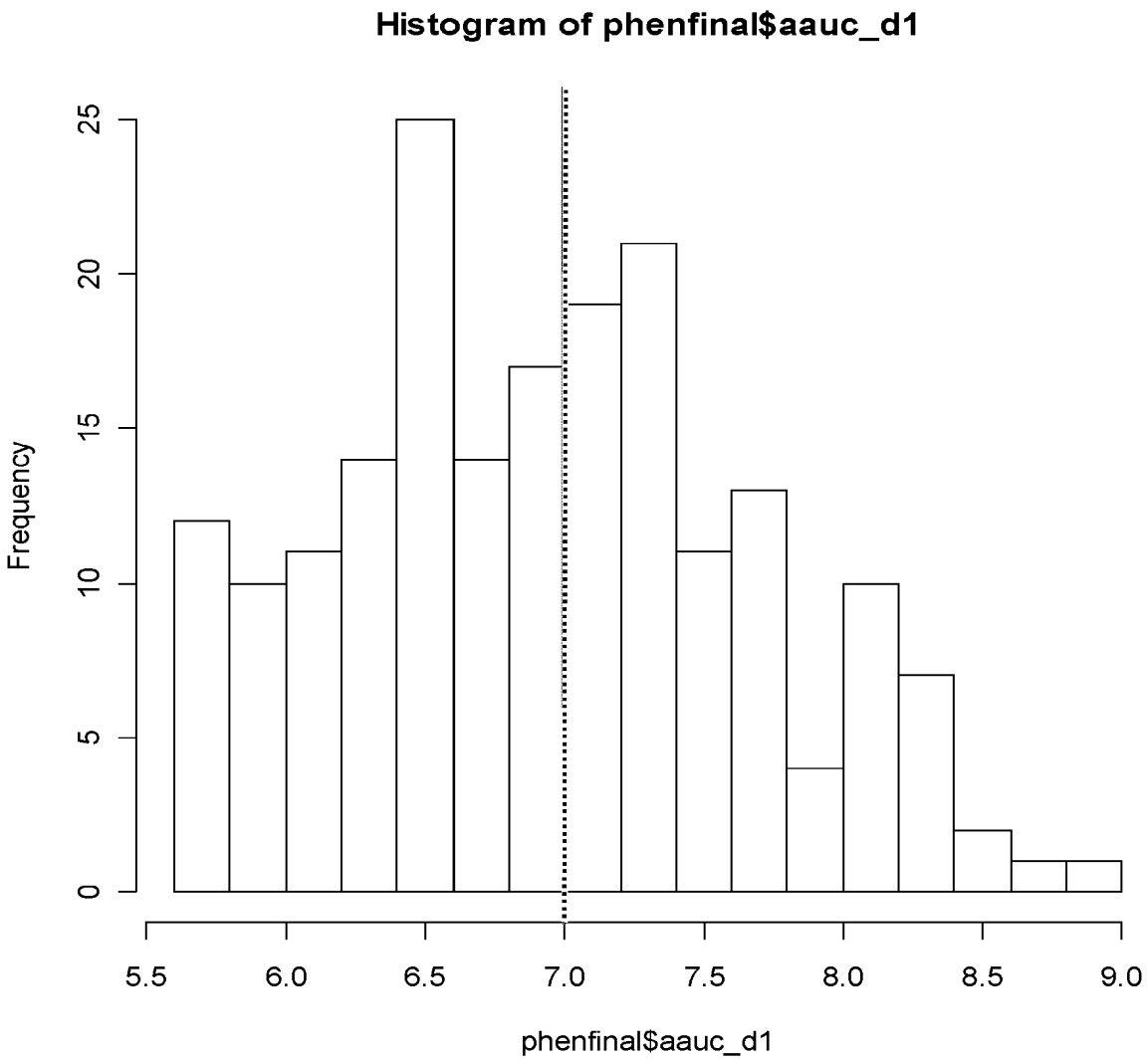

Histogram of phenfinal$aauc_d1
Frequency
0
5
10
15
20
25
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6.5
7.0
7.5
8.0
8.5
9.0
phenfinal$aauc_d1

Fig. 1

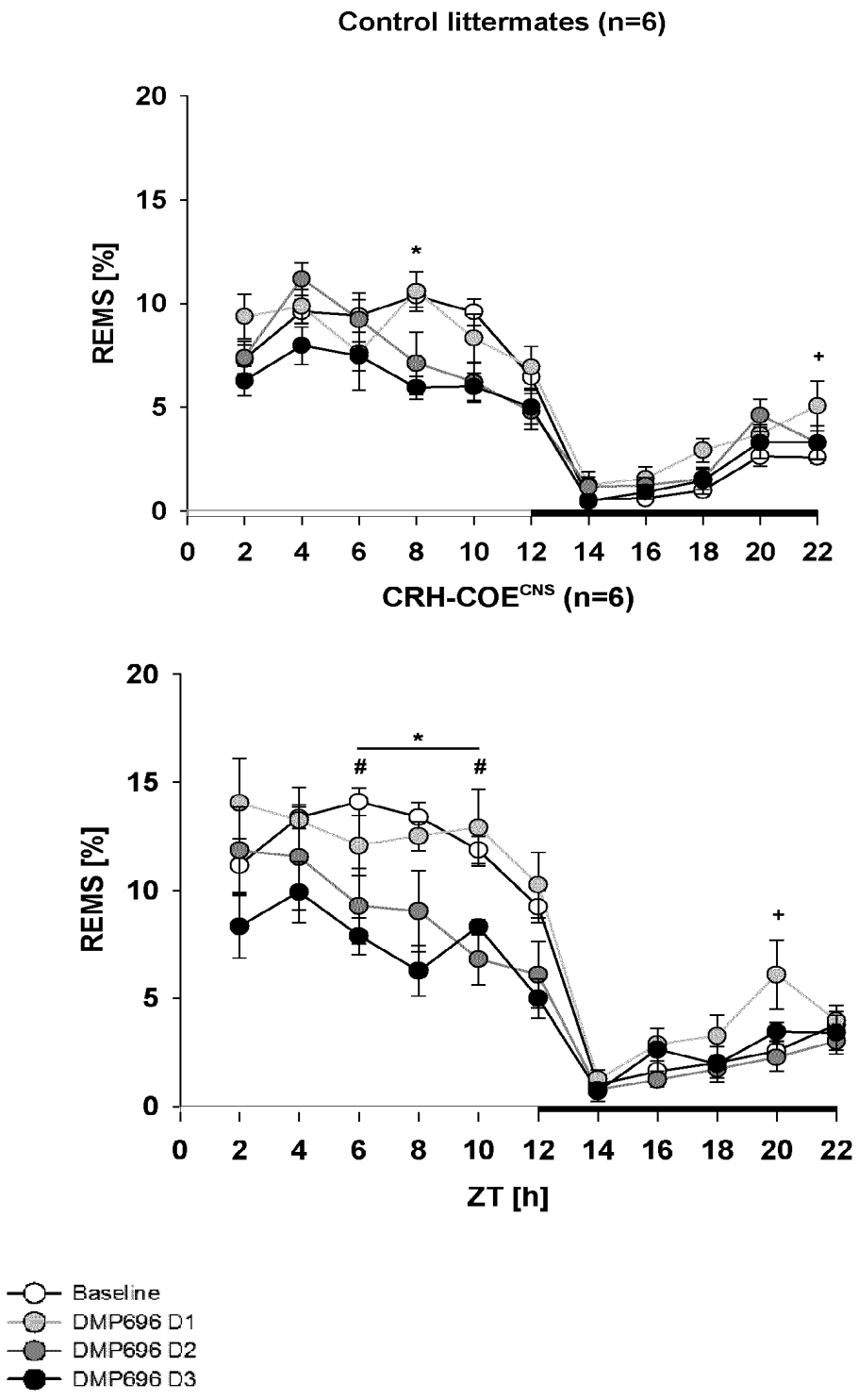

Control littermates (n=6)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22
*
+
CRH-COE^CNS (n=6)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22
*
#
#
+
ZT [h]
Baseline
DMP696 D1
DMP696 D2
DMP696 D3

Fig. 2

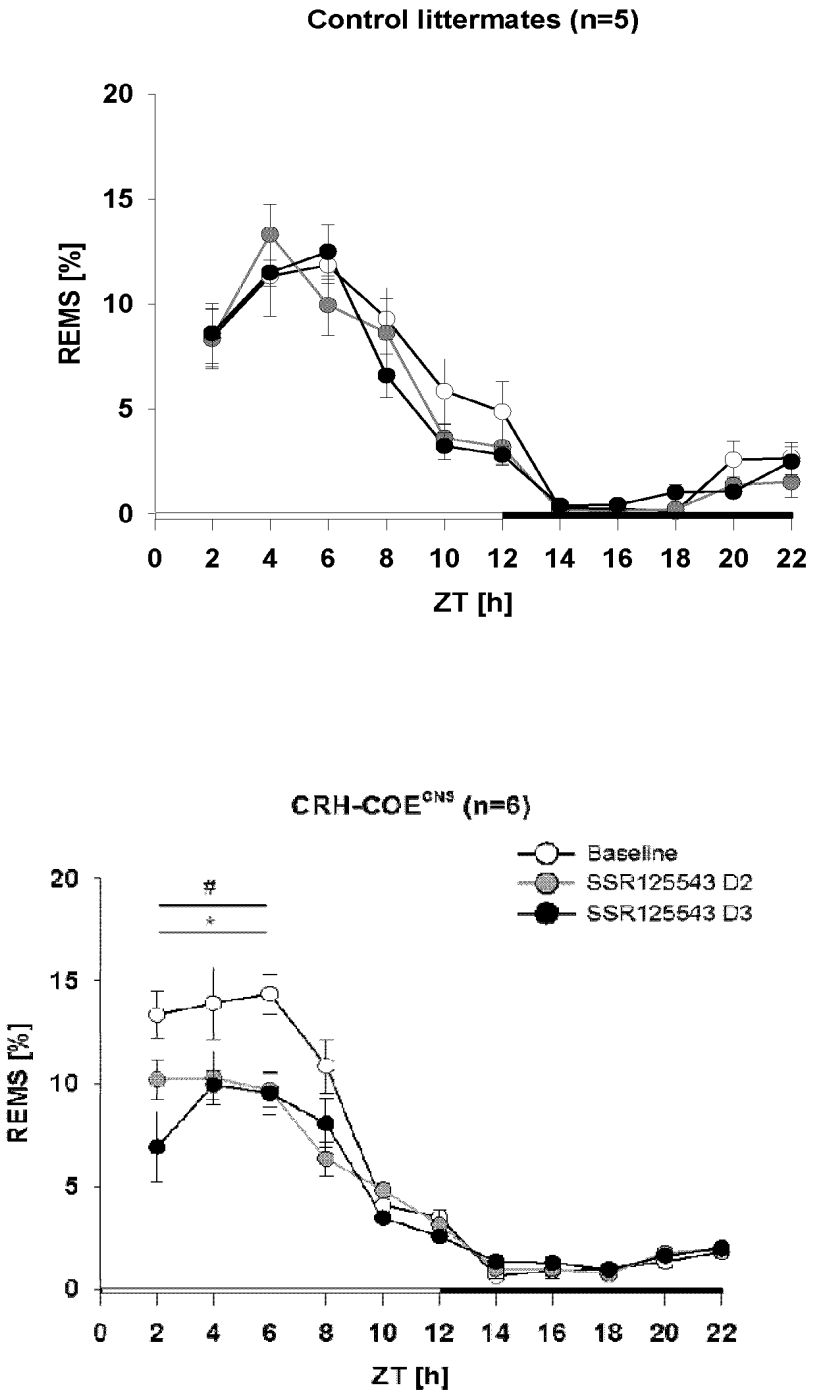

Control littermates (n=5)
REMS [%]
ZT [h]
CRH-COE^CNS (n=6)
Baseline
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SSR125543 D3
#
*

Fig. 3

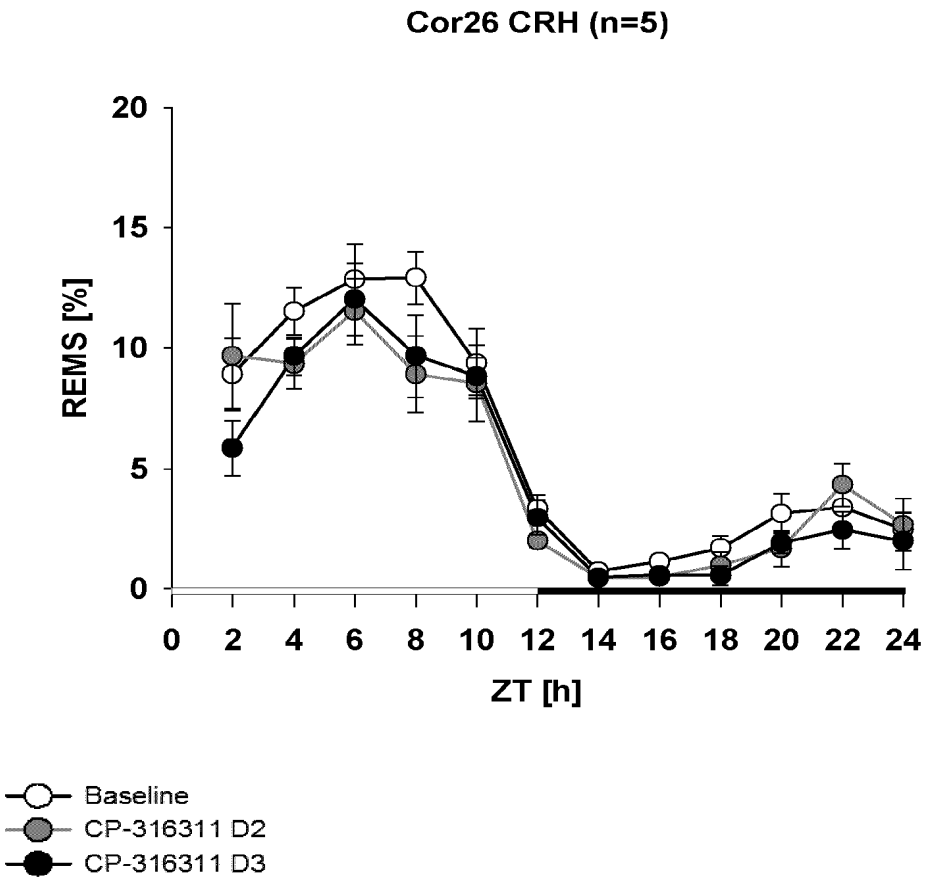

Cor26 CRH (n=5)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24
ZT [h]
Baseline
CP-316311 D2
CP-316311 D3

Fig. 4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,264	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**6961**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: July 24, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: July 24, 2025

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	16	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-8030304	10-04-2011	CHEN et al.	
	002	US-8563718	10-22-2013	RIZZO; John Robert et al.	
	003	US-11708372	07-25-2023	REDDY; Dasharatha et al.	
	004	US-11858932	01-02-2024	BARNES; Christopher et al.	
	005	US-12098152	09-24-2024	BARNES; Christopher et al.	
	006	US-20020013357	01-31-2002	NADKARNI; Sreekant et al.	
	007	US-20030008885	01-09-2003	HE; Liqi et al.	
	008	US-20050209250	09-22-2005	ROMANO; Steve	
	009	US-20060078623	04-13-2006	DHOOT; Nikhil et al.	
	010	US-20090076266	03-19-2009	DAUGULIS; Olafs et al.	
	011	US-20100022560	01-28-2010	CHEN; Zhaogen et al.	
	012	US-20100155595	06-24-2010	GHOSHAL; Amit [Us] et al.	
	013	US-20110136865	06-09-2011	BUNTINX; Erik	
	014	US-20110160168	06-30-2011	DHINGRA; Om	
	015	US-20110166345	07-07-2011	RIZZO; John Robert et al.	
	016	US-20130045979	02-21-2013	SANFILIPPO; Louis	
	017	US-20170333126	11-23-2017	SOBOTKA; Paul	

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	16	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	018	US-20180110554	04-26-2018	ZARINS; Denise Marie et al.	
	019	US-20190262349	08-29-2019	HOWERTON; Alexis et al.	
	020	US-20200255436	08-13-2020	HOWERTON; Alexis et al.	
	021	US-20210015827	01-21-2021	HOWERTON; Alexis et al.	
	022	US-20210038604	02-11-2021	HOWERTON; Alexis et al.	
	023	US-20210137935	05-13-2021	HOWERTON; Alexis et al.	
	024	US-20210322430	10-21-2021	HOWERTON; Alexis et al.	
	025	US-20210361664	11-25-2021	HOWERTON; Alexis et al.	
	026	US-20220133742	05-05-2022	GHOSH; Sangita et al.	
	027	US-20220133742	05-05-2022	GHOSH; Sangita et al.	
	028	US-20220143037	05-12-2022	HOWERTON; Alexis et al.	
	029	US-20230159533	05-25-2023	REDDY; Dasharatha et al.	
	030	US-20230321112	10-12-2023	HOWERTON; Alexis et al.	
	031	US-20230414627	12-28-2023	HOWERTON; Alexis et al.	
	032	US-20240043432	02-08-2024	REDDY; Dasharatha et al.	
	033	US-20240261300	08-08-2024	GHOSH; Sangita et al.	

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

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				Application Number	19/043,264
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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
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Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	034	US-20240293421	09-05-2024	REDDY; Dasharatha et al.	
	035	US-20250064812	02-27-2025	HOWERTON; Alexis et al.	
	036	US-20250177404	06-05-2025	HOWERTON; Alexis et al.	
	037	US-20250195527	06-19-2025	HOWERTON; Alexis et al.	

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	001	CN-101516835-A	08-26-2009	OSURF OHIO STATE UNIVERSITY RE [US]	Abstract:	☒
	002	EP-2094709-B1	09-15-2010	LILLY CO ELI [US]		☐
	003	EP-3984523-A1	04-20-2022	NEUROCRINE BIOSCIENCES INC [US], et al.		☐
	004	JP-2000302693-A	10-31-2000	PFIZER PROD INC.	Abstract:	☒
	005	KR-19990067391-A	08-16-1999	JANSSEN PHARMACEUTICA NV [BE], et al.	Machine Translation:	☒

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	006	WO-0059908-A2	10-12-2000	DU PONT PHARM CO [US]		☐
	007	WO-0123388-A2	04-05-2001	NEUROGEN CORP [US], et al.		☐
	008	WO-02072202-A1	09-19-2002	BRISTOL MYERS SQUIBB PHARMA CO [US]		☐
	009	WO-2005020910-A2	03-10-2005	PHARMACIA CORP [US], et al.		☐
	010	WO-2005063755-A1	07-14-2005	SB PHARMCO INC [US], et al.		☐
	011	WO-2005079868-A2	09-01-2005	SB PHARMCO INC [US], et al.		☐
	012	WO-2006102194-A1	09-28-2006	LILLY CO ELI [US], et al.		☐
	013	WO-2010039678-A1	04-08-2010	LILLY CO ELI [US], et al.		☐
	014	WO-2013160317-A2	10-31-2013	HOLSBOERMASCHMEYER NEUROCHEMIE GMBH [DE]		☐
	015	WO-2020115555-A2	06-11-2020	NEUROCRINE BIOSCIENCES INC [US], et al.		☐

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	016	WO-2021016208-A1	01-28-2021	SPRUCE BIOSCIENCES INC [US]		☐
	017	WO-2022036123-A1	02-17-2022	SPRUCE BIOSCIENCES INC [US]		☐
	018	WO-2023091684-A1	05-25-2023	SPRUCE BIOSCIENCES INC [US]		☐
	019	WO-9413676-A1	06-23-1994	PFIZER [US], et al.		☐
	020	WO-9729109-A1	08-14-1997	JANSSEN PHARMACEUTICA NV [BE], et al.		☐
	021	WO-9803510-A1	01-29-1998	DU PONT MERCK PHARMA [US]		☐
	022	WO-9808847-A1	03-05-1998	PFIZER [US], et al.		☐

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	001	ABCAM CP 154526 Hydrochloride, Non-Peptide CRF1 Receptor Antagonist AB141429. [Internet] ABCAM. Retrieved from URL: https://www.abcam.com/products/biochemicals/cp-154526-hydrochloride-non-peptide-crf1-receptor-antagonist-ab141429.html. 2 pages.	☐
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	006	DO, Hien-Quang et al. A General Method for Copper-Catalyzed Arylation of Arene C-H Bonds. J Am Chem Soc. 130(45):15185-15192 (2008).	☐
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	010	EL-MAOUCHE, Diala et al. Congenital adrenal hyperplasia. Lancet 390:2194-2210 (2017).	☐
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	018	HODGETTS et al. Discovery of N-(1-ethylpropyl)-[3-methoxy-5-(2-methoxy-4-trifluoromethoxyphenyl)-6-methyl-pyrazin-2-yl]amine 59 (NGD 98-2): an orally active corticotropin releasing factor-1 (CRF-1) receptor antagonist. J Med Chem 54:4187-4206 (2011).	☐
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	023	MARKOPOULOS, Marios C. Hyperandrogenism in women with polycystic ovary syndrome persists after menopause. Journal of Clinical Endocrinology and Metabolism 96(3):623-631 (2011).	☐
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	028	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 12,115,166 dated February 10, 2025 (pp 1-59).	☐
	029	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petitioner's Reply to Patent Owner's Response in U.S. Patent No. 10,849,908 dated June 20, 2024 (pp. 1-38) (PGR2021-00088).	☐
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	032	PCT/US2007/078605 International Search Report and Written Opinion dated January 31, 2008.	☐
	033	PCT/US2007/078605 Written Opinion dated March 20, 2009.	☐
	034	PCT/US2009/058722 International Search Report and Written opinion dated January 25, 2010.	☐
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	036	PCT/US2009/058722 Written Opinion dated April 2, 2011.	☐
	037	PCT/US2018/046707 International Search Report and Written Opinion dated October 24, 2018.	☐
	038	PCT/US2018/046760 International Search Report and Written Opinion dated October 24, 2018.	☐
	039	PCT/US2020/042820 International Search Report and Written Opinion dated November 25, 2020.	☐
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	048	TURCU, Adina F. et al. Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016).	☐
	049	U.S. Serial No. 17/586,228 Office Action dated June 10, 2022.	☐
	050	U.S. Serial No. 13/063,226 Office Action dated January 24, 2013.	☐
	051	U.S. Serial No. 16/388,620 Office Action dated July 15, 2019.	☐
	052	U.S. Serial No. 16/388,620 Office Action dated November 25, 2019.	☐
	053	U.S. Serial No. 16/639,540 Office Action dated July 11, 2022.	☐
	054	U.S. Serial No. 16/639,540 Office Action dated March 28, 2024.	☐
	055	U.S. Serial No. 16/639,540 Office Action dated May 25, 2023.	☐

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	056	U.S. Serial No. 16/639,540 Office Action dated November 16, 2021.	☐
	057	U.S. Serial No. 16/639,540 Office Action dated September 28, 2023.	☐
	058	U.S. Serial No. 16/639,541 Office Action dated April 4, 2022.	☐
	059	U.S. Serial No. 17/063,592 Office Action dated December 7, 2021.	☐
	060	U.S. Serial No. 17/078,054 Office Action dated December 14, 2020.	☐
	061	U.S. Serial No. 17/359,411 Office Action dated January 6, 2022.	☐
	062	U.S. Serial No. 17/359,414 Office Action dated November 16, 2021.	☐
	063	U.S. Serial No. 17/586,228 Office Action dated March 30, 2022.	☐
	064	U.S. Serial No. 18/078,649 Office Action dated March 21,2024.	☐
	065	U.S. Serial No. 18/078,649 Office Action dated October 9, 2024.	☐
	066	U.S. Serial No. 18/078,649 Office Action dated September 8, 2023.	☐
	067	U.S. Serial No. 18/307,718 Office Action dated October 12, 2023.	☐
	068	U.S. Serial No. 19/043,275 Office Action dated May 30, 2025.	☐

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				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	13	of	16	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
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	069	VARMA. Excipients used in the Formulation of Tablets. https://www.rroij.com/openaccess/excipients-used-in-the-formulationof-tablets-.php?aid=78260 Revised date: 26/07/2016.	☐
	070	WILLIAMS, John P. Corticotropin-releasing factor 1 receptor antagonists: a patent review. Expert Opin Ther Pat 23(8):1057-68 (2013).	☐
	071	ZHANG et al. D-Level Essay in Statistics, 2009, How to Analyze Change from Baseline. Available at http://www.statistics.du.se/essays/D09 Zhang%20Ling%20&%20Han%20Kun.pdf (6/10/2009).	☐
	072	ZORRILLA, Eric P. et al., Progress in Corticotropin-Releasing Factor-1 Antagonist Development. Drug Discov Today 15(9-10):371-383 (2010).	☐
	073	ZORRILLA, Eric P. et al. The therapeutic potential of CRF1 antagonists for anxiety. Expert opinion on investigational drugs 13(7):799-828 (2004).	☐

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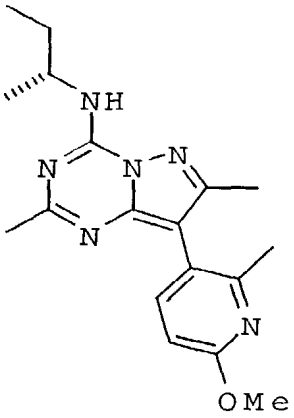
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(54) Title: 4-(2-BUTYLAMINO)-2,7-DIMETHYL-8-(2-METHYL-6-METHOXYPYRID-3-YL) PYRAZOLO-[1,5-A]-1,3,5-TRIAZINE, ITS ENANTIOMERS AND PHARMACEUTICALLY ACCEPTABLE SALTS AS CORTICOTROPIN RELEASING FACTOR RECEPTOR LIGANDS



(I)

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

WO 02/072202 A1

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

Field of the Invention

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

Background of the Invention

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Summary of the Invention

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

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

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

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

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

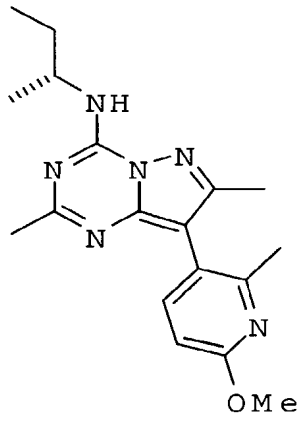
The use of competitive binding assays is considered particularly valuable for screening candidates for new drugs, e.g. to identify new CRF ligands or other compounds having even greater or more selective binding affinity for CRF receptors, which candidates would therefore be potentially useful as drugs.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

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

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

Detailed Description of the Invention

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



(I)

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

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

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

said compound is substantially free of its (S) stereoisomer

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

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

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

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

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

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

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

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

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

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

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

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

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

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

b) detecting the labelled compound bound to the tissue.

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

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

a) a packaging material;

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

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

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

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

Definitions

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

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

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

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

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

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

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

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

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

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

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

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

Syntheses

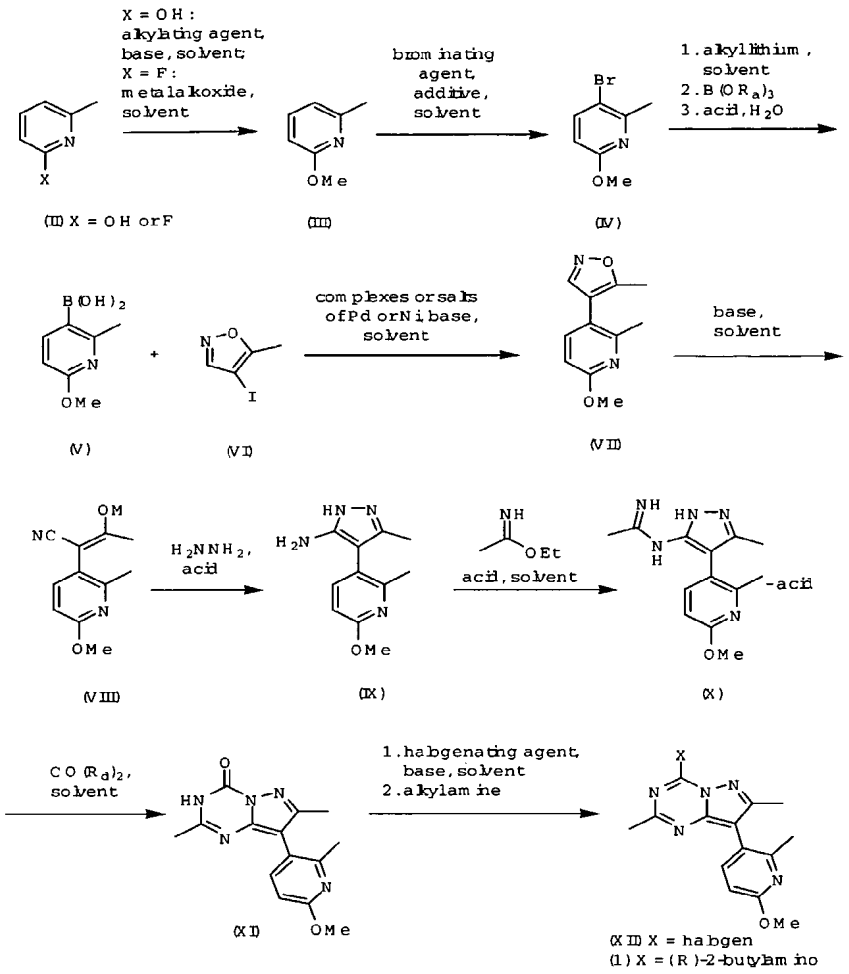
Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes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

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

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

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

Scheme 1



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLES

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

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

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

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

EXAMPLE 1

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

A. 2-Methoxy-6-methylpyridine.

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

B. 2-Methoxy-6-methylpyridine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLE 2

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

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

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

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

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

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

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

Utility

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

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

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

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

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

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

In vivo Biological Assay

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Capsules

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

Soft Gelatin Capsules

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

Tablets

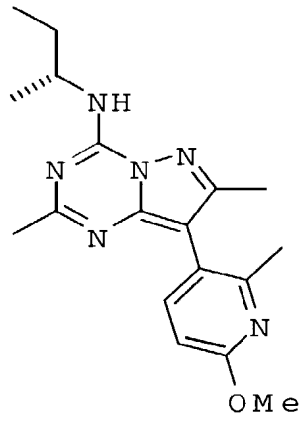
A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase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

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

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

What is claimed is:

1. A compound of Formula (I):



(I)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

b) detecting the labelled compound bound to the tissue.

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

17. An article of manufacture comprising:

a) a packaging material;

b) a compound of claim 1; and

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

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61P 25/00, 25/24; A61K 31/53; C07D 403/00
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

* Special categories of cited documents:

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미합중국 캘리포니아 92129 산 디에고 윌드피시 코트 12341, 중국

(74) 대리인
김석중
최규팔

(77) 심사관
있음

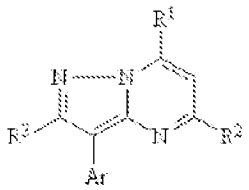
(81) 지정국 국내특허 : 아일랜드,알바니아,오스트레일리아,바베이도스,불가리아,브라질,캐나다,중국,체코,에스토니아,그루지야,헝가리,이스라엘,아이슬란드,일본,대한민국,스리랑카,라이베리아,리투아니아,라트비아,마다가스카르,마케도니아,몽고,멕시코,노르웨이
AP ARIPO특허 : 케냐,레소토,말라위,수단,스와질랜드
EA 유라시아특허 : 아르메니아,키르기즈,몰도바
EP 유럽특허 : 오스트리아,벨기에,스위스,독일,덴마크,스페인,프랑스,영국,그리스,이탈리아,룩셈부르크,모나코,네덜란드,포르투갈,스웨덴

전체 청구항 수 : 총 13 항

(54)CRF 수용체에 대한 길항제로서의 피라졸로피리미딘

(57)요 약

본 발명은 CRF 수용체에 대해 길항성을 갖는 하기 일반식 (I)의 화합물, 그의 입체이성체 및 약제학적으로 허용되는 산부가염, 활성 성분으로서 이들 화합물을 함유하는 약제학적 조성물 및 유효량의 일반식 (I)의 화합물을 투여하여 우울증, 불안 및 약물 남용과 같은 CRF의 과분비와 관련된 질환을 질환을 치료하는 방법에 관한 것이다.



(I)

상기식에서,

R^1 은 NR^4R^5 또는 OR^5 를 나타내며;

R^2 는 C_{1-6}알킬, C_{1-6}알콕시 또는 C_{1-6}알킬티오를 나타내고;

R^3 은 수소, C_{1-6}알킬, C_{1-6}알킬설포닐, C_{1-6}할로설폭시 또는 C_{1-6}알킬티오를 나타내며;

R^4 는 수소, C_{1-6}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, C_{3-6}사이클로알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알콕시카보닐C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬을 나타내고;

R^5 는 C_{1-8}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, Ar^1CH_2, C_{1-6}알콕시C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{3-6}알케닐, 퍼에닐메틸, 푸라닐메틸, C_{1-6}알킬티오C_{1-6}알킬, 모르폴리닐, 모노- 또는 디(C_{1-6}알킬)아미노C_{1-6}알킬, 디(C_{1-6}알킬)아미노, C_{1-6}알킬카르보닐C_{1-6}알킬, 이미다졸릴에 의해 치환된 C_{1-6}알킬, 또는 일반식 -Alk-O-CO-Ar^1 의 래디칼을 나타내거나;

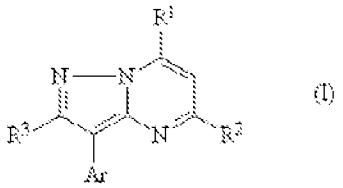
R^4 및 R^5 는 이들이 결합된 질소 원자와 함께, 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 고리을 형성할 수 있다.

This Facsimile Page has been artificially created from KIPO data.

청구의 범위

청구항 1

하기 일반식 (I)의 화합물, 그의 입체이성체 및 약제학적으로 허용되는 산부가염:



(I)

상기식에서,

R^1 은 NR^4R^5 또는 OR^5 를 나타내며;

R^2 는 C_{1-6}알킬, C_{1-6}알킬옥시 또는 C_{1-6}알킬티오를 나타내고;

R^3 은 수소, C_{1-6}알킬, C_{1-6}알킬설포닐, C_{1-6}알킬설폭시 또는 C_{1-6}알킬티오를 나타내며;

R^4 는 수소, C_{1-6}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, C_{3-6}사이클로알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알킬카보닐옥시C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬을 나타내고;

R^5 는 C_{1-8}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, Ar^1CH_2, C_{1-6}알킬옥시C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{3-6}알케닐, 티에닐메틸, 푸라닐메틸, C_{1-6}알킬티오C_{1-6}알킬, 모르폴리닐, 모노- 또는 디(C_{1-6}알킬)아미노C_{1-6}알킬, 디(C_{1-6}알킬)아미노, C_{1-6}알킬카보닐C_{1-6}알킬, 이미다졸릴에 의해 치환된 C_{1-6}알킬, 또는 일반식 -Alk-O-CO-Ar^1 의 래디칼을 나타내거나;

R^4 및 R^5 는 이들이 결합된 질소 원자와 함께, 각각 C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬에 의해 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 그룹을 형성할 수 있으며;

Ar 은 페닐; 할로, C_{1-6}알킬, 트리플루오로메틸, 하이드록시, 시아노, C_{1-6}알킬옥시, 벤질옥시, C_{1-6}알킬티오, 니트로, 아미노 및 모노- 또는 디(C_{1-6}알킬)아미노로 구성된 그룹중에서 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 페닐; 피리디닐; 또는 할로, C_{1-6}알킬, 트리플루오로메틸, 하이드록시, 시아노, C_{1-6}알킬옥시, 벤질옥시, C_{1-6}알킬티오, 니트로, 아미노, 모노- 또는 디(C_{1-6}알킬)아미노 및 피페리디닐로 구성된 그룹중에서 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 피리디닐을 나타내고; 여기에서 치환된 페닐은 하나 또는 그 이상의 할로겐에 의해 임의로 추가로 치환될 수 있으며;

Ar^1 은 페닐; 할로, C_{1-6}알킬, C_{1-6}알킬옥시, 디(C_{1-6}알킬)아미노C_{1-6}알킬, 트리플루오로메틸 및 모르폴리닐에 의해 치환된 C_{1-6}알킬로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 페닐; 또는 피리디닐을 나타내고;

Alk 는 C_{1-6}알칸디일을 나타내며,

단, 이들 화합물중에서 5-메틸-3-페닐-7-(페닐메톡시)-피라졸로[1,5-a]-피리미딘 및 2,5-디메틸-7-(메틸아미노)-3-페닐-피라졸로[1,5-a]피리미딘은 제외된다.

청구항 2

제 1 항에 있어서, R^1 이 OR^5 이고, R^5 는 C_{1-6}알킬이거나; R^1 이 NR^4R^5 이고, R^4 는 수소, C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{1-6}알킬카보닐옥시C_{1-6}알킬 또는 C_{3-6}알케닐이며, R^5 는 C_{1-8}알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알킬옥시C_{1-6}알킬, 페닐메틸 또는 C_{3-6}사이클로알킬메틸이거나, R^4 및 R^5 는 이들이 결합된 질소원자와 함께, 각각 C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬에 의해 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 그룹을 형성하고; R^2 는 C_{1-6}알킬이며; R^3 은 수소, C_{1-6}알킬 또는 C_{1-6}알킬티오이고; Ar 은 할로, C_{1-6}알킬 및 C_{1-6}알킬옥시로 구성된 그룹중에서 선택된 각각 독립적으로 1, 2 또는 3개의 치환체에 의해 치환된 페닐이거나, Ar 은 할로, 아미노, 니트로, 트리플루오로메틸, 모노- 또는 디(C_{1-6}알킬)아미노, 피페리디닐 및 C_{1-6}알킬로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 피리디닐인 화합물.

청구항 3

제 1 항 또는 제 2 항에 있어서, R^1 이 NR^4R^5 이고, R^4 는 C_{2-4}알킬, 하이드록시C_{1-2}알킬, C_{3-4}알케닐 또는 C_{1-2}알킬카보닐옥시C_{2-4}알킬이며, R^5 는 C_{2-4}알킬, C_{3-4}알케닐, 하이드록시C_{2-4}알킬 또는 사이클로프로필메틸이고; R^2 는 C_{1-2}알킬이며; R^3 은 수소, C_{1-2}알킬 또는 C_{1-2}알킬티오인 화합물.

청구항 4

제 1 항 내지 제 3 항중의 어느 한항에 있어서, R^1 이 NR^4R^5 이고, R^4 는 C_{3-4}알킬 또는 알릴이며, R^5 는 C_{2-4}알킬, 알릴 또는 사이클로프로필메틸이고; R^2 는 메틸이며; R^3 은 메틸이고; Ar 은 3-, 4-, 6-, 2,4- 또는 2,4,6-위치가 할로, C_{1-6}알킬 또는 C_{1-6}알킬옥시에 의해 치환된 페닐인 화합물.

청구항 5

제 1 항 내지 제 3 항중의 어느 한항에 있어서, R^1 이 NR^4R^5 이고, R^4 는 C_{3-4}알킬 또는 알릴이며, R^5 는 C_{3-4}알킬, 알릴 또는 사이클로프로필메틸이고; R^2 는 메틸이며; R^3 은 메틸이고; Ar 은 4- 및/또는 6-위치가 메틸 또는 디메틸아미노에 의해 치환된 3-피리디닐인 화합물.

청구항 6

제 1 항에 있어서, 3-[6-(디메틸아미노)-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민 또는 3-[6-(디메틸아미노)-4-메틸-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민, 또는 이들의 입체화학적 이성체 또는 이들의 약제학적으로 허용되는 산부가염인 화합물.

청구항 7

활성성분으로서 치료학적으로 유효한 양의 제 1 항 내지 제 6 항중의 어느 한 항에서 청구한 화합물 및 약제학적으로 허용되는 담체를 함유하는 조성물.

청구항 8

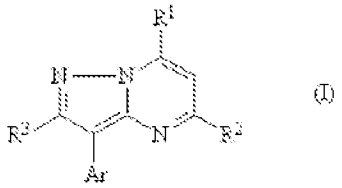
치료학적으로 유효한 양의 제 1 항 내지 제 6 항중의 어느 한 항에서 청구한 화합물을 약제학적으로 허용되는 담체와 완전히 혼합함을 특징으로 하여 제 7 항에서 청구한 조성물을 제조하는 방법.

청구항 9

제 1 항 내지 제 6 항중의 어느 한 항에 있어서, 의약으로서 사용하기 위한 화합물.

청구항 10

부신피질호르몬-방출 인자(CRF)의 과분비로 인한 생리학적 증상 또는 질환 치료용 의약을 제조하기 위한 일반식 (I)의 화합물, 그의 입체이성체 및 약제학적으로 허용되는 산부가염의 용도:



(I)

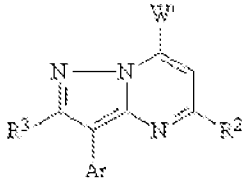
상기식에서,

R^1, R^2, R^3 및 Ar 은 제 1 항에 정의된 바와 같으며,

화합물 5-메틸-3-페닐-7-(페닐메톡시)-피라졸로[1,5-a]-피리미딘 및 2,5-디메틸-7-(메틸아미노)-3-페닐-피라졸로[1,5-a]피리미딘이 포함된다.

청구항 11

일반식 (II')의 화합물, 그의 입체이성체 또는 산부가염:



(II')

상기식에서,

R^2, R^3 및 Ar 은 제 1 항 내지 제 5 항중의 어느 한항에서 정의된 바와 같으며,

W' 는 하이드록시, 할로, 메실옥시 또는 토실옥시를 나타내고,

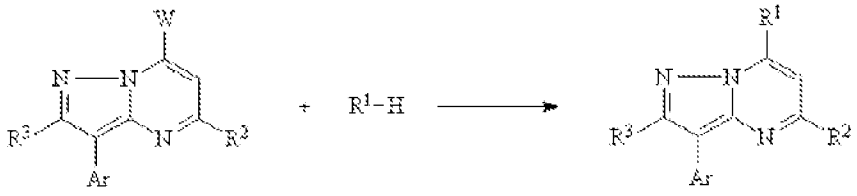
단, Ar 이 비치환된 페닐인 화합물은 제외된다.

청구항 12

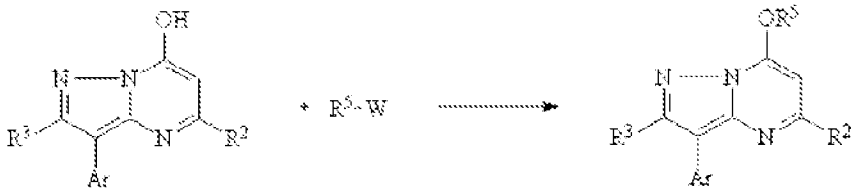
a) 일반식 (II)의 중간체를 반응-불활성 용매중에서 일반식 (III)의 중간체와 반응시키거나;

b) 일반식 (VI)의 중간체를 반응-불활성 용매중에서 적합한 염기의 존재하에 일반식 (VII)의 중간체로 O-알킬화시켜 R^1 이 OR^5 인 일반식 (I)의 화합물로 정의되는 일반식 (I-a)의 화합물을 수득하거나,

필요에 따라 일반식 (I)의 화합물을 당 기술에 공지된 작용 그룹 변환 반응에 따라 일반식 (I)의 다른 화합물로 전환시키고; 필요에 따라 추가로 일반식 (I)의 화합물을 산으로 처리하여 산 부가염을 제조하거나, 반대로 산부가염을 알칼리로 처리하여 유리 염기로 전환시키고; 필요에 따라 이들의 입체화학적 이성체를 제조함을 특징으로 하여 제 1 항에서 청구한 화합물을 제조하는 방법:



(II) (III) (I)



(VI) (VII) (Ⅰa)

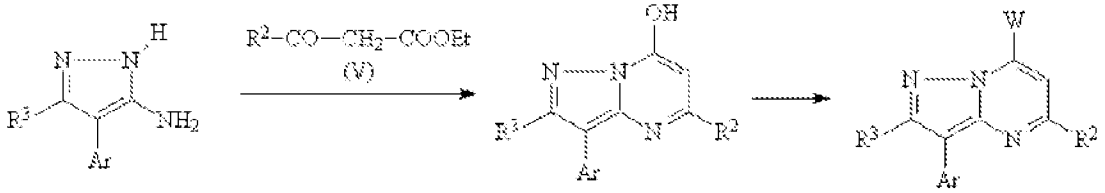
상기 반응식에서,

R^1, R^2, R^3, R^5 및 Ar 은 제 1 항에 정의된 바와 같고,

W 는 이탈 그룹을 나타낸다.

청구항 13

일반식 (IV)의 중간체를 반응-불활성 용매중에서 β-케토 에스테르(V)와 반응시켜 W' 가 하이드록시인 일반식 (II')의 화합물로 정의되는 일반식 (II'-a)의 화합물을 수득하고, 임의로 일반식 (II'-a)의 화합물을 W' 가 하이드록시이외의 것인 일반식 (II')의 화합물로 정의되는 일반식 (II'-b)의 화합물로 전환시키거나, 필요에 따라 일반식 (II')의 화합물을 당 기술에 공지된 작용 그룹 변환 반응에 따라 일반식 (II')의 다른 화합물로 전환시키고; 필요에 따라 추가로 일반식 (II')의 화합물을 산으로 처리하여 산부가염을 제조하거나, 반대로 산부가염을 알칼리로 처리하여 유리 염기로 전환시키고; 필요에 따라 이들의 입체화학적 이성체를 제조함을 특징으로 하여 제 10 항에서 청구한 일반식 (II')의 화합물을 제조하는 방법:



(IV) (II'-a) (II'-b)

상기 반응식에서,

R^2, R^3 및 Ar 은 제 1 항에 정의된 바와 같고,

W' 는 하이드록시, 할로, 메실옥시 또는 토실옥시를 나타낸다.

명세서

발명의 명칭

CRF수용체에 대한 길항제로서의 피라졸로피리미딘

본 발명은 CRF 수용체에 대해 길항성을 갖는 피라졸로피리미딘, 활성 성분으로서 이들 화합물을 함유하는 약제학적 조성물 및 일반적으로 스트레스-관련 질환을 포함한 내분비계, 정신의학계 및 신경계 증상 또는 질환을 치료하기 위한 그의 용도에 관한 것이다.

최초의 부신피질호르몬-방출 인자(CRF)는 양의 시상하부로부터 분리되었고, 41-아미노산 펩타이드인 것으로 확인되었다(참조: Vale et al., Science 213:1394-1397, 1981). 그 후, 인간과 랫트의 CRF 서열이 분리되어 동일한 것으로 확인되었지만, 양의 CRF와는 41개의 아미노산 잔기중에서 7개가 상이하다(참조: Rivier et al., Proc. Natl. Acad. Sci. USA 80:4851, 1983; Shibahara et al., EMBO J. 2:775, 1983). CRF는 내분비계, 신경계 및 면역계 기능을 상당히 변경시키는 것으로 밝혀졌다. CRF는 부신피질호르몬("ACTH"), β-엔도르핀, 및 그밖의 다른 하수체전엽으로부터 프로-오피오멜라노코르틴("POMC")-유도된 펩타이드의 정상적 및 스트레스-방출의 주요한 생리학적 조절제인 것으로 생각된다(참조: Vale et al., Science 213:1394-1397, 1981). 간단히 말하면, CRF는 뇌(DeSouza et al., Science 221:1449-1451, 1984), 하수체(DeSouza et al., Methods Enzymol. 124:560, 1986; Wynn et al., Biochem. Biophys. Res. Comm. 110:602-608, 1983), 부신(Udelsman et al., Nature 319:147-150, 1986) 및 비장(Webster, E.L., and E.B. DeSouza, Endocrinology 122:609-617, 1988)의 전반에 걸쳐 분포된 것으로 확인된 혈장막 수용체와 결합함으로써 그의 생물학적 효과를 개시하는 것으로 생각된다. CRF 수용체는 CRF에 의해 유도된 cAMP의 세포내 생산 증가를 매개하는 GTP-결합 단백질(참조: Perrin et al., Endocrinology 118:1171-1179, 1986)과 커플링한다(참조: Bilezikjian, L.M., 및 W.W. Vale, Endocrinology 113:657-662, 1983).

ACTH 및 POMC의 생산을 촉진하는 역할이외에도, CRF 는 또한 스트레스에 대한 다수의 내분비 자율 및 행동적 응답에 공조하는 것으로 여겨지며, 감정적인 장애의 병태생리에 포함될 수 있다. 또한, CRF는 면역계, 중추신경계, 내분비계 및 심혈관계 간의 커뮤니케이션에 있어서 주요 매개자인 것으로 생각된다(참조: Crofford et al., J. Clin. Invest. 90:2555-2564, 1992; Sapolsky et al., Science 238:522-524, 1987; Tilders et al., Regul. Peptides 5:77-84, 1982). 종합적으로, CRF는 중추 신경계 신경전달물질의 하나이며, 스트레스에 대한 신체의 전체적 응답을 통합하는데 주요한 역할을 하는 것으로 나타났다.

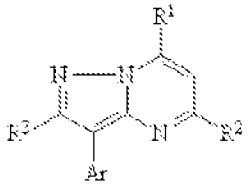
CRF를 뇌에 직접 투입하면 스트레스가 많은 환경에 노출된 동물에게서 관찰된 것과 동일한 행동적, 생리학적 및 내분비 응답이 유도된다. 예를 들어, CRF를 대뇌내심실에 주입하면, 행동이 활발해지고(참조: Sutton et al., Nature 297:331, 1982), 뇌파를 장시간 활성화시키고(참조: Ehlers et al., Brain Res. 2/8332, 1983), 교감신경부신질 경로를 자극하고(참조: Brown et al., Endocrinology 110:928, 1982), 심박수 및 혈압을 증가시키고(참조: Fisher et al., Endocrinology 110:2222, 1982), 산소 소비량을 증가시키고(참조: Brown et al., Life Sciences 30:207, 1982), 위장 운동을 변경시키고(참조: Williams et al., Am. J. Physiol. 253:G582, 1987), 음식 소비를 억제하고(참조: Levine, et al., Neuropharmacology 22:337, 1983), 성적 행동을 변화시키고(참조: Sirinathsinghji et al., Nature 305:232, 1983), 면역 기능을 저하시킨다(참조: Irwin et al., Am. J. Physiol. 255:R744, 1988). 또한, 임상적 데이터는 CRF가 우울증, 불안-관련 장애 및 신경성 식욕부진 상태의 뇌에서 과분비될 수 있음을 시사한다(참조: DeSouza, Ann. Reports in Med. Chem. 25:215-223, 1990).

따라서, 임상적 데이터는 CRF 수용체 길항제가 CRF를 과분비하는 신경정신과적 질환을 치료하는데 유용할 수 있는 신규한 항우울제 및/또는 불안해소제일 수 있음을 시사한다. CRF 수용체 길항제는 예를 들어 치환된 4-티오-5-옥소-3-피라졸린 유도체를 기술하고 있는 미합중국 특허 제 5,063,245호

및 치환된 2-아미노티아졸 유도체를 기술하고 있는 오스트레일리아 특허 제 AU-A41399/93호에 기재되어 있다. WO-92/18504 호 및 JP-32/04877 호에는 항염증제로서 피라졸로[1,5-a]피리미딘이 기재되어 있다. 또한, WO-94/13676 호, WO-94/13677 호 및 WO-95/33750 호에는 CRF 수용체 길항제로서 퓨롤로피리미딘, 피라졸로[3,4-d]피리미딘 및 치환된 푸린이 기재되어 있다. 아릴피라졸로[1,5-a]피리미딘은 잔탄 옥시다제 억제제로서 알려져 있다(참조: Robins et al., J. Heterocyclic Chem. 22:601-634, 1985). JP-42/011,753 호는 안정제 및 소염제로서 유용한 7-메틸아미노-피라졸로[1,5-a]피리미딘 유도체를 기재하고 있다. 또한, JP-61/057,587 호에 항궤양제로서 유용한 피라졸로[1,5-a]피리미딘 유도체가 기재되어 있다.

CRF의 생리학적 중요성 때문에, CRF 수용체를 길항시킬 수 있고, 상당한 CRF 수용체 결합 활성을 갖는 생물학적으로 활성인 작은 분자를 개발하는 것이 주요한 과제로 남아 있다. 이러한 CRF 수용체 길항제는 일반적으로 스트레스-관련 질환을 포함한 내분비계, 정신의학계 및 신경계 증상 또는 질환을 치료하는데 유용하다.

본 발명은 하기 일반식 (I)의 CRF 길항 화합물, 그의 입체이성체 및 약제학적으로 허용되는 산부가염에 관한 것이다:



(I)

상기식에서,

R^1 은 NR^4R^5 또는 OR^5 를 나타내며;

R^2 는 C_{1-6}알킬, C_{1-6}알킬옥시 또는 C_{1-6}알킬티오를 나타내고;

R^3 은 수소, C_{1-6}알킬, C_{1-6}알킬설포닐, C_{1-6}알킬설폭시 또는 C_{1-6}알킬티오를 나타내며;

R^4 는 수소, C_{1-6}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, C_{3-6}사이클로알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알킬카보닐옥시C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬을 나타내고;

R^5 는 C_{1-8}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, Ar^1CH_2, C_{1-6}알킬옥시C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{3-6}알케닐, 티에닐메틸, 푸라닐메틸, C_{1-6}알킬티오C_{1-6}알킬, 모르폴리닐, 모노- 또는 디(C_{1-6}알킬)아미노C_{1-6}알킬, 디(C_{1-6}알킬)아미노, C_{1-6}알킬카보닐C_{1-6}알킬, 이미다졸릴에 의해 치환된 C_{1-6}알킬, 또는 일반식 -Alk-O-CO-Ar^1 의 래디칼을 나타내거나;

R^4 및 R^5 는 이들이 결합된 질소 원자와 함께, 각각 C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬에 의해 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 그룹을 형성할 수 있으며;

Ar 은 페닐; 할로, C_{1-6}알킬, 트리플루오로메틸, 하이드록시, 시아노, C_{1-6}알킬옥시, 벤질옥시, C_{1-6}알킬티오, 니트로, 아미노 및 모노- 또는 디(C_{1-6}알킬)아미노로 구성된 그룹중에서 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 페닐; 피리디닐; 또는 할로, C_{1-6}알킬, 트리플루오로메틸, 하이드록시, 시아노, C_{1-6}알킬옥시, 벤질옥시, C_{1-6}알킬티오, 니트로, 아미노, 모노- 또는 디(C_{1-6}알킬)아미노 및 피페리디닐로 구성된 그룹중에서 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 피리디닐을 나타내고; 여기에서 치환된 페닐은 하나 또는 그 이상의 할로겐에 의해 임의로 추가로 치환될 수 있으며;

Ar^1 은 페닐; 할로, C_{1-6}알킬, C_{1-6}알킬옥시, 디(C_{1-6}알킬)아미노C_{1-6}알킬, 트리플루오로메틸 및 모르폴리닐에 의해 치환된 C_{1-6}알킬로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 페닐; 또는 피리디닐을 나타내고;

Alk 는 C_{1-6}알칸디일을 나타낸다.

또 다른 일면으로 본 발명은 상기 정의된 일반식 (I)의 신규한 화합물에 관한 것이며, 단 화합물 5-메틸-3-페닐-7-(페닐메톡시)-피라졸로[1,5-a]-피리미딘 및 2,5-디메틸-7-(메틸아미노)-3-페닐-피라졸로[1,5-a]피리미딘은 제외된다.

이 단서 조항은 JP-61/057,587 호 및 JP-42/011,753 호에 기재된 화합물을 배제하기 위한 것이다.

상기 정의에서 사용된 것으로, 용어 할로는 플루오로, 클로로, 브로모 및 요오도를 의미하고; C_{1-6}알칸디일은 예를 들어 메틸렌, 1,2-에탄디일, 1,3-프로판디일, 1,4-부탄디일, 1,5-펜탄디일, 1,6-헥산디일 및 이들의 측쇄 이성체와 같은 1 내지 6개의 탄소 원자를 갖는 2가의 직쇄 및 측쇄 포화 탄화수소 래디칼을 의미하며; C_{1-2} 알킬은 메틸 및 에틸과 같은 탄소 원자수 1 내지 2의 직쇄 포화 탄화수소 래디칼을 의미하며; C_{2-4} 알킬은 에틸, 프로필, 부틸, 1-메틸에틸 등과 같은 탄소 원자수 2 내지 4 의 직쇄 및 측쇄 포화 탄화수소 래디칼을 의미하고; C_{3-4} 알킬은 프로필, 부틸, 1-메틸에틸 등과 같은 탄소 원자수 3 내지 4의 직쇄 및 측쇄 포화 탄화수소 래디칼을 의미하며; C_{1-6}알킬은 상기 정의된 C_{1-2}알킬 및 C_{3-4}알킬과 펜틸, 펜틸 이성체, 헥실 및 헥실 이성체와 같은 탄소 원자수 5 내지 6의 그의 고급 동족체를 의미하고; C_{1-8}알킬은 상기 정의된 C_{1-6}알킬 및 예를 들어 헵틸, 옥틸 등과 같은 탄소 원자수 7 내지 8의 그의 고급 동족체를 의미하며; C_{3-6}알케닐은 예를 들어 2-프로페닐, 3-부테닐, 2-펜테닐, 3-펜테닐, 3-메틸-2-부테닐 등과 같은 3 내지 6개의 탄소 원자를 갖고 하나의 이중결합을 포함하는 직쇄 및 측쇄 탄화수소 래디칼을 의미하고; C_{3-6}알케닐이 질소 또는 산소에 결합된 경우, 결합을 형성하는 탄소 원자는 바람직하게는 포화되어있다. C_{3-6}사이클로알킬은 사이클로프로필, 사이클로부틸, 사이클로펜틸 및 사이클로헥실을 포함한다. 하이드록시C_{1-6}알킬은 하이드록실 그룹으로 치환된 C_{1-6}알킬을 의미한다. 호모피페리디닐은 하나의 질소 원자를 포함하는 7 원 포화환이다.

일부 치환체의 특성상, 일반식 (I)의 화합물은 일반적으로 사용되는 R 및 S 명명법으로 표시될 수 있는 하나 또는 그 이상의 비대칭 중심을 포함할 수 있다.

본 발명의 화합물은 염기성 질소 원자를 함유하며, 그 자체로서 유리 염기로서 또는 산부가염의 형태로 존재할 수 있으며, 이들은 모두 본 발명의 한 부분이다. 산부가염은 당 기술에 공지된 방법으로 제조될 수 있으며, 유기 및 무기산으로부터 형성될 수 있다. 적합한 유기산으로는 말레인산, 푸마르산, 벤조산, 아스코르브산, 석신산, 메탄설폰산, 아세트산, 옥살산, 프로피온산, 타르타르산, 살리실산, 시트르산, 글루콘산, 락트산, 만델린산, 신남산, 아스파르트산, 스테아르산, 팔미트산, 글리콜산, 글루탐산 및 벤젠설폰산이 포함된다. 적합한 무기산으로는 염산, 브롬화수소산, 황산, 인산 및 질산이 포함된다.

본 발명의 화합물의 특별한 그룹은 하기 제한중의 하나 이상에 따르는 일반식 (I)의 화합물이다:

a) R^1 이 NR^4R^5 이고, 여기에서 R^4 는 수소, C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{1-6}알킬카보닐옥시C_{1-6}알킬 또는 C_{3-6}알케닐, 특히 C_{2-4}알킬, 하이드록시C_{1-2}알킬, C_{3-4}알케닐 또는 C_{1-2}알킬카보닐옥시C_{2-4}알킬이며, R^5 는 C_{1-8}알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알킬옥시C_{1-6}알킬, 페닐메틸 또는 C_{3-6}사이클로알킬메틸, 특히 C_{2-4}알킬, C_{3-4}알케닐, 하이드록시C_{2-4}알킬 또는 사이클로프로필메틸이거나;

b) R^1 은 OR^5 이고, 여기에서 R^5 는 C_{1-6}알킬, 특히 C_{2-4}알킬이며;

c) R^2 는 C_{1-6}알킬, 특히 C_{1-2}알킬이고;

d) R^3 은 수소, C_{1-6}알킬 또는 C_{1-6}알킬티오, 특히 수소, C_{1-2}알킬 또는 C_{1-2}알킬티오이며;

e) Ar 은 C_{1-6}알킬, C_{1-6}알킬옥시 및 할로로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3 개의 치환체에 의해 치환된 페닐이고, 여기에서 페닐 부위는 바람직하게는 3-, 4-, 6-, 2,4- 또는 2,4,6-위치가 치환되어 있거나; Ar 은 각각 할로, 아미노, 니트로, 트리플루오로메틸, 모노- 또는 디(C_{1-6}알킬)아미노, 피페리디닐 및 C_{1-6}알킬로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3 개의 치환체에 의해 치환된 피리디닐이고, 여기에서 피리디닐 부위는 바람직하게는 2- 또는 3-위치를 통해 분자의 나머지 부분에 부착된다.

다른 특별한 화합물 그룹은 R^1 이 NR^4R^5 이고, 여기에서 R^4 및 R^5 는 이들이 결합된 질소원자와 함께, 각각 C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬에 의해 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 그룹을 형성하는 일반식 (I)의 화합물이다.

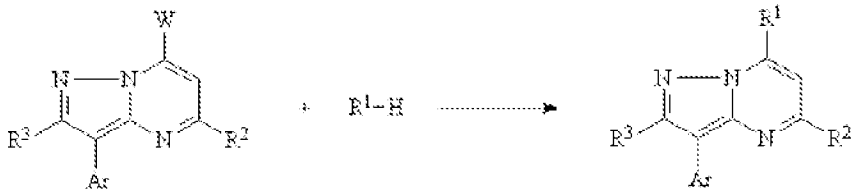
바람직한 화합물은 R^1 이 NR^4R^5 이고, 여기에서 R^4 는 C_{3-4}알킬 또는 알릴, 바람직하게는 프로필이며, R^5 는 C_{2-4}알킬, 알릴 또는 사이클로프로필메틸, 바람직하게는 프로필이고; R^2 는 메틸이며; R^3 은 수소, 메틸 또는 메틸티오, 바람직하게는 프로필이고; Ar 은 할로, 메틸 및 메톡시로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3 개의 치환체에 의해 치환된 페닐, 특히 할로, 메틸 및 디메틸아미노로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3 개의 치환체에 의해 치환된 페닐인 일반식 (I)의 화합물이다.

더욱 바람직하게는 Ar 은 4- 및/또는 6-위치가 메틸 또는 디메틸아미노에 의해 치환된 3-피리디닐이다.

가장 바람직한 화합물은 3-(2,4-디클로로페닐)-5-메틸-7-(N-프로필-N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘, 3-(2,4-디클로로페닐)-5-메틸-7-(N-알릴-N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘, 2-메틸티오-3-(2,4-디클로로페닐)-5-메틸-7-(N,N-디알릴아미노)피라졸로[2,3-a]피리미딘, 2-메틸티오-3-(2,4-디클로로페닐)-5-메틸-7-(N-부틸-N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘, 2-메틸티오-3-(2,4-디클로로페닐)-5-메틸-7-(N-프로필-N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘, 2-메틸-3-(4-클로로페닐)-5-메틸-7-(N,N-디프로필아미노)피라졸로[2,3-a]피리미딘, 3-[6-(디메틸아미노)-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민, 3-[6-(디메틸아미노)-4-메틸-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민 및 3-(2,4-디메톡시페닐)-2,5-디메틸-7-(N-프로필-N-메틸옥시에틸아미노)

피라졸로[2,3-a]피리미딘, 이들의 입체이성체 및 약제학적으로 허용되는 산부가염중에서 선택된 화합물이다.

본 발명의 화합물은 일반적으로 일반식 (II)의 피라졸로피리미딘을 일반식 (III)의 중간체로 알킬화시킴으로써 제조할 수 있다:

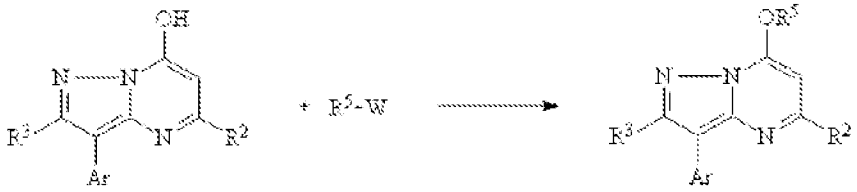


(II) (III) (I)

중간체 (II)에서, W 는 할로, 예를 들어 클로로 또는 브로모, 또는 설포닐옥시 그룹, 예를 들어 메실옥시 또는 토실옥시 그룹과 같은 적합한 이탈 그룹을 나타낸다.

상기 반응은 일반적으로 적합한 용매, 예를 들어 DMF 또는 아세토니트릴과 같은 비양성자성 용매, 에테르, 예를 들어 테트라하이드로푸란중, 바람직하게는 승온에서, 일반식 (III)의 중간체가 휘발성 아민인 경우에 밀폐 반응 용기에서 수행된다.

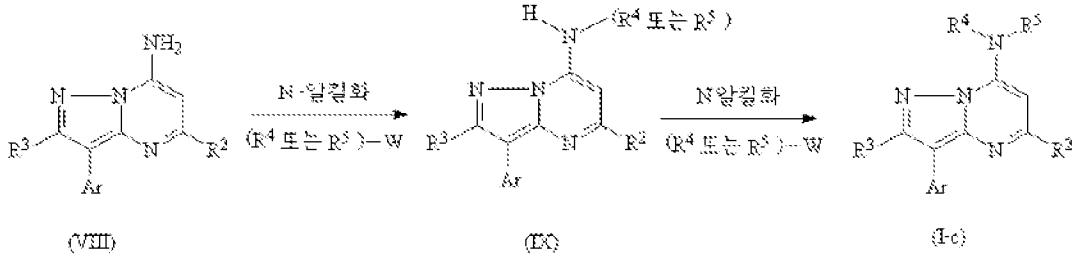
또한, R^1 이 OR^5 인 일반식 (I)의 화합물[이 화합물은 일반식 (I-a)로 표시된다]은 일반식 (VI)의 중간체를 일반식 (VII)의 중간체(여기에서, W 는 상기 정의된 바와 같다)로 O-알킬화시킴으로써 제조할 수 있다:



(VI) (VII) (I-a)

일반식 (I-a)의 화합물을 제조하는 상기 반응은 반응-불활성 용매, 예를 들어 N,N-디메틸포름아미드중에서 적합한 염기, 예를 들어 수소화나트륨의 존재하에 바람직하게는 실온 내지 환류 온도에서 수행될 수 있다.

R^1 이 NR^4R^5 인 일반식 (I)의 화합물[이 화합물은 일반식 (I-c)로 표시된다]은 일반식 (VIII) 또는 (IX)의 화합물을 하기 반응식과 같이 적합한 N-알킬화시킴으로써 제조할 수 있다:



상기 반응식에서, W 는 상기 정의한 바와 같다.

상기 N-알킬화는 반응-불활성 용매, 예를 들어 에테르(예: 테트라하이드로푸란)중에서 바람직하게는 강염기, 예를 들어 NaH의 존재하에 수행된다.

특정의 경우에, 상기 반응은 R^2 가 (R^4 또는 R^5)-W 에 의해 알킬화된, 특히 R^2 가 메틸이고, R^4 또는 R^5 는 C_{1-6}알킬인 부 생성물을 형성할 수 있다.

후술하는 바와 같이, 일반식 (I)의 화합물은 당 기술에 공지된 변환방법에 따라 상호 전환시킬 수 있다.

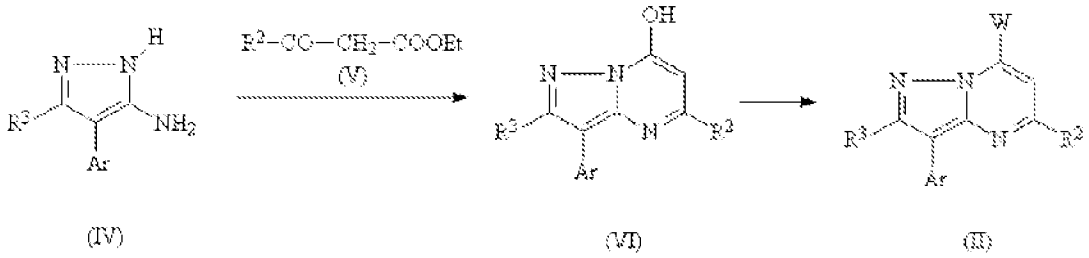
예를 들어, R^3 이 C_{1-6}알킬티오인 일반식 (I)의 화합물은 산화 반응에 의해, 예를 들어 반응-불활성 용매, 예를 들면 디클로로메탄중에서 3-클로로퍼벤조산과 같은 퍼옥사이드로 처리함으로써 R^3 가 C_{1-6}알킬설포닐 또는 C_{1-6}알킬설폭시인 일반식 (I)의 화합물로 전환시킬 수 있다. 산화제의 양 및 다른 반응 파라미터를 조절함으로써 R^3 가 C_{1-6}알킬설포닐 또는 C_{1-6}알킬설폭시인 일반식 (I)의 화합물 또는 이들의 혼합물을 수득할 수 있으며, 이들을 계속해서 통상의 방법, 예를 들어 칼럼 크로마토그래피에 의해 분리할 수 있다.

또한, 일반식 (I)의 화합물은 당 기술에 공지된 반응 또는 작용 그룹 변환방법에 따라 상호 전환시킬 수 있다. 예를 들어, 하이드록시C_{1-6}알킬 그룹을 갖는 일반식 (I)의 화합물은 예를 들어 디클로로메탄과 같은 반응-불활성 용매중에서, 임의로 염기, 예를 들면 피리딘의 존재하에 산 무수물로 처리함으로써 C_{1-6}알킬카보닐옥시C_{1-6}알킬 그룹을 갖는 일반식 (I)의 화합물로 전환시킬 수 있다.

니트로 그룹을 갖는 일반식 (I)의 화합물을 아미노 그룹을 갖는 일반식 (I)의 화합물로 전환시키고, 계속해서 모노- 또는 디(C_{1-6}알킬)아미노 그룹을 갖는 일반식 (I)의 화합물로 전환시킬 수 있다. 또한, 아미노 그룹은 디아조화 반응을 이용하여 할로로 전환시킬 수 있다.

또한, 일반식 (I)의 화합물의 Ar 그룹은 적합한 용매, 예를 들어 아세트산중에서 할로겐화제, 예를 들어 염소 또는 브롬을 사용하여 할로겐화시킬 수 있으며, 임의로 반응은 실온 내지 반응 혼합물의 환류온도에서 수행할 수 있다.

중간체는 로빈스(Robins)등에 의한 문헌[J. Heterocyclic Chem. 22:601-634, 1985]에 기술된 방법에 따라 제조할 수 있다.

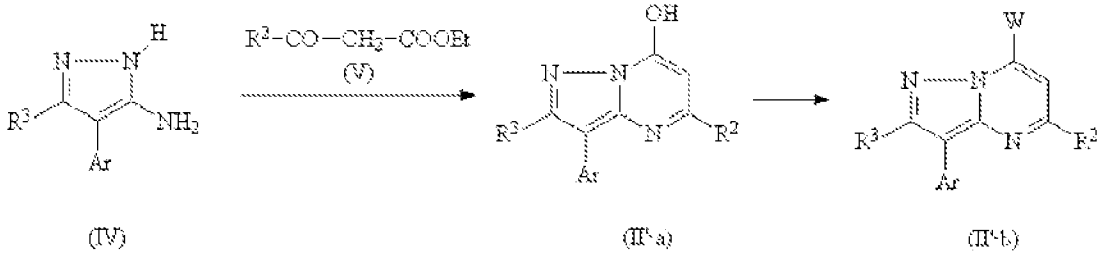


(IV) (VI) (II)

아미노피라졸 유도체(IV) 를 바람직하게는 환류 조건하에 에테르, 예를 들면 THF와 같은 적합한 반응-불활성 용매중에서 β-케토 에스테르(V)와 반응시켜 하이드록시피라졸로피리미딘 (VI)을 수득하고, 예를 들어 중간체 (VI)의 하이드록시 그룹을 메탄설포닐옥시 클로라이드 또는 할로겐화제, 예를 들면 $POCl_3$로 처리하여 이탈 그룹 W로 전환시킴으로써 중간체 (VI)를 일반식 (II)의 중간체로 전환시킨다.

일반식 (VIII)의 중간체는 일반식 (II)의 중간체를 암모니아로 처리하여 제조한다.

한 구체예에서, 본 발명은 또한 W' 가 하이드록시, 할로, 메실옥시 또는 토실옥시를 나타내고, Ar 은 페닐이외의 것인 (II')의 중간체를 제공한다.



(IV) (II'-a) (II'-b)

상기 일반식 (II')의 중간체는 상기 일반식 (II)의 중간체를 제조하기 위해 사용된 방법에 따라 W' 가 하이드록시인 일반식 (II')의 화합물로 정의되는 일반식 (II'-a)의 화합물을 수득하고, 임의로 일반식 (II'-a)의 화합물을 W' 가 하이드록시이외의 것인 일반식 (II')의 화합물로 정의되는 일반식 (II'-b)의 화합물로 전환시킴으로써 제조할 수 있다.

입체이성체는 일반식 (I)의 최종 생성물을 당 기술에 공지된 방법에 따라 분리함으로써, 예를 들어 광학 활성산으로 처리하고, 형성된 부분입체이성체염을 선택적 결정화 또는 칼럼 크로마토그래피에 의해 분리함으로써 제조할 수 있다. 또한, 입체이성체는 상술한 반응도식에서 또는 후술하는 중간체의 제조에 있어서 입체이성체 출발물질을 사용함으로써 제조할 수 있다.

CRF 수용체 길항제로서 화합물의 유효성은 다양한 시험 방법에 의해 결정될 수 있다. 본 발명의 적합한 CRF 길항제는 CRF가 그의 수용체에 특이적으로 결합하는 것을 억제할 수 있으며, CRF 와 관련된 활성을 길항할 수 있다. 일반식 (I)의 화합물은 DeSouza 등에 의한 문헌 (J. Neuroscience 7:88, 1987) 및 Battaglia 등에 의한 문헌 (Synapse I:572, 1987)에 기재된 시험(이들로 한정되지 않는다)을 포함하여 이러한 목적에 일반적으로 사용되는 하나 또는 그 이상의 시험 방법에 의해 CRF 길항제로서의 활성에 대해 평가될 수 있다. 상기 언급된 바와 같이, 적합한 CRF 길항제로는 CRF 수용체에 대해 친화성을 갖는 화합물이 포함된다. CRF 수용체 친화성은 수용체(예를 들어 랫트의 대뇌피질막으로 부터 제조된 수용체)에 대한 방사표지된 CRF(예를 들어 [^{125}I]티로신 CRF)의 결합을 억제하는 화합물의 정도를 측정하는 결합 분석 시험에 의해 결정될 수 있다. DeSouza 등에 의한 문헌 (supra, 1987)에 기술된 방사리간드 결합 분석 시험은 CRF 수용체에 대한 화합물의 친화성을 결정하는 분석법을 제공한다. 이러한 활성은 일반적으로 수용체로부터 방사표지된 리간드

의 50%를 대체시키는데 필요한 화합물의 농도로서 IC_{50}으로 부터 계산되며, 하기 식으로부터 계산된 "K_i"값으로서 기록된다:

$$K_i = (IC_{50}/(1+L/K_D))$$

상기식에서,

L 은 방사리간드이고,

K_D는 수용체에 대한 방사리간드의 친화성이다(참조: Chen 및 Prusoff에 의한 Biochem. Pharmacol. 22:3099, 1973).

CRF 수용체 결합을 억제하는 것 이외에, 화합물의 CRF 수용체를 길항하는 활성이 CRF 와 관련된 활성을 길항시킬 수 있는 화합물의 능력에 의해 결정될 수 있다. 예를 들어, CRF 는 아데닐레이트 사이클라제 활성을 포함하여 각종 생화학적 과정을 자극하는 것으로 공지되어 있다. 따라서, 화합물은, 예를 들어 cAMP 수준을 측정함으로써 CRF-유도된 아데닐레이트 사이클라제의 활성을 길항시킬 수 있는 그의 능력에 의해 CRF 길항제로서 평가될 수 있다. Battaglia 등에 의한 문헌(supra, 1987)에 기술된 CRF-유도된 아데닐레이트 사이클라제의 활성 시험으로 부터 CRF 활성을 길항하는 화합물의 능력을 측정하는 시험을 유도할 수 있다. 따라서, CRF 수용체 길항 활성은 일반적으로 초기 결합 시험(DeSouza(supra, 1987)에 기재된 것과 같이)을 수행하고, 그후에 cAMP 선별 프로토콜(Battaglia(supra, 1987)에 기재된 것과 같이)를 수행하는 과정을 포함하는 시험 기술에 의해 측정될 수 있다. CRF 수용체 결합 친화성과 관련하여, 본 발명의 CRF 수용체 길항제는 10 μM미만의 K_i 를 갖는다. 본 발명의 바람직한 구체예에서, CRF 수용체 길항제는 1 μM미만 및 더욱 바람직하게는 0.25 μM(즉, 250 nM) 미만의 K_i 를 갖는다.

본 발명의 CRF 수용체 길항제는 CRF 수용체 부위에서 활성을 나타내며, 내분비계, 정신의학계 및 신경계 질환 또는 병을 포함한 광범위한 질환 또는 병을 치료하기 위한 치료제로서 사용될 수 있다. 더욱 구체적으로, 본 발명의 CRF 수용체 길항제는 CRF가 과분비됨으로써 나타나는 생리학적 증상 또는 질환을 치료하는데 유용할 수 있다. CRF는 스트레스에 대한 내분비계, 행위적 및 자가 응답을 활성화하고 공조하는 중추 신경계 신경전달물질인 것으로 생각되기 때문에, 본 발명의 CRF 수용체 길항제는 신경정신과적 질환을 치료하는데 사용될 수 있다. 본 발명의 CRF 수용체 길항제에 의해 치료될 수 있는 신경정신과적 질환에는 우울증과 같은 감정 장애; 불안-관련 장애, 예를 들어 범불안 장애, 공황 장애, 강박 장애, 비정상적 공격성, 불안정 협심증 및 반응적 고혈압과 같은 심혈관 이상; 및 신경성 식욕부진, 대식증 및 과민성 장증상과 같은 음식물 섭취 장애가 포함된다. CRF 길항제는 또한 각종 질병 상태를 수반하는 스트레스에 의한 면역 억제뿐만 아니라 출혈을 치료하는데 유용할 수 있다. 본 발명에 따른 CRF 길항제의 또 다른 용도로는 염증성 증상(류마티스성 관절염, 포도막염, 천식, 염증성 장 질환 및 G.I. 운동성과 같은), 쿠싱(Cushing)병, 유아 경련, 간질, 유아 및 성인 발작, 및 각종 약물 남용 및 금단현상(알콜중독 포함)의 치료가 포함된다.

본 발명의 또 다른 구체예에서, 하나 또는 그 이상의 CRF 수용체 길항제를 함유하는 약제학적 조성물이 기재되어 있다. 투여의 목적을 위해, 본 발명의 화합물은 약제학적 조성물로 제형화될 수 있다. 본 발명의 약제학적 조성물은 본 발명의 CRF 수용체 길항제(즉, 일반식 (I)의 화합물) 및 약제학적으로 허용되는 담체 및/또는 희석제를 함유한다. CRF 수용체 길항제는 특정 질환을 치료하는데 효과적인 양, 즉 CRF 수용체 길항 활성을 이루기에 충분한 양으로서, 및 바람직하게는 환자에 허용되는 독성 수준으로 조성물중에 존재한다. 바람직하게는, 본 발명의 약제학적 조성물은 CRF 수용체 길항제를 투여 경로에 따라 1회 복용량당 0.1 ㎎ 내지 250 ㎎, 및 더욱 바람직하게는 1 ㎎ 내지 60 ㎎의 양으로 함유할 수 있다. 적합한 농도 및 복용량은 당 기술자들에 의해 쉽게 결정될 수 있다.

약제학적으로 허용되는 담체 및/또는 희석제는 당해 기술자들에 잘 알려져 있다. 액체 용액으로서 제형화된 조성물에 대해, 허용되는 담체 및/또는 희석제는 염수 및 멸균수를 포함하며, 임의로 항산화제, 완충액, 세균 발육 저지제 및 그밖의 다른 통상적인 첨가제를 함유한다. 조성물은 CRF 수용체 길항제 이외에, 희석제, 분산제, 계면활성제, 결합제 및 윤활제를 함유하는 환제, 캡셀제, 과립제 또는 정제로 제형화될 수 있다. 당해 기술자들은 CRF 수용체 길항제를 문헌 [Remington's, Pharmaceutical Sciences, Gennaro, Ed., Mack Publishing Co., Easton, USA, 1990]에 기술된 바와 같이, 관례에 따라 적합한 방식에 의해 추가로 제형화시킬 수 있다.

또 다른 구체예에서, 본 발명은 내분비계, 정신의학계 및 신경계 증상 또는 질환을 포함한 각종 증상 또는 질환을 치료하는 방법을 제공한다. 이 방법은 본 발명의 화합물을 온혈동물에게 이러한 증상 또는 질환을 치료하기에 충분한 양으로 투여하는 것을 포함한다. 이 방법은 본 발명의 CRF 수용체 길항제를, 바람직하게는 약제학적 조성물의 형태로 전신 투여하는 것을 포함한다. 본 원에 사용된 것으로, 전신 투여는 경구 및 비경구 투여를 포함한다. 경구 투여의 경우에, CRF 수용체 길항제의 적합한 약제학적 조성물은 분제, 과립제, 환제, 정제 및 캡셀제뿐 아니라 액제, 시럽제, 현탁제 및 유제를 포함한다. 이들 조성물은 또한 향미제, 방부제, 현탁제, 농조화제, 유화제 및 그밖의 다른 약제학적으로 허용되는 첨가제를 함유한다. 비경구 투여의 경우에, 본 발명의 화합물은 CRF 수용체 길항제 이외에 완충제, 항산화제, 세균 발육 저지제 및 이러한 용액에 공통적으로 사용되는 그밖의 다른 첨가제를 함유할 수 있는 수성 주사 용액제로 제조될 수 있다.

상술한 바와 같이, 본 발명의 화합물을 투여하여 각종 장애 또는 질환을 치료할 수 있다. 특히, 본 발명의 화합물은 우울증, 감정 장애, 공황 장애, 강박 장애, 비정상적 공격성, 불안정 협심증, 반응적 고혈압, 신경성 식욕부진, 대식증, 과민성 장증상, 스트레스 관련 면역 억제, 졸증, 염증, 루성병, 유아 경련, 간질, 및 각종 약물 남용 및 금단현상을 치료하기 위해 온혈 동물에 투여될 수 있다.

따라서, 본 발명은 부신피질호르몬-방출 인자(CRF)의 과분비로 인한 생리학적 증상 또는 질환 치료용 의약을 제조하기 위한 일반식 (I)의 화합물의 용도를 제공한다; 본 발명은 또한 신규한 일반식 (I)의 화합물의 의약으로서의 용도를 제공한다.

하기 실시예는 설명할 목적으로 제시되었으며, 한정하기 위한 것은 아니다.

실험 부분

이후 "THF"는 테트라하이드로푸란을 의미하고, "DCM"은 디클로로메탄을 의미한다.

A. 중간체의 제조

실시예 A.1

a) 3-아미노-4-(2,4-디클로로페닐)피라졸 및 에틸 아세토아세테이트(2 당량)를 디옥산에 용해시키고, 환류하에서 밤새 가열한다. 혼합물을 진공중에서 농축시키고, 에틸 아세테이트로 희석한다. 2 일 동안 정치시킨 후 형성된 희백색 고체를 진공 여과에 의해 수집하여 3-(2,4-디클로로페닐)-5-메틸-7-하이드록시피라졸로[2,3-a]피리미딘(중간체 1)을 수득한다.

b) 중간체 1(300 ㎎)을 $POCl_3$(1.5 ㎖)와 혼합하고, 1 시간동안 가열하여 환류시킨다. 형성된 자주색 용액을 조심스럽게 빙수에 옮긴다. 생성물을 에틸 아세테이트로 추출하여 포화 중탄산나트륨 및 염수로 세척하고, $MgSO_4$ 상에서 건조시킨 후, 진공중에서 농축시켜 3-(2,4-디클로로페닐-5-메틸-7-클로로피라졸로[2,3-a]피리미딘(중간체 2)을 갈색 고체(260 ㎎, 82%)로 수득한다.

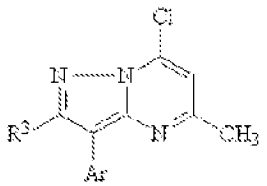
실시예 A.2

a) THF(10 ㎖)중의 수소화나트륨(60%, 25 mmol)의 교반 용액에 THF(10 ㎖)중의 6-(디메틸아미노)-3-피리딘아세토니트릴(10 mmol)을 적가한다. 용액을 10 분동안 교반한 후, 에틸 아세테이트(30 mmol)를 천천히 가한다. 형성된 현탁액을 실온에서 1 시간동안 교반한다. 반응 혼합물을 진공하에서 농축시키고, 에틸 아세테이트/메탄올(1:1)에 용해시킨 다음, 실리카를 통해 여과한다. 여액을 농축시켜 중간체 7을 수득한다.

b) 중간체 7과 히드라진 하이드로브로마이드(100 mmol)의 혼합물을 에탄올/물(9:1, 총 100 ㎖)에 용해시키고, 1 시간동안 환류시킨다. 반응 혼합물을 농축시키고, 잔류물을 에틸 아세테이트와 중탄산나트륨 용액으로 분배한다. 추출물을 합하여 황산나트륨상에서 건조시키고, 여과한 후, 농축건조시킨다. 잔류물을 1,4-디옥산(200 ㎖)에 용해시키고, 에틸 아세토아세테이트의 존재하에서 16 시간동안 환류시킨다. 반응 혼합물을 냉각시키면 회백색 고체가 석출된다. 결정화를 촉진하기 위해 디에틸 에테르를 첨가한 후, 침전을 여과하고, 건조시켜 3-[2-(디메틸아미노)-5-피리디닐]-2,5-디메틸-7-하이드록시피라졸로[2,3-a]피리미딘(중간체 8)을 수득한다.

c) 중간체 8을 $POCl_3$(2 ㎖)에 용해시키고, 2 시간동안 환류시킨다. 반응 혼합물을 냉각시킨 후, 얼음에 붓는다. 고체의 탄산나트륨을 첨가하여 용액을 염기성(pH=9)으로 만든 후, 디에틸 에테르로 추출한다. 유기층을 합하여 황산나트륨상에서 건조시키고, 여과한 다음, 농축시켜 3-[6-(디메틸아미노)-3-피리디닐]-2,5-디메틸-7-클로로-피라졸로[2,3-a]피리미딘(중간체 9)을 수득한다.

하기 표 1에 상기 언급된 실시예중의 하나에 따라 제조된 중간체를 나타내었다:



중간체번호	실시예번호	R^3	Ar
2345613	A.1A.1A.1A.1A.1A.1A	$HCH_3SCH_3HHCH_3$	2,4-디클로로페닐 2,4-디클로로페닐 2,4-디클로로페닐 4-클로로페닐 2,6-디클로로페닐 4-클로로페닐

중간체번호	실시예번호	R^3	Ar
14151617181	[illegible]	[illegible]	3-메톡시페닐 4-메톡시페닐 2,4-디메톡시페닐 3,4-디메톡시페닐 2,4,6-트리메톡시페닐 6-시클릭아미노-3-피리디닐 6-디메틸아미노-4-메틸-3-피리디닐 6-메틸-5-니트로-2-피리디닐 5-클로로-2-피리디닐 6-메틸-3-피리디닐 3-메틸-5-니트로-2-피리디닐

B. 최종 생성물의 제조

실시예 B.1

중간체 2(21 ㎎)와 N-프로필-N-사이클로프로판메틸아민(75 ㎎)의 혼합물을 밀폐 반응 용기중, 100 ℃에서 밤새 가열한다. 1:5 에틸 아세테이트-헥산을 사용하여 예비(preparative) TLC 플레이트 상에서 크로마토그래피하여 3-(2,4-디클로로페닐)-5-메틸-7-(N-프로필-N-사이클로프로판메틸아미노)-피라졸로[2,3-a]피리미딘(화합물 17)(17.4 ㎎) 및 3-(2,4-디클로로페닐)-5-메틸-7-(N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘(화합물 8)(1 ㎎)을 수득한다.

유사한 방법으로, 중간체 2 및 각각 (S)-(-)-로이시놀 (R)-(+)-로이시놀을 출발물질로 하여 (S)-2-[[3-(2,4-디클로로페닐)-5-메틸-7-피라졸로[2,3-a]피리미디닐]아미노]-4-메틸-1-펜탄올(화합물 11) 및 그의 R-유사체(화합물 12)를 제조한다.

실시예 B.2

아세토니트릴(50 ㎖)중의 다-n-프로필아민(13 g) 및 중간체 10(8 g)의 용액을 환류하에서 3 시간동안 가열한다. 혼합물을 에틸 아세테이트를 사용하여 단 실리카겔 플러그를 통하여 여과한 후, 여액을 진공중에서 농축시켜 연한 황색 고체를 수득하고, 이를 에테르-헥산으로 재결정화시켜 3-[6-(디메틸아미노)-4-메틸-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민(화합물 53) 8.9 g(93%)을 수득한다.

화합물 53(8.1 g)을 디에틸 에테르(150 ㎖)와 DCM(50 ㎖)의 혼합물에 용해시키고, 이 혼합물을 교반하면서 디에틸 에테르(1M, 21.3 ㎖)중의 HCl로 적가 처리하여 화합물 53을 그의 염산 부가염으로 전환시킨다. 형성된 회백색 고체를 여과수집하여 3-[6-(디메틸아미노)-4-메틸-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민 모노하이드로클로라이드 8.7 g(98%)을 수득한다.

실시예 B.3

중간체 3(15 ㎎)을 에탄올(0.5 ㎖)에 용해시키고, 소듐 에톡사이드(12 ㎎)의 존재하에서 1 시간동안 교반한다. 실리카겔 상에서 크로마토그래피하여 3-(2,4-디클로로페닐)-7-(에톡시)-5-메틸-2-메틸티오-피라졸로[2,3-a]피리미딘(화합물 50) 을 수득한다.

실시예 B.4

THF(3 ㎖)중의 화합물 6(14 ㎎)의 용액을 실온에서 5 분동안 수소화나트륨(60 ㎎, 과량)으로 처리한 다음, 요오도프로판(0.3 ㎖)으로 처리한다. 반응물을 실온에서 밤새 교반하고, 메탄올(0.5 ㎖)로 퀀치한다(quench). 생성된 혼합물을 예비 TLC 플레이트상에 충전하고 1:5 에틸 아세테이트-헥산으로 전개하여 무색 오일로 3-(2,4-디클로로페닐)-5-메틸-7-[N-(3-메톡시프로필)-N-프로필아미노]-피라졸로[2,3-a]피리미딘(화합물 45)(5.7 ㎎), 3-(2,4-디클로로페닐)-5-부틸-7-[N-(3-메톡시프로필)-N-프로필아미노]-피라졸로[2,3-a]피리미딘(화합물 46)(4 ㎎) 및 3-(2,4-디클로로페닐)-5-부틸-7-[3-메톡시-프로필아미노]-피라졸로[2,3-a]피리미딘(화합물 47)(3.5 ㎎)을 수득한다.

실시예 B.5

화합물 26(8 ㎎)을 DCM(1 ㎖)에 용해시키고, 아세트산 무수물(0.1 ㎖) 및 피리딘(0.1 ㎖)으로 처리한다. 혼합물을 실온에서 밤새 교반하고, 진공중에서 농축시킨다. 잔류물을 에틸 아세테이트로 희석시키고, 단 실리카겔 칼럼을 통해 여과한다. 여액을 농축시켜 3-(2,4-디클로로페닐)-5-메틸-7-[N-(2-아세톡시에틸)-N-벤질아미노]-피라졸로[2,3-a]피리미딘(화합물 27)(8.6 ㎎)을 무색 오일로 수득한다.

실시예 B.6

DCM(3 ㎖)중의 화합물 40(20 ㎎)의 용액을 3-클로로퍼벤조산(19 ㎎)으로 처리한다. 용액을 실온에서 1 시간동안 교반한다. 에틸 아세테이트-헥산(1:1)을 사용하여 실리카겔 칼럼 플레이트상에서 크로마토그래피하여 화합물 43 및 화합물 44 를 수득한다.

실시예 B.7

화합물 55와 무수 에탄올(100 ㎖)중의 활성탄소상의 팔라듐(100 ㎎)의 혼합물을 수소화 유니트에 도입하고, 2.7 10^5 Pa(40 psi)에서 2 시간동안 수소화시킨다. 반응 혼합물을 여과하고, 농축시킨다. 잔류물을 디에틸 에테르에 용해시키고, 농축시켜 3-(5-아미노-3-메틸-2-피리디닐)-2,5-디메틸-N,N-디프로필-피라졸로[2,3-a]피리미딘-7-아민(화합물 56) 1.49 g을 수득한다.

실시예 B.8

ACN(20 ㎖)중의 수성 포름알데하이드(6.4 g) 및 화합물 56(1.39 g)의 교반 용액에 0 ℃에서 소듐 시아노보로하이드라이드(734 ㎎)를 가한다. 빙초산(1 ㎖)을 가하고, 반응 혼합물을 실온에서 2 시간동안 교반한다. 반응 혼합물을 에틸 아세테이트와 포화 수성 중탄산나트륨으로 분배시킨다. 유기층을 염수로 세척하고, 황산나트륨상에서 건조시킨 다음, 여과하고, 농축건조시켜 실리카겔상에서 플래쉬(flash) 칼럼 크로마토그래피($CH_2Cl_2/CH_3OH/NH_4OH$ 150:10:1)에 의해 정제한다. 목적하는 분획을 분리하여 3-[5-(디메틸아미노)-3-메틸-2-피리디닐]-2,5-디메틸-N,N-디프로필-피라졸로[2,3-a]피리미딘-7-아민(화합물 57) 1.30 g을 수득한다.

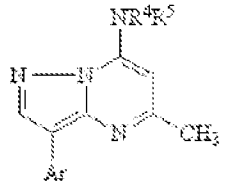
실시예 B.9

빙욕에서 냉각시킨 물(1 ㎖)과 농 HCl(1 ㎖)의 혼합물중의 화합물 56(100 ㎎)의 용액에 물(1 ㎖)중의 아질산나트륨(21 ㎎)의 용액을 가한다. 용액을 빙욕에서 교반하면서 농 HCl중의 염화구리(I)(281 ㎎)의 혼합물에 첨가한다. 고체를 분리하고, 혼합물을 60 ℃로 가열하여 등명한 용액을 수득한다. 반응 혼합물을 NaOH로 염기화시키고, 에틸 아세테이트로 추출한 다음, 염수로 세척하고, 농축시킨다. 예비 TLC에 의해 정제하여 16 ㎎의 화합물 98을 수득한다.

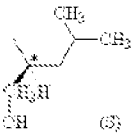
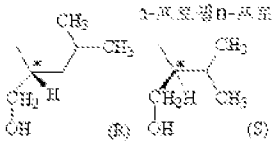
실시예 B.10

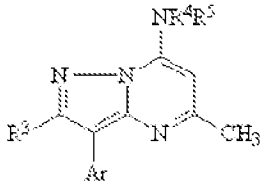
화합물 56(100 ㎎)을 빙욕에서 냉각시킨 플루오로붕산(물중의 48 중량%, 2 ㎖)의 용액에 가한 다음, 물(1 ㎖)중의 아질산나트륨(20 ㎎)의 용액을 가한다. 온도를 10 ℃미만으로 유지시킨다. 고체를 여과하여 수집하고, 건조시킨 후, 중탄산나트륨 수용액과 에틸 아세테이트로 분배한다. 유기층을 염수로 세척하고, 농축시킨 후, 잔류물을 예비 TLC에 의해 정제하여 20 ㎎의 화합물 100을 수득한다.

하기 표 2 내지 5에 상기 실시예중의 하나에 따라 제조된 화합물을 나타내었고, 표 6 및 7 에는 이들 화합물에 대한 분석 데이터를 나타내었다:



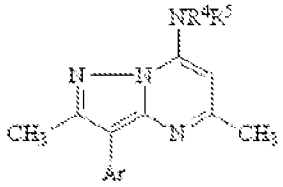
화합물번호	실시예번호	R^4	R^5	Ar
12345678910	B.1B.1B.1

화합물번호	실시예번호	R^4	R^5	Ar
111213141516178889202122232425262728293031323334	8889202122232425262728293031323334		 (S)  (R) (S) 사이클로프로필메틸	n-프로필n-프로필n-프로필



화합물번호	실시예번호	R^3	R^4	R^5	Ar
303132343536	B.1B.1B.1B.1B.1B	CH_3 SCH_3 SCH_2CH_3 $SCH_2CH_2CH_3$ $SCH_2CH_2CH_2CH_3$ $SCH_2CH_2CH_2CH_2CH_3$		3-할로겐 2-메톡시	2,4-디클로로페닐 2,4-디클로로페닐

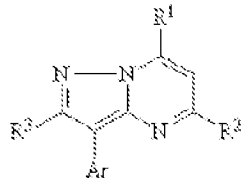
화합물번호	실시예번호	R^3	R^4	R^5	Ar
373	83	94	1	2	3

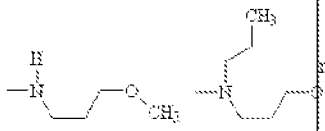


화합물번호	실시예번호	R^4	R^5	Ar
A84951	[illegible]	[illegible]	[illegible] n-프로필n-프로필	4-클로로페닐 2,4-(CH3O(CH2)2O)2C6H3 2-(CH3O(CH2)2O)-4-(CH3O(CH2)2O(CH2)2O)C6H3 2,4-(CH3O(CH2)2O)2-5-(CH3O(CH2)2O(CH2)2O)C6H2 2-(CH3O(CH2)2O)-4,5-(CH3O(CH2)2O(CH2)2O)2C6H2 2,4,5-(CH3O(CH2)2O)3C6H2 2-(CH3O(CH2)2O)-4-(CH3O(CH2)2O(CH2)2O)-5-(CH3O(CH2)2O(CH2)2O(CH2)2O)C6H 2,4-(CH3O(CH2)2O)2-5-(CH3O(CH2)2O(CH2)2O(CH2)2O)C6H 2-(CH3O(CH2)2O)-4,5-(CH3O(CH2)2O(CH2)2O(CH2)2O)2C6H 2,4,5-(CH3O(CH2)2O)3C6H

화합물번호	실시예번호	R^4	R^5	Ar
808182838	[illegible]	[illegible]	[illegible]	[illegible]

화합물번호	실시예번호	R^4	R^5	Ar



화합물번호	실시예번호	R^1	R^2	R^3	Ar
464750	B.4B.4B.3		n-C_4H_9n-C_4H_9HNCH3-S-	CH_3CH_2O-	2,4-디클로로페닐2,4-디클로로페닐2,4-디클로로페닐

분석 데이터

화합물 번호	^{1}H NMR 데이터(CDCl$_3$)	MS M + 1
1	δ 0.45 (m,2H), 0.78 (m,2H), 1.20 (m,1H), 2.84 (s,3H), 3.40 (d,2H), 5.98 (s,1H), 7.41 (dd,1H), 7.52 (d,1H), 7.76 (d,1H), 8.32 (s,1H)	335
2	δ 0.88 (d,3H), 1.05 (d,3H), 1.74 (m,1H), 2.52 (s,3H), 3.20 (t,2H), 5.87 (s,1H), 6.40 (t,1H), 7.30 (dd,1H), 7.47 (d,1H), 7.99 (d,1H), 8.42 (s,1H)	349

화합물 번호	^{1}H NMR 데이터(CDCl$_3$)	MS M + 1
3	δ 1.57 (s,9H), 2.54 (s,3H), 6.05 (s,1H), 6.48 (s,1H), 7.31 (d,1H), 7.47 (s,1H), 7.99 (d,1H), 8.39 (s,1H)	349
4	δ 1.97 (m,2H), 2.43 (s,3H), 3.62 (m,2H), 3.75 (t,3H), 4,00 (brs, 1H), 6.18 (s,1H), 7.39 (dd,1H), 7.52 (d,1H), 8.19 (d,1H), 8.43 (s,1H)	351
5	δ 1.03 (t,6H), 1.60-1.85 (m,4H), 2.56 (s,3H), 3.49 (m,1H), 5.92 (s,1H), 6.19 (d,1H), 7.35 (dd,1H), 7.50 (dd,1H), 8.01 (d,1H), 8.44 (s,1H)	363
6	δ 2.02 (m,2H), 2.51 (s,3H), 3.40 (s,3H), 3.51 (m,4H), 5.91 (s,1H), 6.71 (t,1H), 7.31 (dd,1H), 7.47 (d,1H), 7.99 (d,1H), 8.42 (s,1H)	365
7	δ 1.23 (d,6H), 2.00 (m,2H), 2.52 (s,1H), 3.51 (dd,2H), 3.59 (m,2H), 5.90 (s,1H), 6.92 (t,1H), 7.31 (dd, 1H), 7.46 (d,1H), 8.00 (d,1H), 8.41 (s,1H)	393
8	δ 0.35 (m,2H), 0.68 (m,2H), 1.25 (m,1H), 2.52 (s,3H), 3.23 (dd,2H), 5.88 (s,1H), 6.40 (t,1H), 7.32 (d,1H), 7.48 (s,1H), 7.99 (s,1H), 8.43 (s,1H)	347
9	δ 1.03 (d,3H), 1.06 (d,3H), 1.31 (d,3H), 1.95 (m,1H), 2.52 (s,3H), 3.54 (m,1H), 5.88 (s,1H), 6.23 (d,1H), 7.32 (d,1H), 7.47 (s,1H), 7.98 (d,1H), 8.41 (s,1H)	363
10	δ 0.95 (d,3H), 0.97 (d,3H), 1.40-1.80 (m,3H), 2.53 (s,3H), 3.76 (m,1H), 5.89 (s,1H), 6.12 (d,1H), 7.32 (d,1H), 7.47 (s,1H), 7.97 (d,1H), 8.40 (s,1H)	377
11	δ 0.94 (d,3H), 0.99 (d,3H), 1.53 (m,1H), 1.76 (m,1H), 2.50 (s,3H), 2.93 (brs,1H), 3.48 (m,1H), 3.76 (m,1H), 5.97 (s,1H), 6.22 (d,1H), 7.35 (dd, 1H), 7.51 (d,1H), 7.95 (d,1H), 8.36 (s,	393
12	δ 0.92 (d,3H), 0.97 (d,3H), 1.52 (m,2H), 1.72 (m,1H), 2.47 (s,3H), 3.02 (brs,1H), 3.42 (m,1H), 3.72 (m,2H), 5.94 (s,1H), 6.20 (d,1H), 7.33 (d,1H), 7.49 (s,1H), 7.92 (d,1H), 8.33 (s,	393
13	δ 0.99 (d,6H), 1.98 (m,1H), 2.44 (s,3H), 3.22 (brs, 1H), 3.46 (m,2H), 3.73 (m,1H), 5.88 (s,1H), 6.31 (d,1H), 7.32 (d,1H), 7.48 (s,1H), 7.92 (d,1H), 8.32 (s, 1H)	379
14	δ 0.21 (m,2H), 0.54 (m,2H), 1.10 (m,1H), 2.53 (s,3H), 3.28 (s,3H), 3.91 (d,2H), 5.99 (s,1H), 7.32 (d,1H), 7.48 (s,1H), 7.97 (d,1H), 8.43 (s,1H)	379

화합물 번호	^{1}H NMR 데이터(CDCl$_3$)	MS M + 1
15	δ 0.96 (t,3H), 1.31 (t,3H), 1.38 (m,2H), 1.71 (m,2H), 2.49 (s,3H), 3.74 (t,2H), 3.65 (q,2H), 5.90 (s,1H), 7.30 (dd,1H), 7.46 (d,1H), 7.97 (d,1H), 8.40 (s,1H)	377
16	δ 0.96 (t,6H), 1.73 (m,4H), 2.49 (s,3H), 3.73 (t,4H), 5.88 (s,1H), 7.33 (dd,1H), 7.46 (d,1H), 7.98 (d,1H), 8.40 (s,1H)	377
17	δ 0.26 (m,2H), 0.58 (m,2H), 0.98 (t,3H), 1.18 (m,1H), 1.76 (m,2H), 2.53 (s,3H), 3.76 (d,2H), 3.81 (t,2H), 6.02 (s,1H), 7.34 (dd,1H), 7.49 (dd,1H), 8.44 (s,1H)	389
18	δ 1.04 (t,3H), 1.77 (m,2H), 2.53 (s,3H), 3.47 (t,2H), 3.98 (m,2H), 4.06 (m,2H), 5.52 (brs, 1H), 6.03 (s,1H), 7.33 (d,1H), 7.48 (s,1H), 7.93 (d, 1H), 8.39 (s, 1H)	379
19	δ 0.98 (t,3H), 1.76 (m,2H), 2.50 (s,3H), 3.35 (s,3H), 3.67 (t,2H), 3.72 (m,2H), 4.14 (m,2H), 5.95 (s,3H), 7.29 (d,1H), 7.47 (s,1H), 7.97 (d,1H), 8.39 (s,1H)	393
20	δ 0.96 (t,6H), 1.73 (m,4H), 2.55 (s,3H), 3.74 (t,4H), 5.90 (s,1H), 7.40 (d,2H), 8.04 (d,2H), 8.25 (s,1H)	343
21	δ 0.26 (m,2H), 0.51 (m,2H), 0.92 (t,3H), 1.10 (m,1H), 1.69 (m,2H), 2.72 (s,3H), 3.41 (d,2H), 3.47 (t,2H), 6.17 (s,1H), 7.18 (t,1H), 7.43 (d,2H), 7.99 (s,1H)	389
22	δ 0.93 (t,3H), 1.67 (m,2H), 2.71 (s,3H), 3.32 (s,3H), 3.44 (t,2H), 3.61 (m,2H), 3.68 (m,2H), 6.16 (s,1H), 7.17 (t,1H), 7.41 (d,2H), 7.99 (s,1H)	393
23	δ 0.24 (m,2H), 0.55 (m,2H), 0.95 (t,3H), 1.38 (m,2H), 1.69 (m,2H), 2.51 (s,3H), 3.74 (d,2H), 3.82 (t,2H), 6.00 (s,1H), 7.31 (dd,1H), 7.48 (dd,1H), 7.98 (d,1H), 8.42 (s,1H)	403
24	δ 0.28 (m,2H), 0.50 (m,2H), 0.94 (d,6H), 1.10 (m,1H), 2.05 (m,1H), 2.52 (s,3H), 3.62 (d,2H), 3.82 (d,2H), 6.03 (s,1H), 7.32 (d,1H), 7.47 (s,1H), 7.99 (d,1H), 8.43 (s,1H)	403
25	δ 0.17 (m,2H), 0.47 (m,2H), 0.97 (t,6H), 1.05 (m,1H), 1.67 (m,4H), 2.52 (s,3H), 2.43 (d,2H), 4.71 (m,1H), 6.13 (s,1H), 7.32 (dd,1H), 7.47 (d,1H), 8.02 (d,1H), 8.43 (s,1H)	417
26	δ 2.41 (s,3H), 4.01 (m,2H), 4.15 (m,2H), 4.79 (s,2H), 5.62 (brs, 1H), 6.02 (s,1H), 7.35 (m,6H), 7.48 (s,1H), 7.91 (d,1H), 8.41 (s,1H)	427
27	δ 1.91 (s,3H), 2.47 (s,3H), 4.20 (t,2H), 4.43 (t,2H), 4.96 (s,2H), 6.03 (s,1H), 7.34 (m,6H), 7.49 (s,1H), 7.94 (d,1H), 8.44 (s,1H)	469

28	δ 0.98 (t,3H), 1.74 (m,2H), 1.93 (s,3H), 2.49 (s,3H), 3.59 (m,2H), 4.84 (m,2H), 4.39 (m,2H), 5.95 (s,1H), 7.30 (dd,1H), 7.46 (d,1H), 7.92 (d,1H), 8.38 (s,1H)	421
29	δ 0.28 (m,2H), 0.60 (m,2H), 1.20 (m,1H), 2.51 (s,3H), 3.70 (d,2H), 4.50 (d,2H), 5.29 (d,1H), 5.30 (d,1H), 5.96 (m,1H), 6.05 (s,1H), 7.32 (dd,1H), 7.48 (d,1H), 7.96 (d,1H), 8.44 (s,1H)	387
30	δ 1.07 (t,3H), 1.80 (m,2H), 2.46 (s,3H), 2.55 (s,3H), 3.36 (dt,2H), 5.82 (s,1H), 6.29 (t,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	381
31	δ 1.41 (d,6H), 2.46 (s,3H), 2.55 (s,3H), 3.85 (m,1H), 5.82 (s,1H), 6.08 (d,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	381
32	δ 0.92 (t,3H), 1.01 (t,3H), 1.25-1.80 (m,8H), 2.45 (s,3H), 2.54 (s,3H), 3.48 (m,1H), 5.79 (s,1H), 6.02 (d,1H), 7.27 (d,1H), 7.39 (d,1H), 7.50 (s,1H)	437
33	δ 0.96 (t,3H), 1.20 (t,6H), 1.74 (m, 4H), 2.15 (s,3H), 2.34 (s,3H), 2.41 (s, 3H), 3.56 (t,4H), 3.79 (t,4H), 5.77 (s,1H), 6.41 (s,1H), 7.54 (s,1H)	-
34	δ 2.45 (s,3H), 2.56 (s,3H), 3.93 (s,3H), 4.60 (d,2H), 5.90 (s,1H), 6.70 (t,1H), 6.99 (t,2H), 7.27-7.41 (m,4H), 7.52 (s,1H)	459
35	δ 2.44 (s,3H), 2.60 (s,3H), 3.35 (s,6H), 5.00 (brs,1H), 5.84 (s,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	367
36	δ 1.36 (s,6H), 2.42 (s,3H), 2.59 (s,3H), 3.80 (m,4H), 5.80 (s,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	395
37	δ 0.98 (t,6H), 1.78 (m,4H), 2.40 (s,3H), 2.59 (s,3H), 3.69 (m,4H), 5.74 (s,1H), 7.28 (d,1H), 7.48 (d,1H)	423
38	δ 0.30 (m,2H), 0.62 (m,2H), 0.99 (t,3H), 1.20 (m,1H), 1.81 (m,2H), 2.49 (s,3H), 2.59 (s,3H), 3.65-3.90 (m,4H), 5.87 (s,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	435
39	δ 1.05 (d,3H), 1.38 (d,3H), 2.45 (s,3H), 2.56 (s,3H), 3.40 (m,1H), 5.80 (s,1H), 7.30 (d,1H), 7.37 (d,1H), 7.51 (s,1H)	423
40	δ 0.98 (t,6H), 1.40 (m,4H), 1.75 (m,4H), 2.42 (s,3H), 2.59 (s,3H), 3.71 (m,4H), 5.76 (s,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	451
41	δ 0.29 (m,2H), 0.61 (m,2H), 0.93 (t,3H), 1.20-1.56 (m,3H), 1.75 (m,2H), 2.43 (s,3H), 2.59 (s,3H), 3.65-3.90 (m,4H), 5.88 (s,1H), 7.30 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	449
42	δ 2.42 (s,3H), 2.59 (s,3H), 4.34 (d,4H), 5.30 (m,4H), 5.87 (s,1H), 6.05 (m,2H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	419

화합물 번호	^{1}H NMR 데이터(CDCl$_3$)	MS M + 1
43	δ 0.31 (m,2H), 0.62 (m,2H), 1.00 (t,3H), 1.23 (m,1H), 1.81 (m,1H), 2.49 (s,3H), 3.05 (brs,3H), 3.42-3.95 (m,4H), 6.04 (s,1H), 7.33 (d,1H), 7.50 (s,1H), 7.51 (d,1H)	451
44	δ 0.13 (m,2H), 0.48 (m,2H), 0.90 (t,3H), 1.05 (m,1H), 1.60 (m,2H), 2.64 (s,3H), 3.05 (brs,3H), 3.48 (d,2H), 3.71 (m,2H), 6.04 (s,1H), 7.37 (d,1H), 7.54 (s,1H), 7.60 (d,1H)	485 (+H_2O)
45	δ 0.95 (t,3H), 1.42 (m,2H), 1.98 (m,2H), 2.49 (s,3H), 3.33 (s,3H), 3.56 (m,2H), 3.75 (m,2H), 5.93 (m,1H), 7.31 (d,1H), 7.46 (s,1H), 7.96 (d,1H), 8.40 (s,1H)	407
46	δ 0.91 (t,3H), 0.95 (t,3H), 1.35-2.05 (m,8H), 2.70 (t,2H), 3.33 (s,3H), 3.40 (m,6H), 5.92 (s,1H), 7.30 (d,1H), 7.46 (s,1H), 8.02 (d,1H), 8.41 (s,1H)	449
47	δ 0.87 (t,3H), 1.25 (m,2H), 1.70 (m,2H), 2.04 (m,2H), 2.68 (m,2H), 3.41 (s,3H), 3.56 (m,4H), 5.86 (s,1H), 6.60 (t,1H), 7.31 (d,1H), 7.46 (s,1H), 8.14 (d,1H), 8.50 (s,1H)	407
48	δ 0.95 (t,6H), 1.71 (m,4H), 2.47 (s,3H), 2.55 (s,3H), 3.71 (t,4H), 5.82 (s,1H), 7.39 (d,2H), 7.70 (d,2H)	357
49	δ 0.24 (m,2H), 0.54 (m,2H), 0.96 (t,3H), 1.12 (m,1H), 1.74 (m,2H), 2.35 (s,3H), 2.44 (s,3H), 3.73 (d,2H), 3.76 (t,2H), 5.93 (s,1H), 7.29 (d,1H), 7.35 (d,1H), 7.51 (s,1H)	403
50	δ 1.64 (t,3H), 2.52 (s,3H), 2.60 (s,3H), 4.56 (q,2H), 6.02 (s,3H), 7.30 (d,1H), 7.37 (d,1H), 7.51 (s,1H)	368
52	δ 0.9 (t, 6H), 1.68 (m, 4H), 2.13 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.05 (s, 6H), 3.65 (m, 4H), 5.74 (s, 1H), 6.44 (s, 1H), 8.01 (s, 1H)	M^+ = 366
53	δ 0.9 (t, 6H), 1.70 (m, 4H), 2.35 (s, 3H), 2.45 (s, 3H), 3.05 (s, 6H), 3.65 (m, 4H), 5.74 (s, 1H), 6.44 (s, 1H), 8.01 (s, 1H)	M^+ = 380
54	δ 0.95 (t, 6H), 1.73 (m, 4H), 2.52 (s, 3H), 2.76 (s, 3H), 3.73 (t, 4H), 5.85 (s, 1H), 7.68 (dd, 1H), 8.45 (d, 1H), 8.57 (d, 1H)	-
55	δ 0.96 (t, 6H), 1.70 - 1.78 (m, 4H), 2.44 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 3.73 (t, 4H), 5.48 (s, 1H), 8.36 (d, 1H), 9.32 (d, 1H)	383
56	δ 0.93 (t, 6H), 1.66 - 1.73 (m, 4H), 2.19 (s, 3H), 2.36 (s, 3H), 2.42 (s, 3H), 3.71 (t, 4H), 5.79 (s, 1H), 6.39 (d, 1H), 8.05 (d, 1H)	353
57	δ 0.96 (t, 6H), 1.62 - 1.70 (m, 4H), 2.2 (s, 3H), 2.36 (s, 3H), 2.40 (s, 3H), 2.96 (s, 6H), 3.68 (t, 4H), 5.76 (s, 1H), 6.91 (d, 1H), 8.08 (d,1H)	381

화합물번호	질량스펙트럼데이터	화합물번호	질량스펙트럼데이터
58	409 [M+]	95	364 [MH+]
59	365 [M+]	96	395 [MH+]
60	394 [MH+]	97	407 [MH+]
61	380 [MH+]	98	372 [MH+] (Cl^{35})
62	381 [MH+]	99	464 [MH+]
63	381 [MH+]	100	356 [MH+]
64	393 [MH+]	101	426 [MH+] (Cl^{35})
65	350 [MH+]	102	458 [MH+] (Cl^{35})
66	366 [MH+]	103	392 [MH+] (Cl^{35})
67	381 [MH+]	104	408 [MH+] (Cl^{35})
68	399 [MH+]	105	404 [MH+] (Cl^{35})
69	415 [MH+]	106	368 [MH+]
70	411 [MH+]	107	409 [MH+]
71	399 [MH+]	108	421 [MH+]
72	371 [MH+]	109	383 [MH+]
73	397 [MH+]	110	353 [MH+]
74	388 [M+]	111	372 [MH+] (Cl^{35})
75	407 [MH+]	112	366 [MH+]
76	373 [MH+]	113	381 [MH+]
77	359 [MH+]	114	338 [MH+]
78	346 [M+]	115	377 [MH+]
79	373 [MH+]	116	383 [MH+]
80	397 [MH+]	117	399 [MH+]
81	381 [MH+]	118	395 [MH+]
82	393 [MH+]	119	415 [MH+]
83	429 [MH+]	120	385 [MH+]
84	377 [MH+]	121	367 [MH+]
85	409 [MH+]	122	383 [MH+]
86	367 [MH+]	123	383 [MH+]
87	339 [MH+]	124	399 [MH+]
88	381 [MH+]	125	338 [MH+]
89	367 [MH+]	126	353 [MH+]
90	381 [MH+]	127	365 [MH+]
91	393 [MH+]	128	370 [M+]

분석 데이터

화합물번호	질량 스펙트럼 데이터
929394129130131	381 [MH+]409 [MH+]352 [MH+]368 [M+]393 [MH+]379 [MH+]

C. 약물학적 실험

실시예 C.1: CRF 수용체 결합 활성을 갖는 대표적인 화합물

화합물을 DeSouza 등에 의한 문헌 [J. Neurosci. 7:88-100, 1987]에 일반적으로 기재된 표준 방사리간드 결합 분석에 의해 CRF 수용체에 대한 결합 활성에 대해 평가하였다. 여러 방사표지된 CRF 리간드를 분석에 사용하여 CRF 수용체 준타입(subtype)을 갖는 본 발명의 화합물의 결합 활성을 평가할 수 있다. 간단히 말해, 결합 분석은 CRF 수용체로부터 방사표지된 CRF 리간드를 대체시키는 것을 포함한다. 더욱 구체적으로, 결합 분석은 인간 CRF 수용체로 안정하게 형질감염된 튜브 하나당 약 $1x10^6$ 세포를 사용하여 1.5 ㎖의 에펜도르프(Eppendorf) 튜브중에서 수행한다. 각 튜브에 비특이적 결합을 결정하는 CRF(최종 농도, 1 μM), 유로텐신 I 또는 표지되지 않은 사우바긴(sauvagine)을 함유하거나 함유하지 않는 시험 완충액(예를 들어 둘베코(Dulbecco) 인산염 완충염수, 10 mM 의 염화마그네슘, 20 μM의 바시트라신) 약 0.1 ㎖ , [^{125}I]티로신 - 양의 CRF(최종 농도 200 pM 또는 대략 Scatchard 분석에 의해 측정된 K_D) 0.1 ㎖ 및 CRF 수용체를 함유하는 세포의 막 현탁액 0.1 ㎖를 도입한다. 혼합물을 22 ℃에서 2 시간동안 인큐베이션한 후, 원심분리하여 결합 및 유리된 방사리간드를 분리한다. 펠렛을 2회 세척하고, 튜브를 펠렛 바로 위에서 자른 후, 감마-카운터에서 약 80%의 효율로 방사활성에 대해 조사하였다. 비선형 리스트-스퀘어 커브-피팅(non-linear least-square curve-fitting) 프로그램을 사용하여 모든 방사리간드 결합 데이터를 분석하였다. 결합 활성은 수용체로부터 방사표지된 리간드의 50%를 대체시키는데 필요한 화합물의 농도(nM)에 상응한다. 표 2 내지 5에 기재된 바와 같이 화합물 5, 10, 12, 15-17, 19, 23, 24, 26, 27, 29, 31-33, 36-43, 48, 49, 51-54 및 57-130이 ≤250 nM의 K_i 값을 갖는다. 이 시험에서 화합물 17, 29, 38, 41, 42, 48, 49, 51-54, 57, 58, 70, 71, 81-85, 90-92, 101, 103-105, 115, 118, 121-123 및 125가 가장 좋은 점수를 갖는 것으로 확인되었다.

실시예 C.2

CRF 유도된 아데닐레이트 사이클라제 활성

본 발명의 화합물을 또한 각종 기능 시험에 의해 평가할 수 있다. 예를 들어, 본 발명의 화합물을 CRF 유도된 아데닐레이트 사이클라제 활성에 대해 스크리닝할 수 있다. CRF 유도된 아데닐레이트 사이클라제 활성의 측정 시험을 Battaglia 등에 의한 문헌 [Synapse 1:572, 1987]에 일반적으로 기재된 방법을 전체 세포 준비물 분석에 적합하도록 변형시켜 수행할 수 있다. 더욱 구체적으로, 표준 분석 혼합물은 2 mM L-글루타민, 20 mM의 HEPES 및 DMEM 완충액중의 1 mM IMBX를 최종 부피 0.5 ㎖로 함유할 수 있다. 유도 시험에서, 형질감염된 CRF 수용체를 갖는 전체 세포를 24 개의 웰 플레이트에 플레이팅하고, CRF-관련 및 비관련 펩타이드의 농도를 변화시키면서 37 ℃에서 1 시간동안 인큐베이션하여 특정 수용체 준타입의 약물학적 순위를 정한다. 인큐베이션후, 배지를 아스피레이션하고, 웰을 신선한 배지로 1회 부드럽게 행군후, 배지를 아스피레이션한다. 세포내 cAMP 의 양을 측정하기 위하여, 20 mM의 수성 염산 및 95% 에탄올의 용액 300 ㎕를 각 웰에 첨가하고, 생성된 현탁액을 -20 ℃에서 16 내지 18 시간동안 인큐베이션한다. 용액을 꺼내 1.5 ㎖의 에펜도르프 튜브에 도입하고, 웰을 추가의 에탄올/수성 염산 200 ㎕로 세척한 다음, 제 1 분획과 풀링한다(pool). 샘플을 동결건조시키고, 500 ㎕의 소듐 아세테이트 완충액으로 재현탁시킨다. 단일 항체 키트를 사용하여 샘플중의 cAMP 를 측정한다. 화합물의 기능성 측정을 위하여, cAMP 생산의 80%를 유도하는 단일 농도의 CRF 또는 관련 펩타이드를 다양한 농도의 경쟁 화합물(10^{-12} 내지 10^{-6} M)과 함께 인큐베이션한다.

실시예 C.3

플러스-미로(plus-maze) 및 방어적 후퇴 패러다임(defensive withdrawl paradigm)은 실험적 처리에 의한 불안 조장 및 불안 해소 효과에 민감한 탐험적 행위를 측정하기 위해 상호 보완 사용된다. 이들 동물 모델을 본 발명의 화합물의 불안 해소 및 항-스트레스 작용을 조사하기 위하여 사용하였다.

실시예 C.3-a: 고가 플러스-미로 패러다임

이 시험은 동물이 어떠한 방식으로 밝은 공간과 어두운 안전한 공간을 포함하는 접근-회피 상황에 응답할 수 있는지를 예견한다. 두 공간은 모두 지상으로부터 떨어져 있으며, 플러스 부호의 형태로 교차하는 두 개의 주로로 구성되어 있다. 이러한 형태의 접근-회피 상황은 "감정" 및 반응성을 조사하는 고전적인 시험방법이며, 탈억제(진정/최면과 같은) 및 스트레스를 형성하는 처리에 매우 민감하다. 움직임에 제한을 둘 필요는 없으며, 동물이 자유롭게 어둠속에 남아있거나 개방된 팔(open arm)로 탈출하도록 내버려 둔다. 플러스-미로 장치는 네 개의 팔(10 x 50 ㎝)을 90도 각도로 가지며, 바닥으로부터 50 ㎝ 떨어져 위치해 있다. 두 개의 팔은 벽(40 ㎝ 높이)으로 막혀 있고, 두 개의 팔은 장벽이 없다(개방 팔). 대상체를 미로의 중심부에 개별적으로 위치시키고, 5 분동안 네 개의 팔에 대해 자유롭게 접근하도록 한다. 대상체를 문에 있는 창을 통하여 관찰함과 동시에 컴퓨터 모니터상에 랫트의 위치가 온-라인 표시되록 함으로써 관찰한다. 각 팔에서 소비한 시간이 포토셀 빔 및 컴퓨터 프로그램에 의해 자동적으로 기록된다. 미로를 각 시험사이에 젖은 천으로 닦아낸다. 이 실험에서 불안 조장 행위는 개방된 팔에서 소비한 시간의 감소로 측정되고, 항-스트레스 효과는 개방된 팔에서 소비한 시간의 상보적인 증가로 측정된다.

CRF 펩타이드를 사용한 플러스-미로의 타당성

CRF의 중추 투여 및 수개의 실험적 스트레스 요인의 노출은 불안에 싸인 고가 플러스 미로 모델의 탐험성을 억제한다. 사회적인 좌절에 대한 행위적 반응을 측정하는 경우, 스트레스후[25 ㎍ ICV] 또는 스트레스전[1 ㎍ ICN]에 알파-나선형의 CRF (9-41)길항제를 중추 투여하게 되면 사회적인 좌절에 의한 불안 조장 효과가 반전된다. 이러한 CRF 길항제의 항-스트레스 작용은 또한 대뇌 도착후 소뇌편도의 중심핵으로 도달된다[250 ng IC].

랫트에 시험 화합물을 5 분시험 1 시간전에 경구 투여한다. 일부의 그룹을 플러스-미로에 도입시키기 바로 전에 90 초동안 물이 가득찬 풀에 놓고(스트레스 그룹), 대조군 그룹은 우리에서 직접 꺼낸다(비-스트레스 그룹). 비-처리 동물 그룹에 있어서 개방된 팔에서 소비하는 평균 시간 퍼센트가 상당히 감소하는 것으로 관찰되었다(약 36 내지 약 16%). 화합물 53을 2.5 또는 20 ㎎/㎏ 투여하였더니 개방된 팔에서의 소비 시간%가 오차 범위내에서 비처리 그룹과 마찬가지의 수준으로 되돌아 갔다.

실시예 C.3-b: 방어적 후퇴 패러다임

직경 10.2 ㎝이고, 길이 17.1 ㎝인 직류전기가 효르는 원통형의 스틸 챔버를 포함하는 플라스틱 유리의 개방 필드(106 x 92 x 77 ㎝)에서 시험을 수행하였다. 챔버를 한쪽 끝은 개방하고, 개방 필드의 코너로부터 15.0 ㎝ 떨어지고 세로로 정렬되도록 개방 필드의 벽과 나란히 위치시킨다. 개방 끝 부분은 코너와 직면한다. 형광빛을 천장으로 부터 개방 필드에 조명한다. 테스트를 위하여, 동물을 작은 챔버에 놓음으로써 친숙하지 않은 테스트 환경에 도입시킨다. 테스트 시간은 5분이고, 각 테스트후 장치를 연한 아세트산 용액으로 닦아 낸다. 시험 화합물을 5분 테스트 1 시간전에 경구 투여한다. 동물의 행동을 감시하고, 비디오 카메라로 기록한다. 챔버를 탈출하는 잠복기를 측정하고, 이는 개방 필드에 네 개의 모든 발이 놓이는 것으로 정의된다. 입구당 챔버내에서의 평균 시간 길이 및 챔버와 개방 필드사이에 만들어진 통로수를 또한 측정한다. 불안 해소 효과는 폐쇄된 챔버내에서 소비한 평균 시간의 감소로써 측정된다. 랫트에 화합물 53을 0.63, 2.5 및 20 ㎎/㎏ 경구 투여하였을때 챔버에서 평균시간은 약 80초에서 약 20 내지 40초로 감소하였다.

CRF 펩타이드를 사용한 방어적 후퇴의 타당성

알파-나선형 CRF(9-41) 및 CRF 둘 다를 ICV 주입하면 방어적 후퇴 패러다임에서의 행동에 변화가 생긴다. 특히, 이미 장치와 친숙해진 동물에 CRF를 ICV 투여하면 작은 챔버로 부터 나오는 잠복기 및 챔버내에서의 평균 소비시간 모두가 15분 이상으로 증가한다. 유사하게, CRF를 창반에 주사하면 방어적 후퇴 행동에 유사한 변화가 일어나고, 이것은 CRF와 노르아드레날린성 뉴론간의 상호작용이 랫트에서 방어적 후퇴 행동 동안에 동반됨을 의미하는 것이다. 반대로, 경쟁적인 CRF 수용체 길항제인 알파-나선형 CRF(9-14) 또는 d-Phe CRF(12-41)을 ICV 투여하면 친숙한 환경 상태의 구속 스트레스 요인에 대한 CRF 효과가 반전되며, 장치와 친숙하지 않은 동물에게서 챔버내의 평균 시간 및 탈출 잠복기가 상당히 감소된다.

D. 조성물 실시예

하기 실시예는 온혈동물에 전신적으로 또는 국소적으로 투여하기에 적합한 단위 복용형의 본 발명에 따른 대표적인 약제학적 조성물을 예시한다.

실시예에 사용된 "활성성분" (A.I.) 은 일반식 (I)의 화합물, 그의 N-옥사이드, 약제학적으로 허용되는 산 또는 염기 부가염, 입체화학적 이성체에 관한 것이다.

실시예 D.1: 경구용 용액제

메틸 4-하이드록시벤조에이트 9 g 및 프로필 4-하이드록시벤조에이트 1 g 을 비등 정제수 4 ℓ 에 용해시킨다. 이 용액 3 ℓ 에 우선 2,3-디하이드록시부타노산 10 g 을 용해시킨 후, A.I. 20 g 을 용해시킨다. 후자의 용액을 전자의 남아 있는 용액과 합치고, 여기에 1,2,3-프로판트리올 12 ℓ 및 소르비톨 70% 용액 3 ℓ 를 가한다. 사카린 나트륨 40 g 을 물 0.5 ℓ 에 용해시키고, 라즈베리 2 ㎖ 및 구즈베리 에센스 2 ㎖ 를 가한다. 후자의 용액을 전자와 합치고, 용적을 20 ℓ 로 만들기에 적합한 적당량의 물을 가하여 티스푼당(5 ㎖) 당 A.I. 5 ㎎ 을 함유하는 경구용 용액을 수득한다. 생성 용액을 적당한 용기에 충전한다.

실시예 D.2: 캅셀제

A.I. 20 g, 소듐 라우릴설페이트 6 g, 전분 56 g, 락토오스 56 g, 콜로이드성 이산화규소 0.8 g 및 마그네슘 스테아레이트 1.2 g 을 함께 격렬하게 교반한다. 생성된 혼합물을 계속해서 각각 활성성분 20 ㎎ 씩을 함유하는 1000 개의 적합한 경질 젤라틴 캅셀에 충전시킨다.

실시예 D.3: 필름-코팅 정제

정제핵의 제조

A.I. 100 g, 락토오스 570 g 및 전분 200 g 의 혼합물을 잘 혼합한 후에 물 약 200 ㎖ 중의 소듐 도데실설페이트 5 g 및 폴리비닐피롤리돈 10 g 의 용액으로 습윤시킨다. 습윤된 분말 혼합물을 체로 치고 건조시킨 후에 다시 체로 친다. 그후에 미세결정성 셀룰로오스 100 g 및 수소화 식물유 15 g 을 가한다. 전체 혼합물을 잘 혼합시키고, 타정하여 각각 활성성분 10 ㎎ 씩을 함유하는 정제 10,000 정을 수득한다.

코팅(coating)

변성 에탄올 75 ㎖ 중의 메틸셀룰로오스 10 g 의 용액에 디클로로메탄 150 ㎖ 중의 에틸 셀룰로오스 5 g 의 용액을 가한다. 그후, 여기에 디클로로메탄 75 ㎖ 및 1,2,3-프로판트리올 2.5 ㎖ 를 가한다. 폴리에틸렌글리콜 10 g 을 용융시키고 디클로로메탄 75 ㎖ 에 용해시킨다. 후자의 용액을 전자의 용액에 가한 다음, 여기에 마그네슘 옥타데카노에이트 2.5 g, 폴리비닐피롤리돈 5 g 및 농축된

색소 현탁액 30 ㎖ 를 가하고 전체 혼합물을 균질화시킨다. 이렇게 하여 수득한 혼합물로 코팅 장치내에서 정제핵을 코팅한다.

실시예 D.4 : 주사용 용액제

메틸 4-하이드록시벤조에이트 1.8 g 및 프로필 4-하이드록시벤조에이트 0.2 g 을 주사용 비등수 약 0.5 ℓ 에 용해시킨다. 약 50 ℃ 로 냉각시킨 후, 교반하면서 락트산 4 g, 프로필렌 글리콜 0.05 g 및 A.I. 4 g 을 가한다. 용액을 실온으로 냉각시키고, 용적을 1 ℓ 로 만들기에 적합한 적당량의 주사용수를 보충하여 ㎖ 당 4 ㎎ 의 A.I. 용액을 수득한다. 용액을 여과에 의해 멸균시키고, 무균 용기에 충전한다.

실시예 D.5: 좌제

A.I. 3 g 을 폴리에틸렌 글리콜 400 25 ㎖중의 2,3-디하이드록시부탄디오산 3 g 의 용액에 용해시킨다. 계면활성제 12 g 및 트리글리세라이드 300 g을 함께 용융시킨다. 후자의 혼합물을 전자의 용액과 잘 혼합한다. 수득한 혼합물을 37 내지 38 ℃ 온도의 주형에 부어 각각 ㎖당 A.I. 30 ㎎을 함유하는 좌제 100 개를 수득한다.

Google Patents KR19990067391A

Pyrazolopyrimidine As An Antagonist To CRF Receptor

Abstract

Translated from Korean

The present invention provides compounds of formula (I) below having antagonism against CRF receptors, stereoisomers and pharmaceutically acceptable acid addition salts thereof, pharmaceutical compositions containing these compounds as active ingredients and effective amounts of A method of treating a disease associated with hypersecretion of CRF such as depression, anxiety and drug abuse by administering the compound of I).

In the above formula,

R^1 represents NR^4R^5 or OR^5;

R^2 represents C_{1-6} alkyl, C_{1-6} alkyloxy or C_{1-6} alkylthio;

R^3 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfoxy or C_{1-6} alkylthio;

R^4 is hydrogen, C_{1-6} alkyl, mono- or di (C_{3-6} cycloalkyl) methyl, C_{3-6} cycloalkyl, C_{3-6} alkenyl, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxycarbonylC_{1-6} alkyl or C_{1-6} alkyloxyC_{1-6} alkyl;

R^5 is C_{1-6} alkyl, mono- or di (C_{3-6} cycloalkyl) methyl, Ar^1CH_2, C_{1-6} alkyloxyC_{1-6} alkyl, hydroxyC_{1-6} alkyl, C_{3-6} alkenyl, thienylmethyl, furanylmethyl, C_{1-6} alkylthioC_{1-6} alkyl, morpholinyl, mono- or di (C_{1-6} alkyl) aminoC_{1-6} alkyl, di (C_{1-6} alkyl) amino, C_{1-6} alkylcarbonylamino C_{1-6} alkyl, already substituted by an imidazolyl C_{1-6} alkyl, or formula -Alk-O-CO-Ar^1 or represents a radical of ;

R^4 and R^5 together with the nitrogen atom to which they are attached may form an optionally substituted pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group.

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Classifications

C07D487/04 Ortho-condensed systems

View 20 more classifications

Claims (13)

Hide Dependent

Translated from Korean

Compounds of the general formula (I), their stereoisomers and pharmaceutically acceptable acid addition salts: In the above formula, R^1 represents NR^4R^5 or OR^5; R^2 represents C_{1-6} alkyl, C_{1-6} alkyloxy or C_{1-6} alkylthio; R^3 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfoxy or C_{1-6} alkylthio; R^4 is hydrogen, C_{1-6} alkyl, mono- or di (C_{3-6} cycloalkyl) methyl, C_{3-6} cycloalkyl, C_{3-6} alkenyl, hydroxyC_{1-6} alkyl, C_{1-6} alkylcarbonyloxyC_{1-6} alkyl or C_{1-6} alkyloxyC_{1-6} alkyl; R^5 is C_{1-6} alkyl, mono- or di (C_{3-6} cycloalkyl) methyl, Ar^1CH_2, C_{3-6} alkyloxyC_{1-6} alkyl, hydroxyC_{1-6} alkyl, C_{3-6} alkenyl, thienylmethyl, furanylmethyl, C_{1-6} alkylthioC_{1-6} alkyl, morpholinyl, mono- or di (C_{1-6} alkyl) aminoC_{1-6} alkyl, di (C_{1-6} alkyl) amino, C_{1-6} alkylcarbonylamino C_{1-6} alkyl, already substituted by an imidazolyl C_{1-6} alkyl, or formula -Alk-O-CO-Ar^1 or represents a radical of ; R^4 and R^5 together with the nitrogen atom to which they are attached respectively by a C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl, optionally substituted pyrrolidinyl, piperidinyl, homo piperidinyl or Can form morpholinyl groups, Ar is phenyl; Halo, C_{1-6} alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6} alkyloxy, benzyloxy, C_{1-6} alkylthio, nitro, amino and mono- or di (C_{1-6} alkyl Phenyl substituted by 1, 2 or 3 substituents independently selected from the group consisting of amino; Pyridinyl; Or halo, C_{1-6} alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6} alkyloxy, benzyloxy, C_{1-6} alkylthio, nitro, amino, mono- or di (C_{1-6} Pyridinyl substituted by one, two or three substituents independently selected from the group consisting of alkyl) amino and piperidinyl; Substituted phenyl here may optionally be further substituted by one or more halogens; Ar^1 is phenyl; Group consisting of C_{1-6} alkyl substituted by halo, C_{1-6} alkyl, C_{1-6} alkyloxy, di (C_{1-6} alkyl) aminoC_{1-6} alkyl, trifluoromethyl and morpholinyl Phenyl substituted by 1, 2 or 3 substituents each independently selected from; Or pyridinyl; Alk represents C_{1-6} alkanediyl; Provided that among these compounds 5-methyl-3-phenyl-7- (phenylmethoxy) -pyrazolo [1,5-a] pyrimidine and 2,5-dimethyl-7- (methylamino) -3-phenyl -Pyrazolo [1,5-a] pyrimidine is excluded. The compound of claim 1, wherein R^1 is OR^5 and R^5 is C_{1-6} alkyl; R^1 is NR^4R^5, R^5 is hydrogen, C_{1-6} alkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkylcarbonyloxyC_{1-6} alkyl or C_{3-6} alkenyl, R^5 is C_{1-6} alkyl, C_{3-6} alkenyl, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, phenylmethyl or C_{3-6} cycloalkylmethyl, or R^4 and R^5 together with the nitrogen atom to which they are attached respectively by a C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl, optionally substituted pyrrolidinyl, piperidinyl, homo-piperidinyl or morpholinyl To form a silyl group; R^2 is C_{1-6} alkyl; R^3 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylthio; Ar is phenyl each independently substituted by 1, 2 or 3 substituents selected from the group consisting of halo, C_{1-6} alkyl and C_{1-6} alkyloxy, or Ar is halo, amino, nitro, trifluoromethyl , Pyridinyl substituted by 1, 2 or 3 substituents each independently selected from the group consisting of mono- or di (C_{1-6} alkyl) amino, piperidinyl and C_{1-6} alkyl. 3. The compound of claim 1, wherein R^1 is NR^4R^5 and R^4 is C_{2-4} alkyl, hydroxyC_{1-3} alkyl, C_{3-4} alkenyl or C_{1-3} alkylcarbonyl oxyC_{2-4} alkyl, R^5 is C_{2-5} alkyl, C_{3-4} alkenyl, hydroxyC_{3-4} alkyl or cyclopropylmethyl; R^2 is C_{1-3} alkyl; R^3 is hydrogen, C_{1-3} alkyl or C_{1-3} alkylthio. The compound of claim 1, wherein R^1 is NR^4R^5, R^4 is C_{3-4} alkyl or allyl, and R^5 is C_{2-5} alkyl, allyl or cyclopropylmethyl; R^2 is methyl; R^3 is methyl; Ar is a 3-, 4-, 5-, 2,4- or 2,4,6-position wherein phenyl is substituted by halo, C_{1-6} alkyl or C_{1-6} alkyloxy. The compound of claim 1, wherein R^1 is NR^4R^5, R^4 is C_{3-4} alkyl or allyl, and R^5 is C_{3-4} alkyl, allyl or cyclopropylmethyl; R^2 is methyl; R^3 is methyl; Ar is 3-pyridinyl, wherein the 4- and / or 6-position is substituted by methyl or dimethylamino. The compound of claim 1, wherein 3- [5- (dimethylamino) -3-pyridinyl] -2,5-dimethyl-N, N-dipropylpyrazolo [2,3-a] pyrimidin-7-amine or 3- [5- (dimethylamino) -4-methyl-3-pyridinyl] -2,5-dimethyl-N, N-dipropylpyrazolo [2,3-a] pyrimidin-7-amine, or these A stereochemical isomer of or a pharmaceutically acceptable acid addition salt thereof. A composition comprising as an active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 6 and a pharmaceutically acceptable carrier. A method for preparing a composition as claimed in claim 7, characterized in that the therapeutically effective amount of the compound as claimed in any one of claims 1 to 6 is thoroughly mixed with a pharmaceutically acceptable carrier. The compound

according to any one of claims 1 to 8 for use as a medicament. Use of the compounds of formula (I), stereoisomers and pharmaceutically acceptable acid addition salts thereof for the manufacture of a medicament for the treatment of physiological symptoms or diseases due to hypersecretion of corticosteroid-releasing factor (CRF): In the above formula, R^1, R^2, R^3 and Ar are as defined in claim 1. Compound 5-methyl-3-phenyl-7- (phenylmethoxy) -pyrazolo [1,5-a] -pyrimidine and 2,5-dimethyl-7- (methylamino) -3-phenyl-pyrazolo [1,5-a] pyrimidine. Compounds of formula (II '), their stereoisomers or acid addition salts thereof: In the above formula, R^2, R^3 and Ar are as defined in any one of claims 1 to 5, W represents hydroxy, halo, mesyloxy or tosyloxy. However, the compound whose Ar is unsubstituted phenyl is excluded. a) reacting the intermediate of formula (III) with the intermediate of formula (IIII) in a reaction-inert solvent; b) a general formula defined as a compound of formula (I) wherein R^1 is OR^5 by O-alkylating the intermediate of formula (VI) in the reaction-inert solvent with the intermediate of formula (VII) in the presence of a suitable base Obtaining the compound of (Ia), or if necessary, the compound of formula (I) is converted into another compound of formula (I) according to a functional group conversion reaction known in the art; If necessary, the compound of general formula (I) is further treated with an acid to prepare an acid addition salt, or conversely, the acid addition salt is treated with an alkali to convert to a free base; A process for preparing the compound as claimed in claim 1, characterized by preparing these stereochemical isomers as necessary. In the above scheme, R^1, R^2, R^3, R^5 and Ar are as defined in claim 1, W represents an escape group. A compound of formula (II-a) defined as a compound of formula (II ') wherein W is hydroxy by reacting the intermediate of formula (IV) with β-keto ester (V) in a reaction-inert solvent And optionally convert the compound of formula (II-a) to a compound of formula (II-b) defined as a compound of formula (II ') wherein W is other than hydroxy If necessary, the compound of formula (II ') is converted into another compound of formula (II) according to a functional group conversion reaction known in the art; If necessary, the compound of general formula (II ') is further treated with an acid to prepare an acid addition salt, or conversely, the acid addition salt is treated with an alkali to convert to a free base; A process for preparing a compound of formula (II ') as claimed in claim 10, characterized by the preparation of these stereochemical isomers as required: In the above scheme, R^2, R^3 and Ar are as defined in claim 1, W represents hydroxy, halo, mesyloxy or tosyloxy.

Description

Translated from Korean

Pyrazolopyrimidine As An Antagonist To CrF Receptor

The first adrenal cortico hormone-releasing factor (CRF) was isolated from the hypothalamus of sheep and was identified as a 41-amino acid peptide (Vale et al., Science 213: 1394-1397, 1981). Thereafter, human and rat CRF sequences were isolated and identified as identical, but 7 CR out of 41 amino acid residues differed from positive CRF (see Rivier et al., Proc. Natl. Acad. Sci. USA 80: 4851). , 1983; Shibahara et al., EMBO J. 2: 775, 1983). CRF has been found to significantly alter endocrine, nervous and immune system functions. CRF is a major physiological modulator of normal and stress-release of pro-opiomelanocortin ("POMC")-derived peptides from adrenal cortex hormone ("ACTH"), β-endodorphine, and other anterior pituitary (Vale et al., Science 213: 1394-1397, 1981). In short, CRF can be expressed in the brain (DeSouza et al., Science 221: 1449-1451, 1984), the pituitary gland (DeSouza et al., Methods Enzymol. 124: 560, 1986; Wynn et al., Biochem. Comm. 115: 602-608, 1983), adrenal gland (Udelsman et al., Nature 319: 147-150, 1986) and spleen (Webster, EL, and Elf DeSouza, Endocrinology 122: 609-617, 1988). It is thought to initiate its biological effect by binding to plasma membrane receptors found to be distributed over. CRF receptors couple with GTP-binding proteins (Perrin et al., Endocrinology 118: 1171-1179, 1986) that mediate the increased intracellular production of cAMP induced by CRF (Blalastijan, LM, and WW Vale, Endocrinology 113: 657-662, 1983).

In addition to promoting ACTH and POMC production, CRF is also believed to cooperate with a number of endocrine autonomous and behavioral responses to stress and can be included in the pathophysiology of emotional disorders. CRF is also believed to be a major mediator in communication between the immune system, central nervous system, endocrine system and cardiovascular system (Crofford et al., J. Clin. Invest. 90: 2555-2564, 1992; Sapolsky et al. , Science 238: 522-524, 1987; Tilders et al., Regul.Peptides 5: 77-84, 1982). Overall, CRF is one of the central nervous system neurotransmitters and has been shown to play a major role in integrating the body's overall response to stress.

Direct infusion of CRF into the brain induces the same behavioral, physiological and endocrine responses observed in animals exposed to stressful environments. For example, when CRF is injected into the cerebral ventricle, behavior becomes active (Sutton et al., Nature 297: 331, 1982), activates brain waves for a long time (Ehlers et al., Brain Res. 2), / 8332, 1983), stimulate the sympathetic pathway (Brown et al., Endocrinology 110: 928, 1982), increase heart rate and blood pressure (Fisher et al., Endocrinology 110: 2222, 1982)), increase oxygen consumption (Brow et al., Life Sciences 30: 297, 1982), alter gastrointestinal motility (William et al., Am. J. Physiol. 253: G562, 1987), inhibit food consumption (Levine, et al., Neuropharmacology 22: 837, 1983), alter sexual behavior (Sirinathsinghji et al., Nature 305: 232, 1983) and decrease immune function (see Irwin et al., Am. J. Physiol. 255: R744, 1988). In addition, clinical data suggest that CRF may be oversecreted in the brain in depression, anxiety-related disorders and anorexia nervosa (DeSouza, Ann. Reports in Med. Chem. 25: 215-223, 1990). .

Thus, clinical data suggest that the CRF receptor antagonist may be a novel antidepressant and / or anxiolytic agent that may be useful for treating neuropsychiatric disorders that hypersecrete CRF. CRF receptor antagonists are described, for example, in US Pat. No. 5,063,245 describing substituted 4-thio-5-oxo-3-pyrazoline derivatives and Australian Patent No. AU-A41399 describing substituted 2-aminothiazole derivatives. / 98, WO-92 / 18504 and JP-92 / 046877 describe pyrazolo [1,5-a] pyrimidines as anti-inflammatory agents. WO-94 / 13676, WO-94 / 13677 and WO-95 / 33750 also describe pyrrolopyrimidines, pyrazolo [3,4-d] pyrimidines and substituted purines as CRF receptor antagonists. have. Arylpyrazolo [1,5-a] pyrimidines are known as xanthan oxidase inhibitors (Robles et al., J. Heterocyclic Chem. 22: 621-624, 1985). JP-62 / 011,753 describes 7-methylamino-pyrazolo [1,5-a] pyrimidine derivatives useful as stabilizers and anti-inflammatory agents. JP-61 / 057,587 also describes pyrazolo [1,5-a] pyrimidine derivatives useful as antiulcers.

Because of the physiological importance of CRF, the development of biologically active small molecules that can antagonize the CRF receptor and have significant CRF receptor binding activity remains a major challenge. Such CRF receptor antagonists are generally useful for treating endocrine, psychiatric and neurological symptoms or diseases, including stress-related diseases.

The present invention relates to pyrazolopyrimidines having antagonism to the CRF receptor, pharmaceutical compositions containing these compounds as active ingredients and generally for treating endocrine, psychiatric and neurological symptoms or diseases, including stress-related diseases. To its use.

The present invention relates to CRF antagonists of the general formula (I), stereoisomers thereof and pharmaceutically acceptable acid addition salts:

In the above formula,

R^1 represents NR^4R^5 or OR^5;

R^2 represents C_{1-6} alkyl, C_{1-6} alkyloxy or C_{1-6} alkylthio;

R^3 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsuloxy or C_{1-6} alkylthio;

R^4 is hydrogen, C_{1-6} alkyl, mono- or di (C_{3-6} cycloalkyl) methyl, C_{3-6} cycloalkyl, C_{3-6} alkenyl, hydroxyC_{1-6} alkyl, C_{1-6} alkylcarbonyloxyC_{1-6} alkyl or C_{1-6} alkyloxyC_{1-6} alkyl;

R^5 is C_{1-6} alkyl, mono- or di (C_{3-6} cycloalkyl) methyl, Ar^1-CH_2-, C_{1-6} alkyloxyC_{1-6} alkyl, hydroxyC_{1-6} alkyl, C_{3-6} alkenyl, thienylmethyl, furanylmethyl, C_{1-6} alkylthioC_{1-6} alkyl, morpholinyl, mono- or di (C_{1-6} alkyl) aminoC_{1-6} alkyl, di (C_{1-6} alkyl) amino, C_{1-6} alkylcarbonylamino C_{1-6} alkyl, already substituted by an imidazolyl C_{1-6} alkyl, or formula -Alk-O-CO-Ar^1 or represents a radical of ;

R^4 and R^5 together with the nitrogen atom to which they are attached respectively by a C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl, optionally substituted pyrrolidinyl, piperidinyl, homo-piperidinyl or Can form morpholinyl groups;

Ar is phenyl; Halo, C $_{1-6}$ alkyl, trifluoromethyl, hydroxy, cyano, C $_{1-6}$ alkyloxy, benzyloxy, C $_{1-6}$ alkylthio, nitro, amino and mono- or di (C $_{1-6}$ alkyl Phenyl substituted by 1, 2 or 3 substituents independently selected from the group consisting of amino; Pyridinyl; Or halo, C $_{1-6}$ alkyl, trifluoromethyl, hydroxy, cyano, C $_{1-6}$ alkyloxy, benzyloxy, C $_{1-6}$ alkylthio, nitro, amino, mono- or di (C $_{1-6}$ Pyridinyl substituted by one, two or three substituents independently selected from the group consisting of alkyl) amino and piperidinyl; Substituted phenyl here may optionally be further substituted by one or more halogens;

Ar ^{1} is phenyl; Group consisting of C $_{1-6}$ alkyl substituted by halo, C $_{1-6}$ alkyl, C $_{1-6}$ alkyloxy, di (C $_{1-6}$ alkyl) aminoC $_{1-6}$ alkyl, trifluoromethyl and morpholinyl Phenyl substituted by 1, 2 or 3 substituents each independently selected from; Or pyridinyl;

Alk represents C $_{1-6}$ alkanediyl.

In another aspect, the invention relates to a novel compound of formula (I) as defined above, provided that compound 5-methyl-3-phenyl-7- (phenylmethoxy) -pyrazolo [1,5-a] -Pyrimidine and 2,5-dimethyl-7- (methylamino) -3-phenyl pyrazolo [1,5-a] pyrimidine are excluded.

This proviso provision is intended to exclude the compounds described in JP-61 / 057,587 and JP-62 / 011,793.

As used in the above definitions, the term halo means fluoro, chloro, bromo and iodo; C $_{1-6}$ alkanediyl is for example methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and side chains thereof Divalent straight and branched chain saturated hydrocarbon radicals having 1 to 6 carbon atoms such as isomers; C $_{1-2}$ alkyl means straight chain saturated hydrocarbon radical having 1 to 2 carbon atoms such as methyl and ethyl; C $_{2-4}$ alkyl means straight and branched chain saturated hydrocarbon radicals having 2 to 4 carbon atoms such as ethyl, propyl, butyl, 1-methylethyl and the like; C $_{3-4}$ alkyl means straight and branched chain saturated hydrocarbon radicals having 3 to 4 carbon atoms such as propyl, butyl, 1-methylethyl and the like; C $_{1-6}$ alkyl refers to C $_{1-2}$ alkyl and C $_{3-4}$ alkyl as defined above and higher homologues of 5 to 6 carbon atoms such as pentyl, pentyl isomers, hexyl and hexyl isomers; C $_{1-8}$ alkyl means C $_{1-6}$ alkyl as defined above and its higher homologues having 7 to 8 carbon atoms such as, for example, heptyl, octyl and the like; C $_{3-6}$ alkenyl has one to three carbon atoms, for example 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, etc. Straight and branched chain hydrocarbon radicals including double bonds; When C $_{2-6}$ alkenyl is bonded to nitrogen or oxygen, the carbon atoms that form the bond are preferably saturated. C $_{3-6}$ cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Hydroxy C $_{1-6}$ alkyl means C $_{1-6}$ alkyl substituted with a hydroxyl group. Homopiperidinyl is a 7 membered saturated ring containing one nitrogen atom.

Due to the nature of some substituents, compounds of formula (I) may contain one or more asymmetric centers which may be represented by the commonly used R and S nomenclature.

The compounds of the present invention contain basic nitrogen atoms and may themselves exist as free base or in the form of acid addition salts, all of which are part of the present invention. Acid addition salts can be prepared by methods known in the art and can be formed from organic and inorganic acids. Suitable organic acids include maleic acid, fumaric acid, benzoic acid, ascorbic acid, succinic acid, methanesulfonic acid, acetic acid, oxalic acid, propionic acid, tartaric acid, salicylic acid, citric acid, gluconic acid, lactic acid, mandelline acid, cinnamic acid, aspartic acid, stearic acid , Palmitic acid, glycolic acid, glutamic acid and benzenesulfonic acid. Suitable inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid.

A particular group of compounds of the invention are compounds of general formula (I) according to one or more of the following limitations;

a) R ^{1} is NR ^{4} R ^{5}, wherein R ^{4} is hydrogen, C $_{1-6}$ alkyl, hydroxyC $_{1-6}$ alkyl, C $_{1-6}$ alkylcarbonyloxyC $_{1-6}$ alkyl or C $_{3-6}$ Alkenyl, in particular C $_{2-4}$ alkyl, hydroxyC $_{1-2}$ alkyl, C $_{3-4}$ alkenyl or C $_{1-2}$ alkylcarbonyloxyC $_{2-4}$ alkyl, R ^{5} is C $_{1-6}$ alkyl, C $_{3-6}$ alkenyl, hydroxyC $_{1-6}$ alkyl, C $_{1-6}$ alkyloxyC $_{1-6}$ alkyl, phenylmethyl or C $_{3-6}$ cycloalkylmethyl, in particular C $_{2-4}$ alkyl, C $_{3-4}$ alkenyl , HydroxyC $_{2-4}$ alkyl or cyclopropylmethyl;

b) R ^{1} is OR ^{5}, wherein R ^{5} is C $_{1-6}$ alkyl, in particular C $_{2-4}$ alkyl;

c) R ^{2} is C $_{1-6}$ alkyl, in particular C $_{1-2}$ alkyl;

d) R ^{3} is hydrogen, C $_{1-6}$ alkyl or C $_{1-6}$ alkylthio, in particular hydrogen, C $_{1-2}$ alkyl or C $_{1-2}$ alkylthio;

e) Ar is phenyl substituted by 1, 2 or 3 substituents each independently selected from the group consisting of C $_{1-6}$ alkyl, C $_{1-6}$ alkyloxy and halo, wherein the phenyl moiety is preferably 3-, 4-, 5-, 2,4- or 2,4,5-position is substituted; Ar is 1, 2 or 3 each independently selected from the group consisting of halo, amino, nitro, trifluoromethyl, mono- or di (C $_{1-6}$ alkyl) amino, piperidinyl and C $_{1-6}$ alkyl Pyridinyl substituted by a substituent, wherein the pyridinyl moiety is preferably attached to the rest of the molecule via the 2- or 3-position.

Another particular compound group is that R ^{1} is NR ^{4} R ^{5}, wherein R ^{4} and R ^{5} together with the nitrogen atom to which they are attached, are each C $_{1-6}$ alkyl or C $_{1-6}$ alkyloxyC $_{1-6}$ alkyl A compound of formula (I) which forms an optionally substituted pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group.

Preferred compounds are those in which R ^{1} is NR ^{4} R ^{5}, wherein R ^{4} is C $_{3-4}$ alkyl or allyl, preferably propyl, and R ^{5} is C $_{2-3}$ alkyl, allyl or cyclopropylmethyl, preferably propyl ego; R ^{2} is methyl; R ^{3} is hydrogen, methyl or methylthio, preferably propyl; Ar is phenyl substituted by one, two or three substituents each independently selected from the group consisting of halo, methyl and methoxy, in particular one, two or three independently selected from the group consisting of halo, methyl and dimethylamine it is a compound of general formula (I) which is phenyl substituted by a substituent.

More preferably Ar is 3-pyridinyl in which the 4- and / or 6-positions are substituted by methyl or dimethylamino.

Most preferred compounds are 3- (2,4-dichlorophenyl) -5-methyl-7- (N-propyl-N-cyclopropanemethylamino) pyrazolo [2,3-a] pyrimidine, 3- (2, 4-dichlorophenyl) -5-methyl-7- (N-allyl-N-cyclopropanemethylamino) pyrazolo [2,3-a] pyrimidine, 2-methylthio-3- (2,4-dichlorophenyl) -5-methyl-7- (N, N-diallylamino) pyrazolo [2,3-a] pyrimidine, 2-methylthio-3- (2,4-dichlorophenyl) -5-methyl-7 -(N-butyl-N-cyclopropanemethylamino) pyrazolo [2,3-a] pyrimidine, 2-methylthio-3- (2,4-dichlorophenyl) -5-methyl-7- (N-Propyl-N-cyclopropanemethylamino) pyrazolo [2,3-a] pyrimidine, 2-methyl-3- (4-chlorophenyl) -5-methyl-7- (N, N-dipropylamino) pyra Zolo [2,3-a] pyrimidine, 3- [6- (dimethylamino) -3-pyridinyl] -2,5-dimethyl-N, N-dipropylpyrazolo [2,3-a] pyrimidine-7-amine, 3- [6- (dimethylamino) -4-methyl-3-pyridinyl] -2,5-dimethyl-N, N-dipropylpyrazolo [2,3-a] pyrimidin-7 -Amines and 3- (2,4-dimethoxyphenyl) -2,5-dimethyl-7- (N-propyl-N-methyloxyethylamino) pyrazolo [2,3-a] pyrimidine, stereoisomers and drugs thereof Compound selected from scientifically acceptable acid addition salts.

Compounds of the present invention can generally be prepared by alkylating pyrazolopyrimidines of formula (II) with intermediates of formula (III):

In intermediate (III), W represents a suitable leaving group such as halo, for example chloro or bromo, or sulfonyloxy group, for example mesyloxy or tosyloxy group.

The reaction is generally carried out in a suitable solvent, for example an aprotic solvent such as DMF or acetonitrile, ether, for example tetrahydrofuran, preferably at elevated temperature, when the intermediate of formula (III) is a volatile amine in a closed reaction vessel.

In addition, a compound of formula (I) wherein R^1 is OR^6, wherein the compound is represented by formula (Ia), represents an intermediate of formula (VI) with an intermediate of formula (VII), wherein W is By O-alkylation as defined above):

The reaction for preparing the compound of formula (Ia) can be carried out in the presence of a suitable base such as sodium hydride in a reaction-inert solvent such as N, N-dimethylformamide, preferably at room temperature to reflux temperature. Can be.

A compound of formula (I) wherein R^1 is NR^4R^5, wherein the compound is represented by formula (Ic), is characterized by the appropriate N-alkylation of the compound of formula (VIII) or (IX) as Can be manufactured:

In the above scheme, W is as defined above.

Said N-alkylation is carried out in a reaction-inert solvent, for example ether (eg tetrahydrofuran), preferably in the presence of a strong base, for example NaH.

In one particular case, the reaction is R^2 (R^4 or R^5) -N-alkylated by, and in particular R^2 is methyl, R^4 or R^5 may form a C_{1-6} alkyl products have.

As will be described later, the compound of the general formula (I) can be mutually converted according to a conversion method known in the art.

For example, compounds of formula (I) wherein R^3 is C_{1-6} alkylthio are peroxides such as 3-chloroperbenzoic acid, for example, by oxidation reactions, in reaction-inert solvents such as dichloromethane By treatment with R^3 can be converted to a compound of formula (I) wherein R^3 is C_{1-6} alkylsulfonyl or C_{1-6} alkylsulfinyl. By adjusting the amount of oxidizing agent and other reaction parameters, it is possible to obtain compounds of formula (I) or mixtures thereof, wherein R^3 is C_{1-6} alkylsulfonyl or C_{1-6} alkylsulfinyl; Can be separated by, for example, column chromatography.

In addition, the compounds of general formula (I) can be interchanged with each other according to reactions or functional group conversion methods known in the art. For example, a compound of formula (I) having a hydroxyC $_{1-6}$ alkyl group can be treated with an acid anhydride, optionally in the presence of a base, for example pyridine, in a reaction-inert solvent such as, for example, dichloromethane. C_{1-6} can be converted to compounds of formula (I) having alkyl-carbonyl-oxy C_{1-6} alkyl group.

The compound of formula (I) having a nitro group is converted into a compound of formula (I) having an amino group, and then of the formula (I) having a mono- or di (C_{1-6} alkyl) amino group Can be converted to a compound. Amino groups can also be converted to halo using diazotization reactions.

In addition, the Ar group of the compound of general formula (I) may be halogenated using a halogenating agent such as chlorine or bromine in a suitable solvent such as acetic acid and optionally the reaction is carried out at room temperature to the reflux temperature of the reaction mixture. can do.

Intermediates are described by Robins et al. Heterocyclic Chem. 22: 601-634, 1985.

The aminopyrazole derivative (IV) is preferably reacted with β-keto ester (V) in a suitable reaction-inert solvent such as THF under reflux conditions to give hydroxypyrazolopyrimidine (VI) and Conversion of intermediate (VI) to intermediate of formula (II), for example by treatment of the hydroxy group of intermediate (VI) with methanesulfonyloxy chloride or a halogenating agent such as $POCl_3$ to a leaving group W Let's do it.

Intermediates of formula (VIII) are prepared by treating the intermediate of formula (II) with ammonia.

In one embodiment, the invention also provides intermediates of (II ') wherein W' represents hydroxy, halo, mesyloxy or tosyloxy and Ar is other than phenyl.

The intermediate of formula (II ') is defined as a compound of formula (II) wherein W 'is hydroxy according to the method used to prepare the intermediate of formula (II). A compound of formula (II'-b), obtained by obtaining a compound of a) and optionally defining a compound of formula (II'-a) wherein W 'is other than hydroxy It can manufacture by switching to.

Stereoisomers are prepared by separating the final product of formula (I) according to methods known in the art, for example by treating with optically active acids and separating the formed diastereomeric salts by selective crystallization or column chromatography. can do. Stereoisomers may also be prepared by using stereoisomer starting materials in the above schemes or in the preparation of intermediates described below.

The effectiveness of a compound as a CRF receptor antagonist can be determined by various test methods. Suitable CRF antagonists of the present invention can inhibit CRF specifically binding to its receptor and can antagonize the activity associated with CRF. Compounds of formula (I) include, but are not limited to, the tests described in DeSouza et al. (J. Neuroscience 7:88, 1987) and Battaglia et al. (Synapse I: 572, 1987). The activity as a CRF antagonist can be assessed by one or more test methods commonly used in the art. As mentioned above, suitable CRF antagonists include compounds having affinity for the CRF receptor. CRF receptor affinity is a binding assay that measures the degree of a compound that inhibits the binding of radiolabeled CRF (eg $[^{125}I]$ tyrosine CRF) to a receptor (eg, a receptor made from rat cortical membranes). Can be determined by testing. Radioligand binding assays described in DeSouza et al. (Supra, 1987) provide assays to determine affinity of compounds for CRF receptors. This activity is generally calculated from the IC_{50} as the concentration of compound needed to replace 50% of the radiolabeled ligand from the receptor and is reported as the "K_i" value calculated from the following formula:

$$K_i = (IC_{50} / (1 + L / K_D))$$

In the above formula,

L is a radioligand,

K_D is the affinity of the radioligand to the receptor (Biochem. Pharmacol. 22: 3099, 1973 by Chen and Prusoff).

In addition to inhibiting CRF receptor binding, the activity of antagonizing a compound's CRF receptor can be determined by the compound's ability to antagonize the activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Thus, compounds can be evaluated as CRF antagonists by their ability to antagonize the activity of CRF-induced adenylate cyclase, for example by measuring cAMP levels. From the activity test of CRF-induced adenylate cyclase described in Battaglia et al. (Supra, 1987) one can derive a test to determine the ability of a compound to antagonize CRF activity. Thus, CRF receptor antagonistic activity generally involves performing an initial binding test (as described in DeSouza (supra, 1987)) followed by a cAMP selection protocol (as described in Battaglia (supra, 1987)). Can be measured by a test technique. With regard to CRF receptor binding affinity, the CRF receptor antagonists of the invention have a K_i of less than 10 μM. In a preferred embodiment of the invention, the CRF receptor antagonist has a K_i of less than 1 pM and more preferably less than 0.25 μM (ie 250 nM).

CRF receptor antagonists of the present invention exhibit activity at the CRF receptor site and can be used as therapeutic agents for treating a wide variety of diseases or conditions, including endocrine, psychiatric and neurological diseases or conditions. More specifically, the CRF receptor antagonists of the present invention may be useful for treating physiological symptoms or diseases caused by hypersecretion of CRF. Since CRF is thought to be a central nervous system neurotransmitter that activates and coordinates endocrine, behavioral and autonomous responses to stress, the CRF receptor antagonists of the present invention can be used to treat neuropsychiatric diseases. Neuropsychiatric diseases that can be treated by the CRF receptor antagonists of the present invention include emotional disorders such as

depression; Anxiety related disorders such as cardiovascular disorders such as generalized anxiety disorder, panic disorder, obsessive compulsive disorder, abnormal aggression, unstable angina and reactive hypertension; And food intake disorders such as anorexia nervosa, bulimia and irritable bowel symptoms. CRF antagonists may also be useful for treating stroke as well as immune suppression by stress accompanying various disease states. Still other uses of CRF antagonists according to the invention include inflammatory symptoms (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and GI motility), Cushing's disease, infant cramps, epilepsy, infant and adult seizures, and Treatment of various drug abuse and withdrawal (including alcoholism).

In another embodiment of the present invention, pharmaceutical compositions containing one or more CRF receptor antagonists are described. For the purpose of administration, the compounds of the present invention may be formulated in pharmaceutical compositions. The pharmaceutical composition of the invention contains a CRF receptor antagonist of the invention (ie, a compound of formula (I)) and a pharmaceutically acceptable carrier and / or diluent. CRF receptor antagonists are present in the composition in an amount effective to treat a particular disease, ie, an amount sufficient to achieve CRF receptor antagonistic activity, and preferably at a level of toxicity acceptable to the patient. Preferably, the pharmaceutical composition of the present invention may contain the CRF receptor antagonist in an amount of 0.1 mg to 250 mg, and more preferably 1 mg to 60 mg per dose, depending on the route of administration. Suitable concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carriers and / or diluents are well known to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and / or diluents include saline and sterile water and optionally contain antioxidants, buffers, bacteriostatic agents and other conventional additives. The composition may be formulated as pills, capsules, granules or tablets containing diluents, dispersants, surfactants, binders and lubricants, in addition to CRF receptor antagonists. Those skilled in the art can further formulate the CRF receptor antagonist in a suitable manner in accordance with conventional practice, as described in Remington's, Pharmaceutical Sciences, Gennaro, Ed., Mack Publishing Co., Easton, USA, 1990. .

In another embodiment, the present invention provides methods for treating various symptoms or diseases, including endocrine, psychiatric and neurological symptoms or diseases. The method comprises administering a compound of the present invention to a warm blooded animal in an amount sufficient to treat such condition or disease. This method comprises systemic administration of a CRF receptor antagonist of the invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration includes oral and parenteral administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets and capsules, as well as solutions, syrups, suspensions and emulsions. These compositions also contain flavorings, preservatives, suspending agents, thickening agents, emulsifiers and other pharmaceutically acceptable additives. In the case of parenteral administration, the compounds of the present invention may be prepared as aqueous injection solutions which may contain, in addition to CRF receptor antagonists, buffers, antioxidants, bacteriostatic agents and other additives commonly used in such solutions. .

As mentioned above, various disorders or diseases can be treated by administering the compounds of the present invention. In particular, the compounds of the present invention include depression, emotional disorders, panic disorders, obsessive compulsive disorder, abnormal aggressiveness, unstable angina, reactive hypertension, anorexia nervosa, bulimia, irritable bowel symptoms, stress-related immune suppression, stroke, inflammation, Cushing's disease, It may be administered to warm blooded animals to treat infant cramps, epilepsy, and various drug abuse and withdrawal symptoms.

Accordingly, the present invention provides the use of a compound of formula (I) for the manufacture of a medicament for the treatment of physiological symptoms or diseases due to hypersecretion of corticosteroid-releasing factor (CRF). The invention also provides the use of the compounds of the general formula (I) as medicaments.

The following examples are presented for illustrative purposes and are not intended to be limiting.

Experimental part

"THF" means tetrahydrofuran and "DCM" means dichloromethane.

A. Preparation of Intermediates

Example A.1

a) 3-amino-4- (2,4-dichlorophenyl) pyrazole and ethyl acetoacetate (2 equiv) are dissolved in dioxane and heated at reflux overnight. The mixture is concentrated in vacuo and diluted with ethyl acetate. The white off solid formed after standing for 2 days was collected by vacuum filtration to obtain 3- (2,4-dichlorophenyl) -5-methyl-7-hydroxypyrazolo [2,3 a] pyrimidine (intermediate 1) To obtain.

b) Intermediate 1 (300 mg) is mixed with $POCl_3$ (1.5 mL) and heated to reflux for 1 h. The formed purple solution is carefully transferred to ice water. The product was extracted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated in vacuo to afford 3- (2,4-dichlorophenyl-5-methyl-7-chloropyrazolo [2,3 -a] pyrimidine (intermediate 2) is obtained as a brown solid (260 mg, 82%).

Example A.2

a) To a stirred solution of sodium hydride (60%, 25 mmol) in THF (10 mL) is added dropwise &- (dimethylamino) -3-pyridineacetonitrile (10 mmol) in THF (10 mL). The solution is stirred for 10 minutes, then ethyl acetate (30 mmol) is added slowly. The resulting suspension is stirred at room temperature for 1 hour. The reaction mixture is concentrated in vacuo, dissolved in ethyl acetate / methanol (1: 1) and then filtered through silica. Concentrate the filtrate to afford intermediate 7.

b) A mixture of intermediate 7 and hydrazine hydrobromide (100 mmol) is dissolved in ethanol / water (9: 1, 100 mL total) and refluxed for 1 hour. The reaction mixture is concentrated and the residue is partitioned between ethyl acetate and sodium bicarbonate solution. The combined extracts are dried over sodium sulfate, filtered and concentrated to dryness. The residue is dissolved in 1,4-dioxane (200 mL) and refluxed for 16 h in the presence of ethyl acetoacetate. Cooling of the reaction mixture results in precipitation of an off-white solid. Diethyl ether was added to promote crystallization, then the precipitate was filtered and dried to 3- [2- (dimethylamino) -5-pyridinyl] -2,5-dimethyl-7-hydroxypyrazolo [2 , 3-a] pyrimidine (intermediate 8) is obtained.

c) Intermediate 8 is dissolved in $POCl_3$ (2 mL) and refluxed for 2 hours. After cooling the reaction mixture, it is poured on ice. The solution is made basic (pH = 9) by adding solid sodium carbonate and then extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated to 3- [6- (dimethylamino) -3-pyridinyl] -2,5-dimethyl-7-chloro-pyrazolo [2,3-a] pyridine Midine (intermediate 9) is obtained.

Table 1 shows the intermediates prepared according to one of the examples mentioned above:

Intermediate number Example Number R^3 Ar 2345613 A.1A.1A.1A.1A.1A.1 HCH_3 SCH_3 $HHCH_3$ 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 4-chlorophenyl 2,5-dichlorophenyl 4-chlorophenyl

Intermediate number Example Number R^3 Ar 1415161718191011121926 A.1A.1A.1A.1A.1A.2A.2A.2A.2A.1A.1 CH_2CH_3 CH_3 $CH_3CH_2HCH_3$ $CH_3CH_3CH_3CH_3CH_3$ 3-methoxyphenyl 4-methoxyphenyl 2,4-dimethoxyphenyl 3,4-dimethoxyphenyl 2,4,5 trimethoxyphenyl 6-dimethylamino-3-pyridinyl 6-dimethylamino-4- Methyl-3-pyridinyl 6-methyl-5-nitro-2-pyridinyl 5-chloro-2-pyridinyl 6-methyl-3-pyridinyl 3-methyl-5-nitro-2-pyridinyl

B. Preparation of the Final Product

Example B.1

A mixture of intermediate 2 (21 mg) and N-propyl-N-cyclopropanemethylamine (75 mg) is heated overnight at 100 ° C. in a closed reaction vessel. 3- (2,4-dichlorophenyl) -5-methyl-7- (N-propyl-N-cyclopropanemethylamino)-by chromatography on preparative TLC plates using 1: 5 ethyl acetate-hexane Pyrazolo [2,3-a] pyrimidine (Compound 17) (17.4 mg) and 3- (2,4-dichlorophenyl) -5-methyl-7- (N-cyclopropanemethylamine) pyrazolo [2, 3-a] pyrimidine (compound 8) (1 mg) is obtained.

In a similar manner, intermediate (2) and (S)-(-)-roisinol (R)-(+)-roisinol, respectively, were used as starting materials for (S) -2-[[3- (2,4- Prepare dichlorophenyl) -5-methyl-7-pyrazolo [2,3-a] pyrimidinyl] amino] -4-methyl-1-pentanol (Compound 11) and its R-analog (Compound 12). .

Example 8.2

A solution of di-n-propylamine (13 g) and intermediate 10 (8 g) in acetonitrile (50 mL) is heated under reflux for 3 hours. The mixture was filtered through a short silica gel plug with ethyl acetate and then the filtrate was concentrated in vacuo to give a pale yellow solid which was recrystallized from ether-hexane to give 3- [6- (dimethylamino) -4-methyl 8.9 g (93%) of 3-pyridinyl] -2,5-dimethyl-N, N-dipropylpyrazolo [2,3-a] pyrimidin-7-amine (Compound 53) are obtained.

Compound 53 (8.1 g) was dissolved in a mixture of diethyl ether (150 mL) and DCM (50 mL), and the mixture was treated dropwise with HCl in diethyl ether (1M, 21.3 mL) with stirring to give compound 53 a Convert to hydrochloric acid addition salt. The off-white solid formed was collected by filtration to obtain 3- [6- (dimethylamino) -4-methyl-3-pyridinyl] -2,5-dimethyl-N, N-dipropylpyrazolo [2,3-a] pyrimidine 8.7 g (98%) of -7-amine monohydrochloride are obtained.

Example 8.3

Intermediate 3 (15 mg) is dissolved in ethanol (0.5 mL) and stirred in the presence of sodium ethoxide (12 mg) for 1 hour. Chromatography on silica gel affords 3- (2,4-dichlorophenyl) -7- (ethoxy) -5-methyl-2-methylthio-pyrazolo [2,3-a] pyrimidine (Compound 50). .

Example 8.4

A solution of compound 6 (14 mg) in THF (3 mL) was treated with sodium hydride (60 mg, excess) at room temperature for 5 minutes followed by iodopropane (0.3 mL). The reaction is stirred at rt overnight and quenched with methanol (0.5 mL). The resulting mixture was charged onto a preparative TLC plate and developed with 1: 5 ethyl acetate-nucleic acid to give 3- (2,4-dichlorophenyl) -5-methyl-7- [N- (3-methoxypropyl) as colorless oil.) -N-propylamino] -pyrazolo [2,3-a] pyrimidine (Compound 45) (5.7 mg), 3- (2,4-dichlorophenyl) -5-butyl-7- [N- (3 -Methoxypropyl) -N-propylamino] -pyrazolo [2,3-a] pyrimidine (compound 46) (4 mg) and 3- (2,4-dichlorophenyl) -5-butyl-7- [3-methoxy-propylamino] -pyrazolo [2,3-a] pyrimidine (Compound 47) (3.5 mg) is obtained.

Example 8.5

Compound 26 (8 mg) is dissolved in DCM (1 mL) and treated with acetic anhydride (0.1 mL) and pyridine (0.1 mL). The mixture is stirred overnight at room temperature and concentrated in vacuo. The residue is diluted with ethyl acetate and filtered through a silica gel column. The filtrate was concentrated to give 3- (2,4-dichlorophenyl) -5-methyl-7- [N- (2-acetoxyethyl) -N-benzylamino] -pyrazolo [2,3-a] pyrimidine (Compound 27) (8.6 mg) is obtained as a colorless oil.

Example 8.6

A solution of compound 40 (20 mg) in DCM (3 mL) is treated with 3-chloroperbenzoic acid (19 mg). The solution is stirred at room temperature for 1 hour. Chromatography on silica gel column plate with ethyl acetate-hexane (1: 1) affords compound 43 and compound 44.

Example 8.7

A mixture of compound 55 and palladium on activated carbon (100 mg) in anhydrous ethanol (100 mL) is introduced into a hydrogenation unit and hydrogenated at 2.7 10^5 Pa (40 psi) for 2 hours. The reaction mixture is filtered and concentrated. The residue was dissolved in diethyl ether and concentrated to 3- (5-amino-3-methyl-2-pyridinyl) -2,5-dimethyl-N, N-dipropyl-pyrazolo [2,3-a] 1.49 g of pyrimidin-7-amine (compound 56) are obtained.

Example 8.8

To a stirred solution of aqueous formaldehyde (6.4 g) and compound 56 (1.39 g) in ACN (20 mL) was added sodium cyanoborohydride (794 mg) at 0 ° C. Glacial acetic acid (1 mL) is added and the reaction mixture is stirred at room temperature for 2 hours. The reaction mixture is partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to dryness and purified by flash column chromatography on silica gel (CH_2Cl_2 / CH_3OH / NH_4OH 150: 10: 1). do. The desired fractions were separated and 3- [5- (dimethylamino) -3-methyl-2-pyridinyl] -2,5-dimethyl-N, N-dipropyl-pyrazolo [2,3-a] pyrimidine 1.30 g of -7-amine (Compound 57) are obtained.

Example 8.9

To a solution of compound 56 (100 mg) in a mixture of water (1 mL) and concentrated HCl (1 mL) cooled in an ice bath is added a solution of sodium nitrite (21 mg) in water (1 mL). The solution is added to a mixture of copper chloride (I) (281 mg) in concentrated HCl with stirring in an ice bath. The solids are separated and the mixture is heated to 60 ° C. to obtain a clear solution. The reaction mixture is basified with NaOH, extracted with ethyl acetate, washed with brine and concentrated. Purification by preparative TLC affords 16 mg of compound 98.

Example 8.10

Compound 56 (100 mg) was added to a solution of fluoroboric acid (48 wt% in water, 2 mL) cooled in an ice bath, followed by a solution of sodium nitrite (20 mg) in water (1 mL). The temperature is kept below 10 ° C. The solid is collected by filtration, dried and partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The organic layer is washed with brine and concentrated, then the residue is purified by preparative TLC to give 20 mg of compound 100.

Tables 2 to 5 below show compounds prepared according to one of the examples above, and Tables 6 and 7 show analytical data for these compounds:

Compound number Example Number R^4 R^5 Ar 1 2 3 4 5 6 7 8 9 10 8.18.18.18.18.18.18.18.18.18.1 Hydrogen Hydrogen Hydrogen Hydrogen Hydrogen Hydrogen Hydrogen Hydrogen n-propyl 2-methylpropyl 1,1-dimethylethyl 3-hydroxypropyl 3-pentyl $CH_3O(CH_2)_3$ $(CH_3)_2$ $CH_3O(CH_2)_3$ -cyclopropylmethyl 3-methyl 2-butyl 4-methyl-2-pentyl 2,4-dichlorophenyl2,4-dichlorophenyl2,4-dichloropheny2,4-dichloropheny2,4-dichlorophenyl2,4-dichlorophenyl2,4-dichloropheny2,4-dichloropheny2, 4-dichloropheny2,4-dichloropheny

Compound number Example Number R^4 R^5 Ar 1112131415161718192021222 3 8.18.18.18.38.18.28.18.18.18.28.18.18.4 Hydrogen Hydrogen Methylethyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-butyl Cyclopropylmethyl n-butyl n-propyl cyclopropylmethyl $HOCH_2CH_2$ -$CH_3O(CH_2)_2$ -n-propyl cyclopropyl $CH_3O(CH_2)_2$ -cyclopropylmethyl 2,4-dichlorophenyl2,4-dichlorophenyl2,4-dichlorophenyl2,4-dichlorophenyl2,4-dichlorophenyl2,4-dichloropheny2,4-dichloropheny2,4-dichloropheny2, 4-dichlorophenyl4-chloropheny2,6-dichloropheny2,6-dichlorophenyl2,4-dichloropheny

Compound number Example Number R^4 R^5 Ar 242526272829455859606162636465 66 8.18.18.18.58.58.48.48.18.18.18.18.28.18.18.1 2-methylpropyl3-methyl-2-butylHOCH $_2$CH $_2$ -$CH_3COO(CH_2)_2$ -$CH_3COO(CH_2)_2$ -allyl n-propylCH $_3$O (CH $_2$) $_2$ -hydrogen hydrogen n-propylethyl n-propyl n-propyl n-butyl Cyclopropylmethyl cyclopropylmethyl phenylmethyl phenylmethyl n-propyl cyclopropylmethyl $CH_3O(CH_2)_3$ $CH_3O(CH_2)_2$ -$CH_3OCH_2CH(CH_3)$-1-hydroxy-2- Hexyl 1-hydroxy-2-pentyl n-propyl n-butyl cyclopropylmethyl cyclopropylmethyl n-butyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-

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dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2, 4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 6-dimethylamino-2,4-dimethyl-pyridinyl 6-dimethylamino-2,4-dimethyl-3-pyridinyl 6-dimethylamino -2,4-dimethyl-3-pyridinyl 6-methyl-3-pyridinyl 6-methyl-3-pyridinyl

Compound number Example Number R ^{4} R ^{5} Ar 6758697677172 8,18,28,18,18,18,1 n-propyl n-propyl n-propyl n-propylethylethyl Cyclopropylmethyl n-propyl CH $_{3}$ O (CH $_{2}$) $_{2}$ -cyclopropylmethyl n-butyl ethyl 2,4-dimethoxyphenyl2,4,6-trimethoxyphenyl2,4,6-trimethoxyphenyl2,4,5-trimethoxyphenyl2,4,6-trimethoxyphenyl2,4 , 6-trimethoxyphenyl

Compound number Example Number R ^{3} R ^{4} R ^{5} Ar 303132343536 8,18,18,18,18,18,1 CH $_{3}$ SCH $_{3}$ SCH $_{3}$ SCH $_{3}$ SCH $_{3}$ SCH $_{3}$ S Hydrogen Hydrogen Hydrogen Hydrogen Methyl Ethyl n-propyl 2-propyl 3-heptyl 2-methoxyphenylmethyl methyl ethyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl

Compound number Example Number R ^{3} R ^{4} R ^{5} Ar 373839404142434473 8,28,18,18,18,18,18,68, 68,2 CH $_{3}$ SCH $_{3}$ SCH $_{3}$ SCH $_{3}$ SCH $_{3}$ SCH $_{3}$ SCH $_{3}$ SCH $_{3}$ SCH $_{2}$ CH $_{3}$ CH $_{2}$ n-propyl n-propyl 2-propyl n-butyl n-butyl allyl n-propyl n-propyl n-propyl n-propyl cyclopropylmethyl 2-propyl n-butyl cyclopropylmethyl allyl cyclopropylmethyl cyclopropylmethyl n-propyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 2,4-dichlorophenyl 3, 4-dimethoxyphenyl

Compound number Example Number R ^{4} R ^{5} Ar 48495182533545585677475757779879 8,28,18,18,28,28,28,28,78,88,18,18,18,18,18,1 n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl CH $_{3}$ O (CH $_{2}$) $_{2}$ -HOCH $_{2}$ CH $_{2}$ -Hydrogen Hydrogen Hydrogen n-propylcyclopropylmethylCH $_{3}$ O (CH $_{2}$) $_{2}$ -n-propyl n-propyl n-propyl n-propyl n-propyl n-propylCH $_{3}$ O (CH $_{2}$) $_{2}$ -phenylmethyl1-hydroxy 2 -Hexyl1-hydroxy-2-pentylCH $_{3}$ S (CH $_{2}$) $_{2}$ 4-chlorophenyl2,4-dichlorophenyl2,4-dimethoxyphenyl6-dimethylamino-3-pyridinyl6-dimethylamino-4-methyl-3-pyridinyl5-chloro-2-pyridinyl3-methyl -5-nitro-2-pyridinyl5-amino-3-methyl-2-pyridinyl3-dimethylamino-3-methyl-2-pyridinyl4-chlorophenyl4-chlorophenyl4-chlorophenyl4-chlorophenyl 4-chlorophenyl4-chlorophenyl

Compound number Example Number R ^{4} R ^{5} Ar 80818283848586878 8,18,18,18,18,18,18,18,18,1 Hydrogen Ethyl n-propyl n-propylallyl n-butyl hydrogen hydrogen 1-hydroxy-2-hexyl n-butylcyclopropylmethylphenylmethylallyl n-butyl3-pentyl2-propyl4 -methyl-2-pentyl 6-dimethylamino-4-methyl-3-pyridinyl6-dimethylamino-4-methyl-3-pyridinyl6-dimethylamino-4-methyl-3-pyridinyl6-dimethylamino-4-methyl-3- Pyridinyl6-dimethylamino-4-methyl-3-pyridinyl6-dimethylamino-4-methyl-3-pyridinyl6-dimethylamino-4 methyl-3-pyridinyl6-dimethylamino-4 methyl- 3-pyridinyl6-dimethylamino-4 methyl-3-pyridinyl

Compound number Example Number R ^{4} R ^{5} Ar 899091929394959697989 8,18,28,18,18,18,18,18,28,18,88,9 Methyl n-propyl n-propylethyl n-butyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-butyl n-propylcyclopropylmethyl n-butyl n-butyl n-propylcyclopropylmethyl n-propylcyclopropylmethyl n-propyl n-propyl 6-dimethylamino-4-methyl-3-pyridinyl6-dimethylamino-2-methyl-3-pyridinyl6-dimethylamino-2-methyl-3-pyridinyl6-dimethylamino-2-methyl-3- Pyridinyl6-dimethylamino-2-methyl-3-pyridinyl4,6-dimethyl-3-pyridinyl4,6-dimethyl-3-pyridinyl6-dimethylamino-2,4-dimethyl-3-pyridinyl 6-dimethylamino-2,4-dimethyl-3-pyridinyl5-chloro-3-methyl-2-pyridinyl5-iodo-3-methyl-2-pyridinyl

Compound number Example Number R ^{4} R ^{5} Ar 1061011021031041051061073310810911011 8,108,28,18,28,18,18,28,88,88,88,28,28,9 n-propyl n-propyl CH $_{3}$ O (CH $_{2}$) $_{2}$ -n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl CH $_{3}$ O (CH $_{2}$) $_{2}$ -n-propylCH $_{3}$ O (CH $_{2}$) $_{2}$ -cyclopropylmethyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n- profile 5 fluoro-3-methyl-2-pyridinyl3-chloro-5-trifluoromethyl-2-pyridinyl3-chloro-5-trifluoromethyl-2-pyridinyl3,5-dichloro-2 -Pyridinyl3,5-dichloro-2-pyridinyl3,5-dichloro-2-pyridinyl3-methyl-5-methoxy-2-pyridinyl5-diethylamino-3-methyl-2-pyridinyl 6-diethylamino-4-methyl-3-pyridinyl5-N-piperidinyl-3-methyl-2-pyridinyl5-methyl-3-nitro-2-pyridinyl3-amino-5-methyl- 2-pyridinyl3-chloro-5-methyl-2-pyridinyl

Compound number Example Number R ^{4} R ^{5} Ar 1121131141151161171181191201211221231241251261 27 8,28,28,28,18,28,18,18,18,18,18,88,28,18,18,28,28,1 n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl n-propyl hydrogen n-propyl n-propyl n-propylethyl n-propyl n-propyl n-propyl n-propyl n-propylcyclopropylmethyl n-propyl CH $_{3}$ O (CH $_{2}$) $_{2}$ -cyclopropylCH $_{3}$ O (CH $_{2}$) $_{2}$ -HO (CH $_{2}$) $_{2}$ -n-propyl n-propyl n- Butyl 2-hydroxypropyl n-propyl n-propylcyclopropylmethyl 3-methylamino-5-methyl-2-pyridinyl3-dimethylamino-5-methyl-2-pyridinyl2-methyl-5-pyridinyl4-isopropylphenyl3,4-dimethoxyphenyl3,4- Dimethoxyphenyl2,4-dimethoxyphenyl2,4-dimethoxyphenyl2,4-dimethoxyphenyl5-methylamino-3-methyl-2-pyridinyl2,4-dimethoxyphenyl2,4-dimethoxy Phenyl2,4-dimethoxyphenyl4-methoxyphenyl3-methoxyphenyl3-methoxyphenyl

Compound number Example Number R ^{4} and R ^{5} form together Ar 128129130131 8,18,18,18,1 4-chlorophenyl4-chlorophenyl6-dimethylamino-4-methyl-3-pyridinyl6-dimethylamino-4-methyl-3-pyridinyl

Compound number Example Number R ^{1} R ^{2} R ^{3} Ar 464756 8,48,48,3 CH $_{3}$ CH $_{2}$ O- nC $_{4}$ H $_{9}$ nC $_{4}$ H $_{9}$ CH $_{3}$ NHCH $_{3}$ -3- 2,4-dichlorophenyl2,4-dichlorophenyl2,4-dichlorophenyl

Analysis data Compound number Mass spectral data 92939412913013 1 381 [MH $^{+}$] 409 [MH $^{+}$] 352 [MH $^{+}$] 368 [M $^{+}$] 393 [MH $^{+}$] 379 [MH $^{+}$]

C. Pharmacological Experiment

Example C.1 Representative Compounds Having CRF Receptor Binding Activity

The compound is described in DeSouza et al. Neurosci. 7: 88-100, 1987, was evaluated for binding activity to the CRF receptor by standard radioligand binding assays generally described. Several radiolabeled CRF ligands can be used in the assay to assess the binding activity of a compound of the invention having a CRF receptor subtype. In short, binding assays include replacing radiolabeled CRF ligands from CRF receptors. More specifically, binding assays are performed in 1.5 ml Eppendorf tubes using about 1 × 10 ^{6} cells per tube stably transfected with human CRF receptors. Test buffers with or without CRF (final concentration, 1 μM), eumtensin I or unlabeled sauvagine to determine nonspecific binding to each tube (e.g. Dulbecco phosphate buffered saline, 10 mM magnesium chloride, 20 μM bacitracin) about 0.1 mL, [^{125} I] tyrosine-positive CRF (final concentration ~200 pM or approximately K $_{D}$ measured by Scatchard analysis) and CRF receptor introduce 0.1 ml of the membrane suspension of cells. The mixture is incubated at 22 ° C. for 2 hours and then centrifuged to separate bound and free spin ligands. The pellet was washed twice, the tube was cut directly above the pellet and then irradiated for radioactivity at an efficiency of about 80% in a gamma counter. All radioligand binding data were analyzed using a non-linear least-square curve-fitting program. Binding activity corresponds to the concentration of compound (nM) required to replace 50% of the radiolabeled ligand from the receptor. Compounds 5, 10, 12, 15-17, 19, 23, 24, 26, 27, 29, 31-33, 36-43, 48, 49, 51-54 and 57-130 as described in Tables 2-5 This has a K $_{i}$ value of ≤ 250 nM.

Compound 17, 29, 38, 41, 42, 48, 49, 51-54, 57, 58, 70, 71, 81-85, 90-92, 101, 103-105, 115, 118, 121- In this test 123 and 125 were found to have the best scores.

Example C.2

CRF-induced adenylate cyclase activity

The compounds of the present invention can also be evaluated by various functional tests. For example, compounds of the invention can be screened for CRF induced adenylate cyclase activity. Assays for measuring CRF induced adenylate cyclase activity can be performed by modifying the methods generally described in Battaglia et al. (Synapse 1: 572, 1987) to suit whole cell preparation assays. More specifically, the standard assay mixture may contain 2 mM L-glutamine, 20 mM HEPES and 1 mM IMBX in DMEM buffer at a final volume of 0.5 ml. In the induction test, whole cells with transfected CRF receptors were plated in 24 well plates and incubated at 37 ° C.

for 1 hour with varying concentrations of CRF-associated and unrelated peptides for pharmacological ranking of specific receptor subtypes. Determine. After incubation, the medium is aspirated, the wells are rinsed once with fresh medium and the medium is aspirated. To determine the amount of intracellular cAMP, 300 µl of a solution of 20 mM aqueous hydrochloric acid and 95% ethanol is added to each well and the resulting suspension is incubated at -20 ° C. for 16-18 hours. The solution is taken out and introduced into a 1.5 ml Eppendorf tube and the wells are washed with additional 200 µl of ethanol / aqueous hydrochloric acid and then pooled with the first fraction. Samples are lyophilized and resuspended with 500 µl sodium acetate buffer. CAMP in the sample is measured using a single antibody kit. For the functional measurement of the compound, and incubated a single concentration of CRF or related peptides that result in 80% of cAMP production with competing compounds (10^{-12} to 10^{-6} M) of various concentrations.

Example C.3

The plus-maze and defensive withdrawl paradigm are complementary to measure exploratory behavior sensitive to anxiety-promoting and anxiety-relieving effects by experimental treatment. These animal models were used to investigate the anti-anxiety and anti-stress action of the compounds of the present invention.

Example C.3-a: Expensive Plus-Maze Paradigm

This test predicts how the animal can respond to access-avoidance situations, including bright and dark safe spaces. Both spaces are separated from the ground and consist of two mains crossing in the form of a plus sign. This type of approach-avoidance situation is a classical test method for investigating "emotions" and responsiveness and is very sensitive to disinhibition (such as calm / hypnosis) and stress-forming processes. There is no need to limit movement and allow the animal to freely remain in the dark or escape with an open arm. The plus-maze device has four arms (10 x 50 cm) at an angle of 90 degrees and is located 50 cm from the floor. The two arms are blocked by a wall (40 cm high) and the two arms have no barriers (open arms). The subjects are individually placed in the center of the maze and allowed free access to four arms for 5 minutes. Observe the object through the window in the door and at the same time make the rat's position on-line display on the computer monitor. The time spent in each arm is automatically recorded by the photocell beam and the computer program. Wipe the maze with a damp cloth between each test. In this experiment, anxiety-promoting behavior is measured as a decrease in the time spent in the open arm, and the anti-stress effect is measured as a complementary increase in the time spent in the open arm.

Validity of Plus-Maze with CRF Peptides

Central administration of CRF and exposure to several experimental stressors inhibit the exploratoryness of an expensive plus maze model wrapped in anxiety. When measuring behavioral responses to social frustration, centralized administration of alpha-helix CRF (9-41) antagonizes post-stress [25 µg ICV] or prestress [1 µg ICN] promotes social frustration. The effect is reversed. The anti-stress action of these CRF antagonists also reaches the central nucleus of the cerebellar tonsils after arrival of the cerebral [250 ng IC].

Rats are administered orally with test compounds 1 hour before the 5 minute test. Some groups are placed in a pool full of water for 90 seconds (stress group) just before introduction into the plus-maze, and the control group is taken directly from the cage (non-stress group). It was observed that the average percentage of time spent in open arms was significantly reduced (about 36 to about 16%) in the non-treated animals group. When Compound 53 was administered 2.5 or 20 mg / kg, the percentage of time spent in the open arm returned to the same level as the untreated group within the margin of error.

Example C.3-b: Defensive Retreat Paradigm

The test was carried out in an open field (106 x 92 x 77 cm) of plastic glass comprising a cylindrical steel chamber with a direct current flowing 19.2 cm in diameter and 17.1 cm deep. The chamber is open at one end and placed side by side with the wall of the open field so that it is vertically aligned 15.5 cm from the corner of the open field. The open end faces with the corner. The fluorescent light is illuminated from the ceiling into the open field. For testing, animals are introduced into an unfamiliar test environment by placing them in a small chamber. The test time is 5 minutes and after each test the device is wiped off with a mild acetic acid solution. Test compounds are administered orally 5 minutes before the test. Monitor animal behavior and record with video camera. The latency to escape the chamber is measured, which is defined as all four feet in the open field. The average length of time in the chamber per inlet and the number of passages made between the chamber and the open field are also measured. Anxiety relief effects are measured as a reduction in the mean time spent in a closed chamber. When oral administration of Compound 53 to rats was 0.63, 2.5 and 20 mg / kg, the mean time in the chamber decreased from about 80 seconds to about 30 to 40 seconds.

Feasibility of Defensive Retraction Using CRF Peptides

ICV injection of both alpha-helix CRF (9-41) and CRF results in changes in behavior in the defensive retreat paradigm. In particular, ICV administration of CRF to animals already familiar with the device increases both the latency from the small chamber and the average time spent in the chamber to more than 15 minutes. Similarly, the injection of CRF into the platen produces a similar change in protective retraction behavior, meaning that the interaction between CRF and noradrenaline neurons is accompanied during protective retraction behavior in rats. Conversely, ICV administration of competitive CRF receptor antagonists, alpha-helical CRF (9-14) or d-Phe CRF (12-41), reverses the effect of CRF on restraint stressors in familiar environmental conditions and is not device-friendly. The average time in the chamber and the escape latency in animals are significantly reduced.

B. Composition Examples

The following examples illustrate representative pharmaceutical compositions according to the invention in unit dosage forms suitable for systemic or topical administration to warm blooded animals.

"Active ingredient" (A.I.) used in the examples relates to a compound of formula (I), an N-oxide thereof, a pharmaceutically acceptable acid or base addition salt, a stereochemical isomer.

Example B.1 Oral Solution

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 L of boiling purified water. Firstly, 10 g of 2,3-dihydroxybutanoic acid was dissolved in 3 L of this solution, followed by A.I. 20 g are dissolved. The latter solution is combined with the former remaining solution, to which 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added. 40 g of sodium saccharin is dissolved in 0.5 L of water, and 2 ml of raspberry and 2 ml of gooseberry essence are added. Combine the latter solution with the former and add A.I. per teaspoon (5 ml) by adding an appropriate amount of water suitable to bring the volume to 20 l. An oral solution containing 5 mg is obtained. The resulting solution is filled into a suitable container.

Example B.2: Capsule

A.I. 20 g, 6 g sodium laurylsulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is then charged into 1000 suitable hard gelatin capsules each containing 20 mg of active ingredient.

Example B.3 Film-Coated Tablets

Preparation of Purified Nuclei

A.I. A mixture of 100 g, 570 g of lactose and 200 g of starch is mixed well and then wetted with a solution of 5 g of sodium dodecyl sulfate and 10 g of polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then 100 g of microcrystalline cellulose and 15 g of hydrogenated vegetable oil are added. The entire mixture is mixed well and compressed to give 10,000 tablets each containing 10 mg of the active ingredient.

Coating

A solution of 5 g of ethyl cellulose in 150 ml of dichloromethane is added to a solution of 10 g of methyl cellulose in 75 ml of modified ethanol. Thereafter, 75 ml of dichloromethane and 2.5 ml of 1,2,3-propanetriol are added thereto. 10 g of polyethylene glycol is melted and dissolved in 75 ml of dichloromethane. The latter solution is added to the former solution, to which 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated pigment suspension are added and the entire mixture is homogenized. The tablet core is then coated in a coating apparatus with the mixture thus obtained.

Example D.4 Injectable Solution

1.8 g of methyl 4-hydroxybenzoate and 0.2 g of propyl 4-hydroxybenzoate are dissolved in about 0.5 L of injectable boiling water. After cooling to about 50 ° C., 4 g of lactic acid, 0.05 g of propylene glycol and A.I. 4 g is added. The solution is cooled to room temperature and supplemented with an appropriate amount of water for injection to bring the volume to 1 L, 4 mg of A.I. Obtain a solution. The solution is sterilized by filtration and filled into sterile containers.

Example D.5: Suppositories

A.I. 3 g are dissolved in a solution of 3 g of 2,3-dihydroxybutanedioic acid in 25 ml of polyethylene glycol 400. 12 g of surfactant and 300 g of triglyceride are melted together. The latter mixture is mixed well with the former solution. The resulting mixture was poured into a mold at a temperature of 37-38 ° C. to A.I. 100 suppositories containing 30 mg are obtained.

Patent Citations (4)

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JPH0211763A *	1988-06-29	1990-01-16	Raimuzo Kk	Tai-type composite member and its production
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US6191131B1	1997-07-23	2001-02-20	Dupont Pharmaceuticals Company	Azolo triazines and pyrimidines
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WO1999051607A1	1998-04-02	1999-10-14	Neurogen Corporation	Aminoalkyl substituted 5,6,7,8-tetrahydro-9h pyrimidino[2,3-b]indole and 5,6,7,8-tetrahydro-9h-pyrimidino[4,5-b]indole derivatives; crf1 specific ligands
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			Company	
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AR045967A1 *	2003-12-22	2005-01-04	Sb Pharmco Inc	PIRAZOL COMPOUND [1,5-A] PYRIMIDINE, PHARMACEUTICAL COMPOSITION THAT INCLUDES IT AND ITS USE TO PREPARE SUCH COMPOSITION
US20070293511A1 *	2003-12-22	2007-12-20	Sb Pharmco Puerto Rico Inc. And Neurocrine Biosciences, Inc., A Corporation	Crf Receptor Antagonists and Methods
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AU2018210196B2	2017-01-23	2022-06-02	Revolution Medicines, Inc.	Pyridine compounds as allosteric SHP2 inhibitors
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KR20200070259A	2017-10-12	2020-06-17	레볼루션 메디슨즈, 인크.	Pyridine, pyrazine and triazine compounds as allosteric SHP2 inhibitors
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* Cited by examiner, † Cited by third party, ‡ Family to family citation

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Priority And Related Applications

Applications Claiming Priority (3)

Application	Filing date	Title
US1127996P	1996-02-07	
US60/011279	1996-02-07	
US2788896P	1996-10-08	
US60/027,688	1996-10-08	
US60/027688	1996-10-08	

Legal Events

Date	Code	Title	Description
1999-04-13	A201	Request for examination	
2003-07-30	E902	Notification of reason for refusal	
2003-12-11	N231	Notification of change of applicant	
2004-02-11	E701	Decision to grant or registration of patent right	
2004-02-24	GRNT	Written decision to grant	
2012-02-08	FPAY	Annual fee payment	Payment date: 20120209 Year of fee payment: 9
2013-02-25	LAPS	Lapse due to unpaid annual fee	

Data provided by IFI CLAIMS Patent Services

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(86) 국제출원번호 PCT/EP1997/00459
국제출원일자 1997년01월30일

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(30) 우선권주장 60/011279 1996년02월07일 미국(US)
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뉴로크린 바이오사이언시즈 인코퍼레이티드
미합중국 캘리포니아 92121-1102 산 디에고 사이언스 파크 로드 3050 ㄷ, 미국

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김석중
최규팔

(77) 심사관
있음

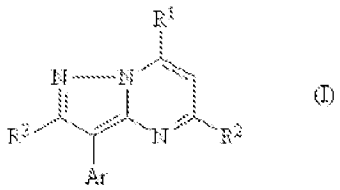
(81) 지정국 국내특허 : 아일랜드,알바니아,오스트레일리아,바베이도스,불가리아,브라질,캐나다,중국,체크,에스토니아,그루지야,헝가리,이스라엘,아이슬란드,일본,대한민국,스리랑카,라이베리아,리투아니아,라트비아,마다가스카르,마케도니아,몽고,멕시코,노르웨이
AP ARIPO특허 : 케냐,레소토,말라위,수단,스와질랜드
EA 유라시아특허 : 아르메니아,키르기즈,몰도바
EP 유럽특허 : 오스트리아,벨기에,스위스,독일,덴마크,스페인,프랑스,영국,그리스,이탈리아,룩셈부르크,모나코,네덜란드,포르투칼,스웨덴

전체 청구항 수 : 총 13 항

(54)CRF 수용체에 대한 길항제로서의 피라졸로피리미딘

(57)요 약

본 발명은 CRF 수용체에 대해 길항성을 갖는 하기 일반식 (I)의 화합물, 그의 입체이성체 및 약제학적으로 허용되는 산부가염, 활성 성분으로서 이들 화합물을 함유하는 약제학적 조성물 및 유효량의 일반식 (I)의 화합물을 투여하여 우울증, 불안 및 약물 남용과 같은 CRF의 과분비와 관련된 질환을 질환을 치료하는 방법에 관한 것이다.



(I)

상기식에서,

R^1 은 NR^4R^5 또는 OR^5 를 나타내며;

R^2 는 C_{1-6}알킬, C_{1-6}알콕시 또는 C_{1-6}알킬티오를 나타내고;

R^3 은 수소, C_{1-6}알킬, C_{1-6}알킬설포닐, C_{1-6}할로설폭시 또는 C_{1-6}알킬티오를 나타내며;

R^4 는 수소, C_{1-6}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, C_{3-6}사이클로알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알콕시카보닐C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬을 나타내고;

R^5 는 C_{1-8}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, Ar^1CH_2, C_{1-6}알콕시C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{3-6}알케닐, 퍼에닐메틸, 푸라닐메틸, C_{1-6}알킬티오C_{1-6}알킬, 모르폴리닐, 모노- 또는 디(C_{1-6}알킬)아미노C_{1-6}알킬, 디(C_{1-6}알킬)아미노, C_{1-6}알킬카르보닐C_{1-6}알킬, 이미다졸릴에 의해 치환된 C_{1-6}알킬, 또는 일반식 -Alk-O-CO-Ar^1 의 레디칼을 나타내거나;

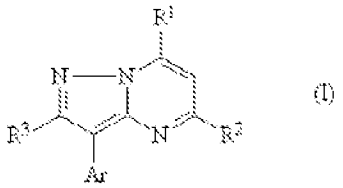
R^4 및 R^5 는 이들이 결합된 질소 원자와 함께, 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 고리을 형성할 수 있다.

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청구의 범위

청구항 1

하기 일반식 (I)의 화합물, 그의 입체이성체 및 약제학적으로 허용되는 산부가염:



(I)

상기식에서,

R^1 은 NR^4R^5 또는 OR^5 를 나타내며;

R^2 는 C_{1-6}알킬, C_{1-6}알킬옥시 또는 C_{1-6}알킬티오를 나타내고;

R^3 은 수소, C_{1-6}알킬, C_{1-6}알킬설포닐, C_{1-6}알킬설폭시 또는 C_{1-6}알킬티오를 나타내며;

R^4 는 수소, C_{1-6}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, C_{3-6}사이클로알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알킬카보닐옥시C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬을 나타내고;

R^5 는 C_{1-8}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, Ar^1CH_2, C_{1-6}알킬옥시C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{3-6}알케닐, 티에닐메틸, 푸라닐메틸, C_{1-6}알킬티오C_{1-6}알킬, 모르폴리닐, 모노- 또는 디(C_{1-6}알킬)아미노C_{1-6}알킬, 디(C_{1-6}알킬)아미노, C_{1-6}알킬카보닐C_{1-6}알킬, 이미다졸릴에 의해 치환된 C_{1-6}알킬, 또는 일반식 -Alk-O-CO-Ar^1 의 래디칼을 나타내거나;

R^4 및 R^5 는 이들이 결합된 질소 원자와 함께, 각각 C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬에 의해 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 그룹을 형성할 수 있으며;

Ar 은 페닐; 할로, C_{1-6}알킬, 트리플루오로메틸, 하이드록시, 시아노, C_{1-6}알킬옥시, 벤질옥시, C_{1-6}알킬티오, 니트로, 아미노 및 모노- 또는 디(C_{1-6}알킬)아미노로 구성된 그룹중에서 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 페닐; 피리디닐; 또는 할로, C_{1-6}알킬, 트리플루오로메틸, 하이드록시, 시아노, C_{1-6}알킬옥시, 벤질옥시, C_{1-6}알킬티오, 니트로, 아미노, 모노- 또는 디(C_{1-6}알킬)아미노 및 피페리디닐로 구성된 그룹중에서 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 피리디닐을 나타내고; 여기에서 치환된 페닐은 하나 또는 그 이상의 할로겐에 의해 임의로 추가로 치환될 수 있으며;

Ar^1 은 페닐; 할로, C_{1-6}알킬, C_{1-6}알킬옥시, 디(C_{1-6}알킬)아미노C_{1-6}알킬, 트리플루오로메틸 및 모르폴리닐에 의해 치환된 C_{1-6}알킬로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 페닐; 또는 피리디닐을 나타내고;

Alk 는 C_{1-6}알칸디일을 나타내며,

단, 이들 화합물중에서 5-메틸-3-페닐-7-(페닐메톡시)-피라졸로[1,5-a]-피리미딘 및 2,5-디메틸-7-(메틸아미노)-3-페닐-피라졸로[1,5-a]피리미딘은 제외된다.

청구항 2

제 1 항에 있어서, R^1 이 OR^5 이고, R^5 는 C_{1-6}알킬이거나; R^1 이 NR^4R^5 이고, R^4 는 수소, C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{1-6}알킬카보닐옥시C_{1-6}알킬 또는 C_{3-6}알케닐이며, R^5 는 C_{1-8}알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알킬옥시C_{1-6}알킬, 페닐메틸 또는 C_{3-6}사이클로알킬메틸이거나, R^4 및 R^5 는 이들이 결합된 질소원자와 함께, 각각 C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬에 의해 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 그룹을 형성하고; R^2 는 C_{1-6}알킬이며; R^3 은 수소, C_{1-6}알킬 또는 C_{1-6}알킬티오이고; Ar 은 할로, C_{1-6}알킬 및 C_{1-6}알킬옥시로 구성된 그룹중에서 선택된 각각 독립적으로 1, 2 또는 3개의 치환체에 의해 치환된 페닐이거나, Ar 은 할로, 아미노, 니트로, 트리플루오로메틸, 모노- 또는 디(C_{1-6}알킬)아미노, 피페리디닐 및 C_{1-6}알킬로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 피리디닐인 화합물.

청구항 3

제 1 항 또는 제 2 항에 있어서, R^1 이 NR^4R^5 이고, R^4 는 C_{2-4}알킬, 하이드록시C_{1-2}알킬, C_{3-4}알케닐 또는 C_{1-2}알킬카보닐옥시C_{2-4}알킬이며, R^5 는 C_{2-4}알킬, C_{3-4}알케닐, 하이드록시C_{2-4}알킬 또는 사이클로프로필메틸이고; R^2 는 C_{1-2}알킬이며; R^3 은 수소, C_{1-2}알킬 또는 C_{1-2}알킬티오인 화합물.

청구항 4

제 1 항 내지 제 3 항중의 어느 한항에 있어서, R^1 이 NR^4R^5 이고, R^4 는 C_{3-4}알킬 또는 알릴이며, R^5 는 C_{2-4}알킬, 알릴 또는 사이클로프로필메틸이고; R^2 는 메틸이며; R^3 은 메틸이고; Ar 은 3-, 4-, 6-, 2,4- 또는 2,4,6-위치가 할로, C_{1-6}알킬 또는 C_{1-6}알킬옥시에 의해 치환된 페닐인 화합물.

청구항 5

제 1 항 내지 제 3 항중의 어느 한항에 있어서, R^1 이 NR^4R^5 이고, R^4 는 C_{3-4}알킬 또는 알릴이며, R^5 는 C_{3-4}알킬, 알릴 또는 사이클로프로필메틸이고; R^2 는 메틸이며; R^3 은 메틸이고; Ar 은 4- 및/또는 6-위치가 메틸 또는 디메틸아미노에 의해 치환된 3-피리디닐인 화합물.

청구항 6

제 1 항에 있어서, 3-[6-(디메틸아미노)-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민 또는 3-[6-(디메틸아미노)-4-메틸-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민, 또는 이들의 입체화학적 이성체 또는 이들의 약제학적으로 허용되는 산부가염인 화합물.

청구항 7

활성성분으로서 치료학적으로 유효한 양의 제 1 항 내지 제 6 항중의 어느 한 항에서 청구한 화합물 및 약제학적으로 허용되는 담체를 함유하는 조성물.

청구항 8

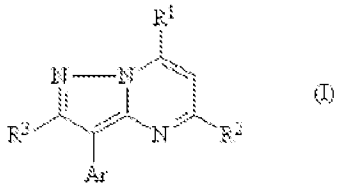
치료학적으로 유효한 양의 제 1 항 내지 제 6 항중의 어느 한 항에서 청구한 화합물을 약제학적으로 허용되는 담체와 완전히 혼합함을 특징으로 하여 제 7 항에서 청구한 조성물을 제조하는 방법.

청구항 9

제 1 항 내지 제 6 항중의 어느 한 항에 있어서, 의약으로서 사용하기 위한 화합물.

청구항 10

부신피질호르몬-방출 인자(CRF)의 과분비로 인한 생리학적 증상 또는 질환 치료용 의약을 제조하기 위한 일반식 (I)의 화합물, 그의 입체이성체 및 약제학적으로 허용되는 산부가염의 용도:



(I)

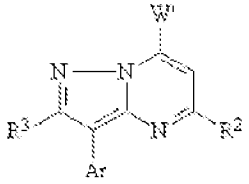
상기식에서,

R^1, R^2, R^3 및 Ar 은 제 1 항에 정의된 바와 같으며,

화합물 5-메틸-3-페닐-7-(페닐메톡시)-피라졸로[1,5-a]-피리미딘 및 2,5-디메틸-7-(메틸아미노)-3-페닐-피라졸로[1,5-a]피리미딘이 포함된다.

청구항 11

일반식 (II')의 화합물, 그의 입체이성체 또는 산부가염:



(II')

상기식에서,

R^2, R^3 및 Ar 은 제 1 항 내지 제 5 항중의 어느 한항에서 정의된 바와 같으며,

W' 는 하이드록시, 할로, 메실옥시 또는 토실옥시를 나타내고,

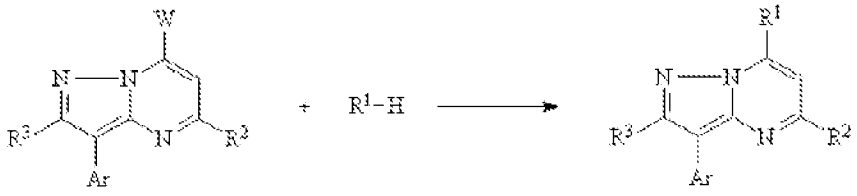
단, Ar 이 비치환된 페닐인 화합물은 제외된다.

청구항 12

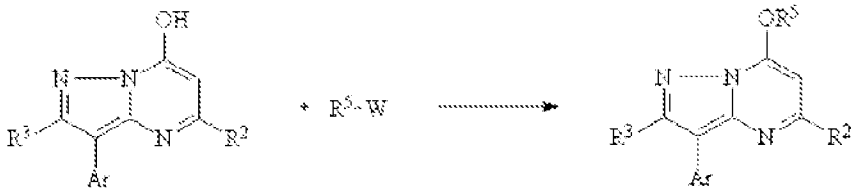
a) 일반식 (II)의 중간체를 반응-불활성 용매중에서 일반식 (III)의 중간체와 반응시키거나;

b) 일반식 (VI)의 중간체를 반응-불활성 용매중에서 적합한 염기의 존재하에 일반식 (VII)의 중간체로 O-알킬화시켜 R^1 이 OR^5 인 일반식 (I)의 화합물로 정의되는 일반식 (I-a)의 화합물을 수득하거나,

필요에 따라 일반식 (I)의 화합물을 당 기술에 공지된 작용 그룹 변환 반응에 따라 일반식 (I)의 다른 화합물로 전환시키고; 필요에 따라 추가로 일반식 (I)의 화합물을 산으로 처리하여 산 부가염을 제조하거나, 반대로 산부가염을 알칼리로 처리하여 유리 염기로 전환시키고; 필요에 따라 이들의 입체화학적 이성체를 제조함을 특징으로 하여 제 1 항에서 청구한 화합물을 제조하는 방법:



(II) (III) (I)



(VI) (VII) (Ia)

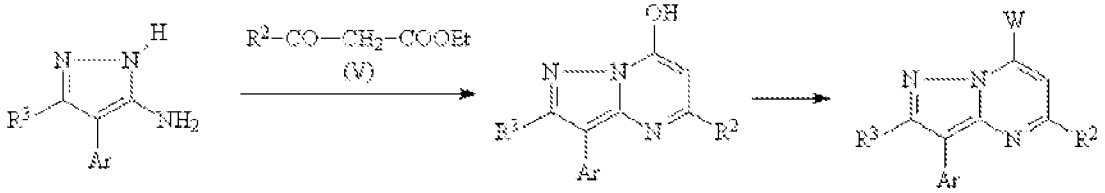
상기 반응식에서,

R^1, R^2, R^3, R^5 및 Ar 은 제 1 항에 정의된 바와 같고,

W 는 이탈 그룹을 나타낸다.

청구항 13

일반식 (IV)의 중간체를 반응-불활성 용매중에서 β-케토 에스테르(V)와 반응시켜 W' 가 하이드록시인 일반식 (II')의 화합물로 정의되는 일반식 (II'-a)의 화합물을 수득하고, 임의로 일반식 (II'-a)의 화합물을 W' 가 하이드록시이외의 것인 일반식 (II')의 화합물로 정의되는 일반식 (II'-b)의 화합물로 전환시키거나, 필요에 따라 일반식 (II')의 화합물을 당 기술에 공지된 작용 그룹 변환 반응에 따라 일반식 (II')의 다른 화합물로 전환시키고; 필요에 따라 추가로 일반식 (II')의 화합물을 산으로 처리하여 산부가염을 제조하거나, 반대로 산부가염을 알칼리로 처리하여 유리 염기로 전환시키고; 필요에 따라 이들의 입체화학적 이성체를 제조함을 특징으로 하여 제 10 항에서 청구한 일반식 (II')의 화합물을 제조하는 방법:



(IV) (II'-a) (II'-b)

상기 반응식에서,

R^2, R^3 및 Ar 은 제 1 항에 정의된 바와 같고,

W' 는 하이드록시, 할로, 메실옥시 또는 토실옥시를 나타낸다.

명세서

발명의 명칭

CRF수용체에 대한 길항제로서의 피라졸로피리미딘
본 발명은 CRF 수용체에 대해 길항성을 갖는 피라졸로피리미딘, 활성 성분으로서 이들 화합물을 함유하는 약제학적 조성물 및 일반적으로 스트레스-관련 질환을 포함한 내분비계, 정신의학계 및 신경계 증상 또는 질환을 치료하기 위한 그의 용도에 관한 것이다.

최초의 부신피질호르몬-방출 인자(CRF)는 양의 시상하부로부터 분리되었고, 41-아미노산 펩타이드인 것으로 확인되었다(참조: Vale et al., Science 213:1394-1397, 1981). 그 후, 인간과 랫트의 CRF 서열이 분리되어 동일한 것으로 확인되었지만, 양의 CRF와는 41개의 아미노산 잔기중에서 7개가 상이하다(참조: Rivier et al., Proc. Natl. Acad. Sci. USA 80:4851, 1983; Shibahara et al., EMBO J. 2:775, 1983). CRF는 내분비계, 신경계 및 면역계 기능을 상당히 변경시키는 것으로 밝혀졌다. CRF는 부신피질호르몬("ACTH"), β-엔도르핀, 및 그밖의 다른 하수체전엽으로부터 프로-오피오멜라노코르틴("POMC")-유도된 펩타이드의 정상적 및 스트레스-방출의 주요한 생리학적 조절제인 것으로 생각된다(참조: Vale et al., Science 213:1394-1397, 1981). 간단히 말하면, CRF는 뇌(DeSouza et al., Science 221:1449-1451, 1984), 하수체(DeSouza et al., Methods Enzymol. 124:560, 1986; Wynn et al., Biochem. Biophys. Res. Comm. 110:602-608, 1983), 부신(Udelsman et al., Nature 319:147-150, 1986) 및 비장(Webster, E.L., and E.B. DeSouza, Endocrinology 122:609-617, 1988)의 전반에 걸쳐 분포된 것으로 확인된 혈장막 수용체와 결합함으로써 그의 생물학적 효과를 개시하는 것으로 생각된다. CRF 수용체는 CRF에 의해 유도된 cAMP의 세포내 생산 증가를 매개하는 GTP-결합 단백질(참조: Perrin et al., Endocrinology 118:1171-1179, 1986)과 커플링한다(참조: Bilezikjian, L.M., 및 W.W. Vale, Endocrinology 113:657-662, 1983).

ACTH 및 POMC의 생산을 촉진하는 역할이외에도, CRF 는 또한 스트레스에 대한 다수의 내분비 자율 및 행동적 응답에 공조하는 것으로 여겨지며, 감정적인 장애의 병태생리에 포함될 수 있다. 또한, CRF는 면역계, 중추신경계, 내분비계 및 심혈관계 간의 커뮤니케이션에 있어서 주요 매개자인 것으로 생각된다(참조: Crofford et al., J. Clin. Invest. 90:2555-2564, 1992; Sapolsky et al., Science 238:522-524, 1987; Tilders et al., Regul. Peptides 5:77-84, 1982). 종합적으로, CRF는 중추 신경계 신경전달물질의 하나이며, 스트레스에 대한 신체의 전체적 응답을 통합하는데 주요한 역할을 하는 것으로 나타났다.

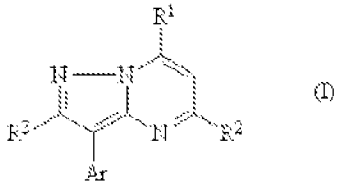
CRF를 뇌에 직접 투입하면 스트레스가 많은 환경에 노출된 동물에게서 관찰된 것과 동일한 행동적, 생리학적 및 내분비 응답이 유도된다. 예를 들어, CRF를 대뇌내심실에 주입하면, 행동이 활발해지고(참조: Sutton et al., Nature 297:331, 1982), 뇌파를 장시간 활성화시키고(참조: Ehlers et al., Brain Res. 2/8332, 1983), 교감신경부신질 경로를 자극하고(참조: Brown et al., Endocrinology 110:928, 1982), 심박수 및 혈압을 증가시키고(참조: Fisher et al., Endocrinology 110:2222, 1982), 산소 소비량을 증가시키고(참조: Brown et al., Life Sciences 30:207, 1982), 위장 운동을 변경시키고(참조: Williams et al., Am. J. Physiol. 253:G582, 1987), 음식 소비를 억제하고(참조: Levine, et al., Neuropharmacology 22:337, 1983), 성적 행동을 변화시키고(참조: Sirinathsinghji et al., Nature 305:232, 1983), 면역 기능을 저하시킨다(참조: Irwin et al., Am. J. Physiol. 255:R744, 1988). 또한, 임상적 데이터는 CRF가 우울증, 불안-관련 장애 및 신경성 식욕부진 상태의 뇌에서 과분비될 수 있음을 시사한다(참조: DeSouza, Ann. Reports in Med. Chem. 25:215-223, 1990).

따라서, 임상적 데이터는 CRF 수용체 길항제가 CRF를 과분비하는 신경정신과적 질환을 치료하는데 유용할 수 있는 신규한 항우울제 및/또는 불안해소제일 수 있음을 시사한다. CRF 수용체 길항제는 예를 들어 치환된 4-티오-5-옥소-3-피라졸린 유도체를 기술하고 있는 미합중국 특허 제 5,063,245호

및 치환된 2-아미노티아졸 유도체를 기술하고 있는 오스트레일리아 특허 제 AU-A41399/93호에 기재되어 있다. WO-92/18504 호 및 JP-32/04877 호에는 항염증제로서 피라졸로[1,5-a]피리미딘이 기재되어 있다. 또한, WO-94/13676 호, WO-94/13677 호 및 WO-95/33750 호에는 CRF 수용체 길항제로서 퓨롤로피리미딘, 피라졸로[3,4-d]피리미딘 및 치환된 푸린이 기재되어 있다. 아릴피라졸로[1,5-a]피리미딘은 잔탄 옥시다제 억제제로서 알려져 있다(참조: Robins et al., J. Heterocyclic Chem. 22:601-634, 1985). JP-42/011,753 호는 안정제 및 소염제로서 유용한 7-메틸아미노-피라졸로[1,5-a]피리미딘 유도체를 기재하고 있다. 또한, JP-61/057,587 호에 항궤양제로서 유용한 피라졸로[1,5-a]피리미딘 유도체가 기재되어 있다.

CRF의 생리학적 중요성 때문에, CRF 수용체를 길항시킬 수 있고, 상당한 CRF 수용체 결합 활성을 갖는 생물학적으로 활성인 작은 분자를 개발하는 것이 주요한 과제로 남아 있다. 이러한 CRF 수용체 길항제는 일반적으로 스트레스-관련 질환을 포함한 내분비계, 정신의학계 및 신경계 증상 또는 질환을 치료하는데 유용하다.

본 발명은 하기 일반식 (I)의 CRF 길항 화합물, 그의 입체이성체 및 약제학적으로 허용되는 산부가염에 관한 것이다:



(I)

상기식에서,

R^1 은 NR^4R^5 또는 OR^5 를 나타내며;

R^2 는 C_{1-6}알킬, C_{1-6}알킬옥시 또는 C_{1-6}알킬티오를 나타내고;

R^3 은 수소, C_{1-6}알킬, C_{1-6}알킬설포닐, C_{1-6}알킬설폭시 또는 C_{1-6}알킬티오를 나타내며;

R^4 는 수소, C_{1-6}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, C_{3-6}사이클로알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알킬카보닐옥시C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬을 나타내고;

R^5 는 C_{1-8}알킬, 모노- 또는 디(C_{3-6}사이클로알킬)메틸, Ar^1CH_2, C_{1-6}알킬옥시C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{3-6}알케닐, 티에닐메틸, 푸라닐메틸, C_{1-6}알킬티오C_{1-6}알킬, 모르폴리닐, 모노- 또는 디(C_{1-6}알킬)아미노C_{1-6}알킬, 디(C_{1-6}알킬)아미노, C_{1-6}알킬카보닐C_{1-6}알킬, 이미다졸릴에 의해 치환된 C_{1-6}알킬, 또는 일반식 -Alk-O-CO-Ar^1 의 래디칼을 나타내거나;

R^4 및 R^5 는 이들이 결합된 질소 원자와 함께, 각각 C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬에 의해 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 그룹을 형성할 수 있으며;

Ar 은 페닐; 할로, C_{1-6}알킬, 트리플루오로메틸, 하이드록시, 시아노, C_{1-6}알킬옥시, 벤질옥시, C_{1-6}알킬티오, 니트로, 아미노 및 모노- 또는 디(C_{1-6}알킬)아미노로 구성된 그룹중에서 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 페닐; 피리디닐; 또는 할로, C_{1-6}알킬, 트리플루오로메틸, 하이드록시, 시아노, C_{1-6}알킬옥시, 벤질옥시, C_{1-6}알킬티오, 니트로, 아미노, 모노- 또는 디(C_{1-6}알킬)아미노 및 피페리디닐로 구성된 그룹중에서 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 피리디닐을 나타내고; 여기에서 치환된 페닐은 하나 또는 그 이상의 할로겐에 의해 임의로 추가로 치환될 수 있으며;

Ar^1 은 페닐; 할로, C_{1-6}알킬, C_{1-6}알킬옥시, 디(C_{1-6}알킬)아미노C_{1-6}알킬, 트리플루오로메틸 및 모르폴리닐에 의해 치환된 C_{1-6}알킬로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3개의 치환체에 의해 치환된 페닐; 또는 피리디닐을 나타내고;

Alk 는 C_{1-6}알칸디일을 나타낸다.

또 다른 일면으로 본 발명은 상기 정의된 일반식 (I)의 신규한 화합물에 관한 것이며, 단 화합물 5-메틸-3-페닐-7-(페닐메톡시)-피라졸로[1,5-a]-피리미딘 및 2,5-디메틸-7-(메틸아미노)-3-페닐-피라졸로[1,5-a]피리미딘은 제외된다.

이 단서 조항은 JP-61/057,587 호 및 JP-42/011,753 호에 기재된 화합물을 배제하기 위한 것이다.

상기 정의에서 사용된 것으로, 용어 할로는 플루오로, 클로로, 브로모 및 요오도를 의미하고; C_{1-6}알칸디일은 예를 들어 메틸렌, 1,2-에탄디일, 1,3-프로판디일, 1,4-부탄디일, 1,5-펜탄디일, 1,6-헥산디일 및 이들의 측쇄 이성체와 같은 1 내지 6개의 탄소 원자를 갖는 2가의 직쇄 및 측쇄 포화 탄화수소 래디칼을 의미하며; C_{1-2} 알킬은 메틸 및 에틸과 같은 탄소 원자수 1 내지 2의 직쇄 포화 탄화수소 래디칼을 의미하며; C_{2-4} 알킬은 에틸, 프로필, 부틸, 1-메틸에틸 등과 같은 탄소 원자수 2 내지 4 의 직쇄 및 측쇄 포화 탄화수소 래디칼을 의미하고; C_{3-4} 알킬은 프로필, 부틸, 1-메틸에틸 등과 같은 탄소 원자수 3 내지 4의 직쇄 및 측쇄 포화 탄화수소 래디칼을 의미하며; C_{1-6}알킬은 상기 정의된 C_{1-2}알킬 및 C_{3-4}알킬과 펜틸, 펜틸 이성체, 헥실 및 헥실 이성체와 같은 탄소 원자수 5 내지 6의 그의 고급 동족체를 의미하고; C_{1-8}알킬은 상기 정의된 C_{1-6}알킬 및 예를 들어 헵틸, 옥틸 등과 같은 탄소 원자수 7 내지 8의 그의 고급 동족체를 의미하며; C_{3-6}알케닐은 예를 들어 2-프로페닐, 3-부테닐, 2-펜테닐, 3-펜테닐, 3-메틸-2-부테닐 등과 같은 3 내지 6개의 탄소 원자를 갖고 하나의 이중결합을 포함하는 직쇄 및 측쇄 탄화수소 래디칼을 의미하고; C_{3-6}알케닐이 질소 또는 산소에 결합된 경우, 결합을 형성하는 탄소 원자는 바람직하게는 포화되어있다. C_{3-6}사이클로알킬은 사이클로프로필, 사이클로부틸, 사이클로펜틸 및 사이클로헥실을 포함한다. 하이드록시C_{1-6}알킬은 하이드록실 그룹으로 치환된 C_{1-6}알킬을 의미한다. 호모피페리디닐은 하나의 질소 원자를 포함하는 7 원 포화환이다.

일부 치환체의 특성상, 일반식 (I)의 화합물은 일반적으로 사용되는 R 및 S 명명법으로 표시될 수 있는 하나 또는 그 이상의 비대칭 중심을 포함할 수 있다.

본 발명의 화합물은 염기성 질소 원자를 함유하며, 그 자체로서 유리 염기로서 또는 산부가염의 형태로 존재할 수 있으며, 이들은 모두 본 발명의 한 부분이다. 산부가염은 당 기술에 공지된 방법으로 제조될 수 있으며, 유기 및 무기산으로부터 형성될 수 있다. 적합한 유기산으로는 말레인산, 푸마르산, 벤조산, 아스코르브산, 석신산, 메탄설폰산, 아세트산, 옥살산, 프로피온산, 타르타르산, 살리실산, 시트르산, 글루콘산, 락트산, 만델린산, 신남산, 아스파르트산, 스테아르산, 팔미트산, 글리콜산, 글루탐산 및 벤젠설폰산이 포함된다. 적합한 무기산으로는 염산, 브롬화수소산, 황산, 인산 및 질산이 포함된다.

본 발명의 화합물의 특별한 그룹은 하기 제한중의 하나 이상에 따르는 일반식 (I)의 화합물이다:

a) R^1 이 NR^4R^5 이고, 여기에서 R^4 는 수소, C_{1-6}알킬, 하이드록시C_{1-6}알킬, C_{1-6}알킬카보닐옥시C_{1-6}알킬 또는 C_{3-6}알케닐, 특히 C_{2-4}알킬, 하이드록시C_{1-2}알킬, C_{3-4}알케닐 또는 C_{1-2}알킬카보닐옥시C_{2-4}알킬이며, R^5 는 C_{1-8}알킬, C_{3-6}알케닐, 하이드록시C_{1-6}알킬, C_{1-6}알킬옥시C_{1-6}알킬, 페닐메틸 또는 C_{3-6}사이클로알킬메틸, 특히 C_{2-4}알킬, C_{3-4}알케닐, 하이드록시C_{2-4}알킬 또는 사이클로프로필메틸이거나;

b) R^1 은 OR^5 이고, 여기에서 R^5 는 C_{1-6}알킬, 특히 C_{2-4}알킬이며;

c) R^2 는 C_{1-6}알킬, 특히 C_{1-2}알킬이고;

d) R^3 은 수소, C_{1-6}알킬 또는 C_{1-6}알킬티오, 특히 수소, C_{1-2}알킬 또는 C_{1-2}알킬티오이며;

e) Ar 은 C_{1-6}알킬, C_{1-6}알킬옥시 및 할로로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3 개의 치환체에 의해 치환된 페닐이고, 여기에서 페닐 부위는 바람직하게는 3-, 4-, 6-, 2,4- 또는 2,4,6-위치가 치환되어 있거나; Ar 은 각각 할로, 아미노, 니트로, 트리플루오로메틸, 모노- 또는 디(C_{1-6}알킬)아미노, 피페리디닐 및 C_{1-6}알킬로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3 개의 치환체에 의해 치환된 피리디닐이고, 여기에서 피리디닐 부위는 바람직하게는 2- 또는 3-위치를 통해 분자의 나머지 부분에 부착된다.

다른 특별한 화합물 그룹은 R^1 이 NR^4R^5 이고, 여기에서 R^4 및 R^5 는 이들이 결합된 질소원자와 함께, 각각 C_{1-6}알킬 또는 C_{1-6}알킬옥시C_{1-6}알킬에 의해 임의로 치환된 피롤리디닐, 피페리디닐, 호모피페리디닐 또는 모르폴리닐 그룹을 형성하는 일반식 (I)의 화합물이다.

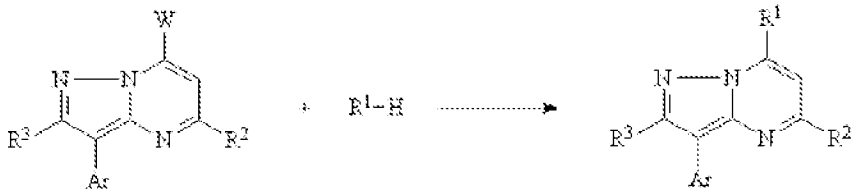
바람직한 화합물은 R^1 이 NR^4R^5 이고, 여기에서 R^4 는 C_{3-4}알킬 또는 알릴, 바람직하게는 프로필이며, R^5 는 C_{2-4}알킬, 알릴 또는 사이클로프로필메틸, 바람직하게는 프로필이고; R^2 는 메틸이며; R^3 은 수소, 메틸 또는 메틸티오, 바람직하게는 프로필이고; Ar 은 할로, 메틸 및 메톡시로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3 개의 치환체에 의해 치환된 페닐, 특히 할로, 메틸 및 디메틸아미노로 구성된 그룹중에서 각각 독립적으로 선택된 1, 2 또는 3 개의 치환체에 의해 치환된 페닐인 일반식 (I)의 화합물이다.

더욱 바람직하게는 Ar 은 4- 및/또는 6-위치가 메틸 또는 디메틸아미노에 의해 치환된 3-피리디닐이다.

가장 바람직한 화합물은 3-(2,4-디클로로페닐)-5-메틸-7-(N-프로필-N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘, 3-(2,4-디클로로페닐)-5-메틸-7-(N-알릴-N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘, 2-메틸티오-3-(2,4-디클로로페닐)-5-메틸-7-(N,N-디알릴아미노)피라졸로[2,3-a]피리미딘, 2-메틸티오-3-(2,4-디클로로페닐)-5-메틸-7-(N-부틸-N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘, 2-메틸티오-3-(2,4-디클로로페닐)-5-메틸-7-(N-프로필-N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘, 2-메틸-3-(4-클로로페닐)-5-메틸-7-(N,N-디프로필아미노)피라졸로[2,3-a]피리미딘, 3-[6-(디메틸아미노)-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민, 3-[6-(디메틸아미노)-4-메틸-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민 및 3-(2,4-디메톡시페닐)-2,5-디메틸-7-(N-프로필-N-메틸옥시에틸아미노)

피라졸로[2,3-a]피리미딘, 이들의 입체이성체 및 약제학적으로 허용되는 산부가염중에서 선택된 화합물이다.

본 발명의 화합물은 일반적으로 일반식 (II)의 피라졸로피리미딘을 일반식 (III)의 중간체로 알킬화시킴으로써 제조할 수 있다:

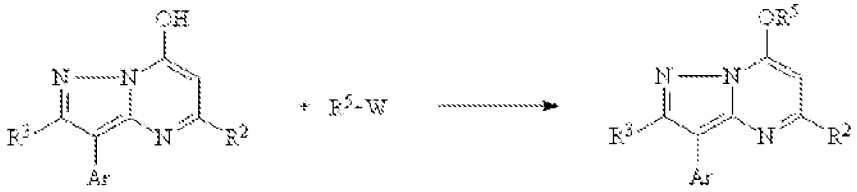


(II) (III) (I)

중간체 (II)에서, W 는 할로, 예를 들어 클로로 또는 브로모, 또는 설포닐옥시 그룹, 예를 들어 메실옥시 또는 토실옥시 그룹과 같은 적합한 이탈 그룹을 나타낸다.

상기 반응은 일반적으로 적합한 용매, 예를 들어 DMF 또는 아세토니트릴과 같은 비양성자성 용매, 에테르, 예를 들어 테트라하이드로푸란중, 바람직하게는 승온에서, 일반식 (III)의 중간체가 휘발성 아민인 경우에 밀폐 반응 용기에서 수행된다.

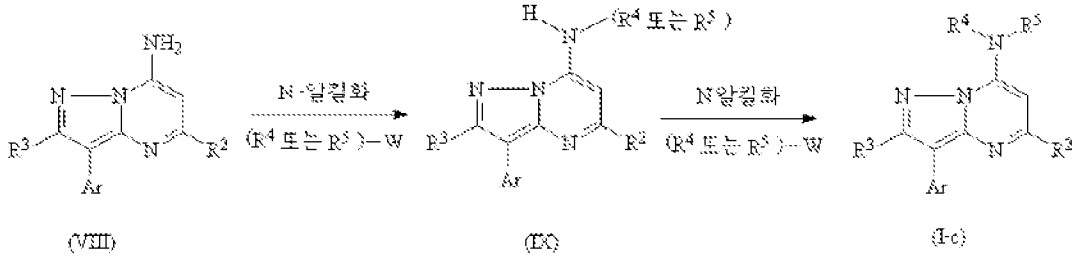
또한, R^1 이 OR^5 인 일반식 (I)의 화합물[이 화합물은 일반식 (I-a)로 표시된다]은 일반식 (VI)의 중간체를 일반식 (VII)의 중간체(여기에서, W 는 상기 정의된 바와 같다)로 O-알킬화시킴으로써 제조할 수 있다:



(VI) (VII) (I-a)

일반식 (I-a)의 화합물을 제조하는 상기 반응은 반응-불활성 용매, 예를 들어 N,N-디메틸포름아미드중에서 적합한 염기, 예를 들어 수소화나트륨의 존재하에 바람직하게는 실온 내지 환류 온도에서 수행될 수 있다.

R^1 이 NR^4R^5 인 일반식 (I)의 화합물[이 화합물은 일반식 (I-c)로 표시된다]은 일반식 (VIII) 또는 (IX)의 화합물을 하기 반응식과 같이 적합한 N-알킬화시킴으로써 제조할 수 있다:



상기 반응식에서, W 는 상기 정의한 바와 같다.

상기 N-알킬화는 반응-불활성 용매, 예를 들어 에테르(예: 테트라하이드로푸란)중에서 바람직하게는 강염기, 예를 들어 NaH의 존재하에 수행된다.

특정의 경우에, 상기 반응은 R^2 가 (R^4 또는 R^5)-W 에 의해 알킬화된, 특히 R^2 가 메틸이고, R^4 또는 R^5 는 C_{1-6}알킬인 부 생성물을 형성할 수 있다.

후술하는 바와 같이, 일반식 (I)의 화합물은 당 기술에 공지된 변환방법에 따라 상호 전환시킬 수 있다.

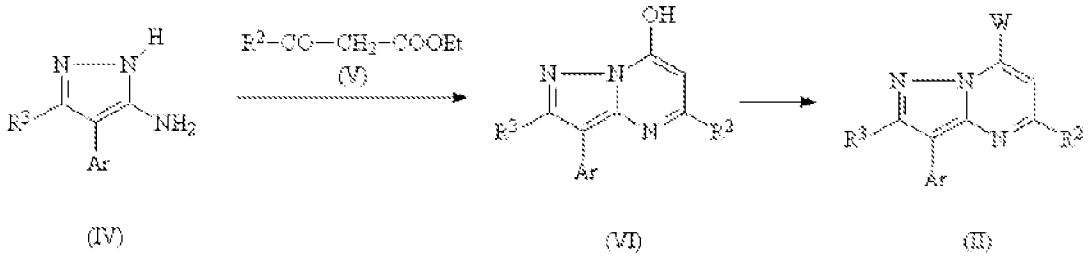
예를 들어, R^3 이 C_{1-6}알킬티오인 일반식 (I)의 화합물은 산화 반응에 의해, 예를 들어 반응-불활성 용매, 예를 들면 디클로로메탄중에서 3-클로로퍼벤조산과 같은 퍼옥사이드로 처리함으로써 R^3 가 C_{1-6}알킬설포닐 또는 C_{1-6}알킬설폭시인 일반식 (I)의 화합물로 전환시킬 수 있다. 산화제의 양 및 다른 반응 파라미터를 조절함으로써 R^3 가 C_{1-6}알킬설포닐 또는 C_{1-6}알킬설폭시인 일반식 (I)의 화합물 또는 이들의 혼합물을 수득할 수 있으며, 이들을 계속해서 통상의 방법, 예를 들어 칼럼 크로마토그래피에 의해 분리할 수 있다.

또한, 일반식 (I)의 화합물은 당 기술에 공지된 반응 또는 작용 그룹 변환방법에 따라 상호 전환시킬 수 있다. 예를 들어, 하이드록시C_{1-6}알킬 그룹을 갖는 일반식 (I)의 화합물은 예를 들어 디클로로메탄과 같은 반응-불활성 용매중에서, 임의로 염기, 예를 들면 피리딘의 존재하에 산 무수물로 처리함으로써 C_{1-6}알킬카보닐옥시C_{1-6}알킬 그룹을 갖는 일반식 (I)의 화합물로 전환시킬 수 있다.

니트로 그룹을 갖는 일반식 (I)의 화합물을 아미노 그룹을 갖는 일반식 (I)의 화합물로 전환시키고, 계속해서 모노- 또는 디(C_{1-6}알킬)아미노 그룹을 갖는 일반식 (I)의 화합물로 전환시킬 수 있다. 또한, 아미노 그룹은 디아조화 반응을 이용하여 할로로 전환시킬 수 있다.

또한, 일반식 (I)의 화합물의 Ar 그룹은 적합한 용매, 예를 들어 아세트산중에서 할로겐화제, 예를 들어 염소 또는 브롬을 사용하여 할로겐화시킬 수 있으며, 임의로 반응은 실온 내지 반응 혼합물의 환류온도에서 수행할 수 있다.

중간체는 로빈스(Robins)등에 의한 문헌[J. Heterocyclic Chem. 22:601-634, 1985]에 기술된 방법에 따라 제조할 수 있다.

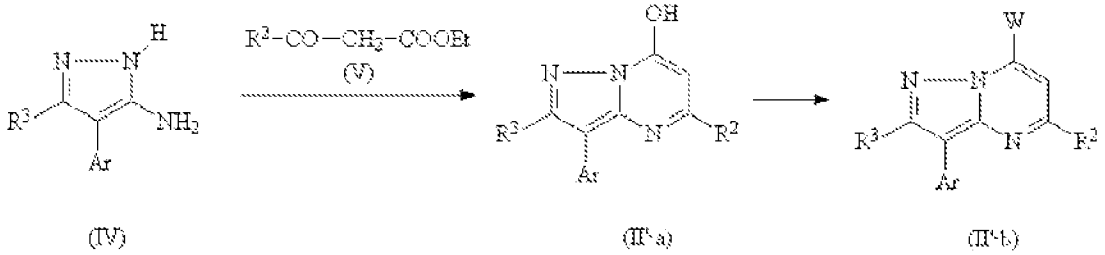


(IV) (VI) (II)

아미노피라졸 유도체(IV) 를 바람직하게는 환류 조건하에 에테르, 예를 들면 THF와 같은 적합한 반응-불활성 용매중에서 β-케토 에스테르(V)와 반응시켜 하이드록시피라졸로피리미딘 (VI)을 수득하고, 예를 들어 중간체 (VI)의 하이드록시 그룹을 메탄설포닐옥시 클로라이드 또는 할로겐화제, 예를 들면 $POCl_3$로 처리하여 이탈 그룹 W로 전환시킴으로써 중간체 (VI)를 일반식 (II)의 중간체로 전환시킨다.

일반식 (VIII)의 중간체는 일반식 (II)의 중간체를 암모니아로 처리하여 제조한다.

한 구체예에서, 본 발명은 또한 W' 가 하이드록시, 할로, 메실옥시 또는 토실옥시를 나타내고, Ar 은 페닐이외의 것인 (II')의 중간체를 제공한다.



(IV) (II'-a) (II'-b)

상기 일반식 (II')의 중간체는 상기 일반식 (II)의 중간체를 제조하기 위해 사용된 방법에 따라 W' 가 하이드록시인 일반식 (II')의 화합물로 정의되는 일반식 (II'-a)의 화합물을 수득하고, 임의로 일반식 (II'-a)의 화합물을 W' 가 하이드록시이외의 것인 일반식 (II')의 화합물로 정의되는 일반식 (II'-b)의 화합물로 전환시킴으로써 제조할 수 있다.

입체이성체는 일반식 (I)의 최종 생성물을 당 기술에 공지된 방법에 따라 분리함으로써, 예를 들어 광학 활성산으로 처리하고, 형성된 부분입체이성체염을 선택적 결정화 또는 칼럼 크로마토그래피에 의해 분리함으로써 제조할 수 있다. 또한, 입체이성체는 상술한 반응도식에서 또는 후술하는 중간체의 제조에 있어서 입체이성체 출발물질을 사용함으로써 제조할 수 있다.

CRF 수용체 길항제로서 화합물의 유효성은 다양한 시험 방법에 의해 결정될 수 있다. 본 발명의 적합한 CRF 길항제는 CRF가 그의 수용체에 특이적으로 결합하는 것을 억제할 수 있으며, CRF 와 관련된 활성을 길항할 수 있다. 일반식 (I)의 화합물은 DeSouza 등에 의한 문헌 (J. Neuroscience 7:88, 1987) 및 Battaglia 등에 의한 문헌 (Synapse I:572, 1987)에 기재된 시험(이들로 한정되지 않는다)을 포함하여 이러한 목적에 일반적으로 사용되는 하나 또는 그 이상의 시험 방법에 의해 CRF 길항제로서의 활성에 대해 평가될 수 있다. 상기 언급된 바와 같이, 적합한 CRF 길항제로는 CRF 수용체에 대해 친화성을 갖는 화합물이 포함된다. CRF 수용체 친화성은 수용체(예를 들어 랫트의 대뇌피질막으로 부터 제조된 수용체)에 대한 방사표지된 CRF(예를 들어 [^{125}I]티로신 CRF)의 결합을 억제하는 화합물의 정도를 측정하는 결합 분석 시험에 의해 결정될 수 있다. DeSouza 등에 의한 문헌 (supra, 1987)에 기술된 방사리간드 결합 분석 시험은 CRF 수용체에 대한 화합물의 친화성을 결정하는 분석법을 제공한다. 이러한 활성은 일반적으로 수용체로부터 방사표지된 리간드

의 50%를 대체시키는데 필요한 화합물의 농도로서 IC_{50}으로 부터 계산되며, 하기 식으로부터 계산된 "K_i"값으로서 기록된다:

$$K_i = (IC_{50}/(1+L/K_D))$$

상기식에서,

L 은 방사리간드이고,

K_D는 수용체에 대한 방사리간드의 친화성이다(참조: Chen 및 Prusoff에 의한 Biochem. Pharmacol. 22:3099, 1973).

CRF 수용체 결합을 억제하는 것 이외에, 화합물의 CRF 수용체를 길항하는 활성이 CRF 와 관련된 활성을 길항시킬 수 있는 화합물의 능력에 의해 결정될 수 있다. 예를 들어, CRF 는 아데닐레이트 사이클라제 활성을 포함하여 각종 생화학적 과정을 자극하는 것으로 공지되어 있다. 따라서, 화합물은, 예를 들어 cAMP 수준을 측정함으로써 CRF-유도된 아데닐레이트 사이클라제의 활성을 길항시킬 수 있는 그의 능력에 의해 CRF 길항제로서 평가될 수 있다. Battaglia 등에 의한 문헌(supra, 1987)에 기술된 CRF-유도된 아데닐레이트 사이클라제의 활성 시험으로 부터 CRF 활성을 길항하는 화합물의 능력을 측정하는 시험을 유도할 수 있다. 따라서, CRF 수용체 길항 활성은 일반적으로 초기 결합 시험(DeSouza(supra, 1987)에 기재된 것과 같이)을 수행하고, 그후에 cAMP 선별 프로토콜(Battaglia(supra, 1987)에 기재된 것과 같이)를 수행하는 과정을 포함하는 시험 기술에 의해 측정될 수 있다. CRF 수용체 결합 친화성과 관련하여, 본 발명의 CRF 수용체 길항제는 10 μM미만의 K_i 를 갖는다. 본 발명의 바람직한 구체예에서, CRF 수용체 길항제는 1 μM미만 및 더욱 바람직하게는 0.25 μM(즉, 250 nM) 미만의 K_i 를 갖는다.

본 발명의 CRF 수용체 길항제는 CRF 수용체 부위에서 활성을 나타내며, 내분비계, 정신의학계 및 신경계 질환 또는 병을 포함한 광범위한 질환 또는 병을 치료하기 위한 치료제로서 사용될 수 있다. 더욱 구체적으로, 본 발명의 CRF 수용체 길항제는 CRF가 과분비됨으로써 나타나는 생리학적 증상 또는 질환을 치료하는데 유용할 수 있다. CRF는 스트레스에 대한 내분비계, 행위적 및 자가 응답을 활성화하고 공조하는 중추 신경계 신경전달물질인 것으로 생각되기 때문에, 본 발명의 CRF 수용체 길항제는 신경정신과적 질환을 치료하는데 사용될 수 있다. 본 발명의 CRF 수용체 길항제에 의해 치료될 수 있는 신경정신과적 질환에는 우울증과 같은 감정 장애; 불안-관련 장애, 예를 들어 범불안 장애, 공황 장애, 강박 장애, 비정상적 공격성, 불안정 협심증 및 반응적 고혈압과 같은 심혈관 이상; 및 신경성 식욕부진, 대식증 및 과민성 장증상과 같은 음식물 섭취 장애가 포함된다. CRF 길항제는 또한 각종 질병 상태를 수반하는 스트레스에 의한 면역 억제뿐만 아니라 출혈을 치료하는데 유용할 수 있다. 본 발명에 따른 CRF 길항제의 또 다른 용도로는 염증성 증상(류마티스성 관절염, 포도막염, 천식, 염증성 장 질환 및 G.I. 운동성과 같은), 쿠싱(Cushing)병, 유아 경련, 간질, 유아 및 성인 발작, 및 각종 약물 남용 및 금단현상(알콜중독 포함)의 치료가 포함된다.

본 발명의 또 다른 구체예에서, 하나 또는 그 이상의 CRF 수용체 길항제를 함유하는 약제학적 조성물이 기재되어 있다. 투여의 목적을 위해, 본 발명의 화합물은 약제학적 조성물로 제형화될 수 있다. 본 발명의 약제학적 조성물은 본 발명의 CRF 수용체 길항제(즉, 일반식 (I)의 화합물) 및 약제학적으로 허용되는 담체 및/또는 희석제를 함유한다. CRF 수용체 길항제는 특정 질환을 치료하는데 효과적인 양, 즉 CRF 수용체 길항 활성을 이루기에 충분한 양으로서, 및 바람직하게는 환자에 허용되는 독성 수준으로 조성물중에 존재한다. 바람직하게는, 본 발명의 약제학적 조성물은 CRF 수용체 길항제를 투여 경로에 따라 1회 복용량당 0.1 ㎎ 내지 250 ㎎, 및 더욱 바람직하게는 1 ㎎ 내지 60 ㎎의 양으로 함유할 수 있다. 적합한 농도 및 복용량은 당 기술자들에 의해 쉽게 결정될 수 있다.

약제학적으로 허용되는 담체 및/또는 희석제는 당해 기술자들에 잘 알려져 있다. 액체 용액으로서 제형화된 조성물에 대해, 허용되는 담체 및/또는 희석제는 염수 및 멸균수를 포함하며, 임의로 항산화제, 완충액, 세균 발육 저지제 및 그밖의 다른 통상적인 첨가제를 함유한다. 조성물은 CRF 수용체 길항제 이외에, 희석제, 분산제, 계면활성제, 결합제 및 윤활제를 함유하는 환제, 캡셀제, 과립제 또는 정제로 제형화될 수 있다. 당해 기술자들은 CRF 수용체 길항제를 문헌 [Remington's, Pharmaceutical Sciences, Gennaro, Ed., Mack Publishing Co., Easton, USA, 1990]에 기술된 바와 같이, 관례에 따라 적합한 방식에 의해 추가로 제형화시킬 수 있다.

또 다른 구체예에서, 본 발명은 내분비계, 정신의학계 및 신경계 증상 또는 질환을 포함한 각종 증상 또는 질환을 치료하는 방법을 제공한다. 이 방법은 본 발명의 화합물을 온혈동물에게 이러한 증상 또는 질환을 치료하기에 충분한 양으로 투여하는 것을 포함한다. 이 방법은 본 발명의 CRF 수용체 길항제를, 바람직하게는 약제학적 조성물의 형태로 전신 투여하는 것을 포함한다. 본 원에 사용된 것으로, 전신 투여는 경구 및 비경구 투여를 포함한다. 경구 투여의 경우에, CRF 수용체 길항제의 적합한 약제학적 조성물은 분제, 과립제, 환제, 정제 및 캡셀제뿐 아니라 액제, 시럽제, 현탁제 및 유제를 포함한다. 이들 조성물은 또한 향미제, 방부제, 현탁제, 농조화제, 유화제 및 그밖의 다른 약제학적으로 허용되는 첨가제를 함유한다. 비경구 투여의 경우에, 본 발명의 화합물은 CRF 수용체 길항제 이외에 완충제, 항산화제, 세균 발육 저지제 및 이러한 용액에 공통적으로 사용되는 그밖의 다른 첨가제를 함유할 수 있는 수성 주사 용액제로 제조될 수 있다.

상술한 바와 같이, 본 발명의 화합물을 투여하여 각종 장애 또는 질환을 치료할 수 있다. 특히, 본 발명의 화합물은 우울증, 감정 장애, 공황 장애, 강박 장애, 비정상적 공격성, 불안정 협심증, 반응적 고혈압, 신경성 식욕부진, 대식증, 과민성 장증상, 스트레스 관련 면역 억제, 졸증, 염증, 루성병, 유아 경련, 간질, 및 각종 약물 남용 및 금단현상을 치료하기 위해 온혈 동물에 투여될 수 있다.

따라서, 본 발명은 부신피질호르몬-방출 인자(CRF)의 과분비로 인한 생리학적 증상 또는 질환 치료용 의약을 제조하기 위한 일반식 (I)의 화합물의 용도를 제공한다; 본 발명은 또한 신규한 일반식 (I)의 화합물의 의약으로서의 용도를 제공한다.

하기 실시예는 설명할 목적으로 제시되었으며, 한정하기 위한 것은 아니다.

실험 부분

이후 "THF"는 테트라하이드로푸란을 의미하고, "DCM"은 디클로로메탄을 의미한다.

A. 중간체의 제조

실시예 A.1

a) 3-아미노-4-(2,4-디클로로페닐)피라졸 및 에틸 아세토아세테이트(2 당량)를 디옥산에 용해시키고, 환류하에서 밤새 가열한다. 혼합물을 진공중에서 농축시키고, 에틸 아세테이트로 희석한다. 2 일 동안 정치시킨 후 형성된 희백색 고체를 진공 여과에 의해 수집하여 3-(2,4-디클로로페닐)-5-메틸-7-하이드록시피라졸로[2,3-a]피리미딘(중간체 1)을 수득한다.

b) 중간체 1(300 ㎎)을 $POCl_3$(1.5 ㎖)와 혼합하고, 1 시간동안 가열하여 환류시킨다. 형성된 자주색 용액을 조심스럽게 빙수에 옮긴다. 생성물을 에틸 아세테이트로 추출하여 포화 중탄산나트륨 및 염수로 세척하고, $MgSO_4$ 상에서 건조시킨 후, 진공중에서 농축시켜 3-(2,4-디클로로페닐-5-메틸-7-클로로피라졸로[2,3-a]피리미딘(중간체 2)을 갈색 고체(260 ㎎, 82%)로 수득한다.

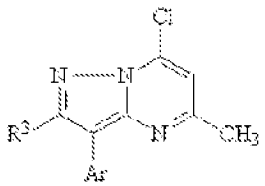
실시예 A.2

a) THF(10 ㎖)중의 수소화나트륨(60%, 25 mmol)의 교반 용액에 THF(10 ㎖)중의 6-(디메틸아미노)-3-피리딘아세토니트릴(10 mmol)을 적가한다. 용액을 10 분동안 교반한 후, 에틸 아세테이트(30 mmol)를 천천히 가한다. 형성된 현탁액을 실온에서 1 시간동안 교반한다. 반응 혼합물을 진공하에서 농축시키고, 에틸 아세테이트/메탄올(1:1)에 용해시킨 다음, 실리카를 통해 여과한다. 여액을 농축시켜 중간체 7을 수득한다.

b) 중간체 7과 히드라진 하이드로브로마이드(100 mmol)의 혼합물을 에탄올/물(9:1, 총 100 ㎖)에 용해시키고, 1 시간동안 환류시킨다. 반응 혼합물을 농축시키고, 잔류물을 에틸 아세테이트와 중탄산나트륨 용액으로 분배한다. 추출물을 합하여 황산나트륨상에서 건조시키고, 여과한 후, 농축건조시킨다. 잔류물을 1,4-디옥산(200 ㎖)에 용해시키고, 에틸 아세토아세테이트의 존재하에서 16 시간동안 환류시킨다. 반응 혼합물을 냉각시키면 회백색 고체가 석출된다. 결정화를 촉진하기 위해 디에틸 에테르를 첨가한 후, 침전을 여과하고, 건조시켜 3-[2-(디메틸아미노)-5-피리디닐]-2,5-디메틸-7-하이드록시피라졸로[2,3-a]피리미딘(중간체 8)을 수득한다.

c) 중간체 8을 $POCl_3$(2 ㎖)에 용해시키고, 2 시간동안 환류시킨다. 반응 혼합물을 냉각시킨 후, 얼음에 붓는다. 고체의 탄산나트륨을 첨가하여 용액을 염기성(pH=9)으로 만든 후, 디에틸 에테르로 추출한다. 유기층을 합하여 황산나트륨상에서 건조시키고, 여과한 다음, 농축시켜 3-[6-(디메틸아미노)-3-피리디닐]-2,5-디메틸-7-클로로-피라졸로[2,3-a]피리미딘(중간체 9)을 수득한다.

하기 표 1에 상기 언급된 실시예중의 하나에 따라 제조된 중간체를 나타내었다:



중간체번호	실시예번호	R^3	Ar
2345613	A.1A.1A.1A.1A.1A.1A	$HCH_3SCH_3HHCH_3$	2,4-디클로로페닐 2,4-디클로로페닐 2,4-디클로로페닐 4-클로로페닐 2,6-디클로로페닐 4-클로로페닐

중간체번호	실시예번호	R^3	Ar
14151617181	[illegible]	[illegible]	3-메톡시페닐 4-메톡시페닐 2,4-디메톡시페닐 3,4-디메톡시페닐 2,4,6-트리메톡시페닐 6-시클로헥실아미노-3-피리디닐 6-디메틸아미노-4-메틸-3-피리디닐 6-메틸-5-니트로-2-피리디닐 5-클로로-2-피리디닐 6-메틸-3-피리디닐 3-메틸-5-니트로-2-피리디닐

B. 최종 생성물의 제조

실시예 B.1

중간체 2(21 ㎎)와 N-프로필-N-사이클로프로판메틸아민(75 ㎎)의 혼합물을 밀폐 반응 용기중, 100 ℃에서 밤새 가열한다. 1:5 에틸 아세테이트-헥산을 사용하여 예비(preparative) TLC 플레이트 상에서 크로마토그래피하여 3-(2,4-디클로로페닐)-5-메틸-7-(N-프로필-N-사이클로프로판메틸아미노)-피라졸로[2,3-a]피리미딘(화합물 17)(17.4 ㎎) 및 3-(2,4-디클로로페닐)-5-메틸-7-(N-사이클로프로판메틸아미노)피라졸로[2,3-a]피리미딘(화합물 8)(1 ㎎)을 수득한다.

유사한 방법으로, 중간체 2 및 각각 (S)-(-)-로이시놀 (R)-(+)-로이시놀을 출발물질로 하여 (S)-2-[[3-(2,4-디클로로페닐)-5-메틸-7-피라졸로[2,3-a]피리미디닐]아미노]-4-메틸-1-펜탄올(화합물 11) 및 그의 R-유사체(화합물 12)를 제조한다.

실시예 B.2

아세토니트릴(50 ㎖)중의 다-n-프로필아민(13 g) 및 중간체 10(8 g)의 용액을 환류하에서 3 시간동안 가열한다. 혼합물을 에틸 아세테이트를 사용하여 단 실리카겔 플러그를 통하여 여과한 후, 여액을 진공중에서 농축시켜 연한 황색 고체를 수득하고, 이를 에테르-헥산으로 재결정화시켜 3-[6-(디메틸아미노)-4-메틸-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민(화합물 53) 8.9 g(93%)을 수득한다.

화합물 53(8.1 g)을 디에틸 에테르(150 ㎖)와 DCM(50 ㎖)의 혼합물에 용해시키고, 이 혼합물을 교반하면서 디에틸 에테르(1M, 21.3 ㎖)중의 HCl로 적가 처리하여 화합물 53을 그의 염산 부가염으로 전환시킨다. 형성된 회백색 고체를 여과수집하여 3-[6-(디메틸아미노)-4-메틸-3-피리디닐]-2,5-디메틸-N,N-디프로필피라졸로[2,3-a]피리미딘-7-아민 모노하이드로클로라이드 8.7 g(98%)을 수득한다.

실시예 B.3

중간체 3(15 ㎎)을 에탄올(0.5 ㎖)에 용해시키고, 소듐 에톡사이드(12 ㎎)의 존재하에서 1 시간동안 교반한다. 실리카겔 상에서 크로마토그래피하여 3-(2,4-디클로로페닐)-7-(에톡시)-5-메틸-2-메틸티오-피라졸로[2,3-a]피리미딘(화합물 50) 을 수득한다.

실시예 B.4

THF(3 ㎖)중의 화합물 6(14 ㎎)의 용액을 실온에서 5 분동안 수소화나트륨(60 ㎎, 과량)으로 처리한 다음, 요오도프로판(0.3 ㎖)으로 처리한다. 반응물을 실온에서 밤새 교반하고, 메탄올(0.5 ㎖)로 퀀치한다(quench). 생성된 혼합물을 예비 TLC 플레이트상에 충전하고 1:5 에틸 아세테이트-헥산으로 전개하여 무색 오일로 3-(2,4-디클로로페닐)-5-메틸-7-[N-(3-메톡시프로필)-N-프로필아미노]-피라졸로[2,3-a]피리미딘(화합물 45)(5.7 ㎎), 3-(2,4-디클로로페닐)-5-부틸-7-[N-(3-메톡시프로필)-N-프로필아미노]-피라졸로[2,3-a]피리미딘(화합물 46)(4 ㎎) 및 3-(2,4-디클로로페닐)-5-부틸-7-[3-메톡시-프로필아미노]-피라졸로[2,3-a]피리미딘(화합물 47)(3.5 ㎎)을 수득한다.

실시예 B.5

화합물 26(8 ㎎)을 DCM(1 ㎖)에 용해시키고, 아세트산 무수물(0.1 ㎖) 및 피리딘(0.1 ㎖)으로 처리한다. 혼합물을 실온에서 밤새 교반하고, 진공중에서 농축시킨다. 잔류물을 에틸 아세테이트로 희석시키고, 단 실리카겔 칼럼을 통해 여과한다. 여액을 농축시켜 3-(2,4-디클로로페닐)-5-메틸-7-[N-(2-아세톡시에틸)-N-벤질아미노]-피라졸로[2,3-a]피리미딘(화합물 27)(8.6 ㎎)을 무색 오일로 수득한다.

실시예 B.6

DCM(3 ㎖)중의 화합물 40(20 ㎎)의 용액을 3-클로로퍼벤조산(19 ㎎)으로 처리한다. 용액을 실온에서 1 시간동안 교반한다. 에틸 아세테이트-헥산(1:1)을 사용하여 실리카겔 칼럼 플레이트상에서 크로마토그래피하여 화합물 43 및 화합물 44 를 수득한다.

실시예 B.7

화합물 55와 무수 에탄올(100 ㎖)중의 활성탄소상의 팔라듐(100 ㎎)의 혼합물을 수소화 유니트에 도입하고, 2.7 10^5 Pa(40 psi)에서 2 시간동안 수소화시킨다. 반응 혼합물을 여과하고, 농축시킨다. 잔류물을 디에틸 에테르에 용해시키고, 농축시켜 3-(5-아미노-3-메틸-2-피리디닐)-2,5-디메틸-N,N-디프로필-피라졸로[2,3-a]피리미딘-7-아민(화합물 56) 1.49 g을 수득한다.

실시예 B.8

ACN(20 ㎖)중의 수성 포름알데하이드(6.4 g) 및 화합물 56(1.39 g)의 교반 용액에 0 ℃에서 소듐 시아노보로하이드라이드(734 ㎎)를 가한다. 빙초산(1 ㎖)을 가하고, 반응 혼합물을 실온에서 2 시간동안 교반한다. 반응 혼합물을 에틸 아세테이트와 포화 수성 중탄산나트륨으로 분배시킨다. 유기층을 염수로 세척하고, 황산나트륨상에서 건조시킨 다음, 여과하고, 농축건조시켜 실리카겔상에서 플래쉬(flash) 칼럼 크로마토그래피($CH_2Cl_2/CH_3OH/NH_4OH$ 150:10:1)에 의해 정제한다. 목적하는 분획을 분리하여 3-[5-(디메틸아미노)-3-메틸-2-피리디닐]-2,5-디메틸-N,N-디프로필-피라졸로[2,3-a]피리미딘-7-아민(화합물 57) 1.30 g을 수득한다.

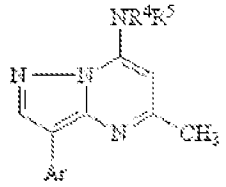
실시예 B.9

빙욕에서 냉각시킨 물(1 ㎖)과 농 HCl(1 ㎖)의 혼합물중의 화합물 56(100 ㎎)의 용액에 물(1 ㎖)중의 아질산나트륨(21 ㎎)의 용액을 가한다. 용액을 빙욕에서 교반하면서 농 HCl중의 염화구리(I)(281 ㎎)의 혼합물에 첨가한다. 고체를 분리하고, 혼합물을 60 ℃로 가열하여 등명한 용액을 수득한다. 반응 혼합물을 NaOH로 염기화시키고, 에틸 아세테이트로 추출한 다음, 염수로 세척하고, 농축시킨다. 예비 TLC에 의해 정제하여 16 ㎎의 화합물 98을 수득한다.

실시예 B.10

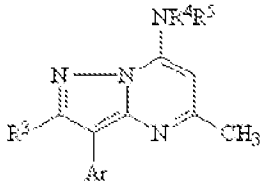
화합물 56(100 ㎎)을 빙욕에서 냉각시킨 플루오로붕산(물중의 48 중량%, 2 ㎖)의 용액에 가한 다음, 물(1 ㎖)중의 아질산나트륨(20 ㎎)의 용액을 가한다. 온도를 10 ℃미만으로 유지시킨다. 고체를 여과하여 수집하고, 건조시킨 후, 중탄산나트륨 수용액과 에틸 아세테이트로 분배한다. 유기층을 염수로 세척하고, 농축시킨 후, 잔류물을 예비 TLC에 의해 정제하여 20 ㎎의 화합물 100을 수득한다.

하기 표 2 내지 5에 상기 실시예중의 하나에 따라 제조된 화합물을 나타내었고, 표 6 및 7 에는 이들 화합물에 대한 분석 데이터를 나타내었다:



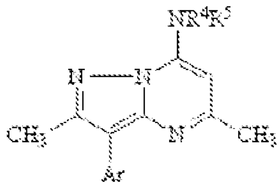
화합물번호	실시예번호	R^4	R^5	Ar
12345678910	B.1B.1B.1B.1B.1B.1B.1B.1B.1B.1	[illegible]	n-프로필 2-메틸프로필 1,1-디메틸에틸 3-하이드록시프로필 2-메톡시에틸 [illegible] 테트라하이드로푸릴메틸 $(CH_3)_2CH_3O(CH_2)_3$- 사이클로프로필메틸 3-메틸-2-부틴 4-메틸-2-펜틴	2,4-디클로로페닐2,4-디클로로페닐2,4-디클로로페닐2,4-디클로로페

화합물번호	실시예번호	R^4	R^5	Ar
111213141516178889202122232425262728293031323334	8889202122232425262728293031323334	수소원자n-프로필n-프로필n-프로필



화합물번호	실시예번호	R^3	R^4	R^5	Ar
303132343536	B.1B.1B.1B.1B.1B	CH_3 SCH_3 SCH_2CH_3 $SCH_2CH_2CH_3$ $SCH_2CH_2CH_2CH_3$ $SCH_2CH_2CH_2CH_2CH_3$	CH_3 SCH_3 SCH_2CH_3 $SCH_2CH_2CH_3$ $SCH_2CH_2CH_2CH_3$ $SCH_2CH_2CH_2CH_2CH_3$	3-할로겐 2-메톡시	2,4-디클로로페닐 2,4-디클로로페닐

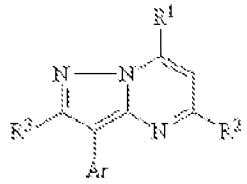
화합물번호	실시예번호	R^3	R^4	R^5	Ar
373	83	94	1	2	3

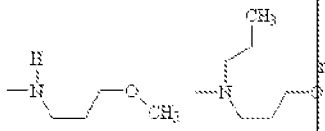


화합물번호	실시예번호	R^4	R^5	Ar
484951525[illegible]	[illegible]	[illegible]	[illegible] n-프로필 n-프로필 n-프로필 사이클로프로필메틸 $CH_3O(CH_2)_2$- n-프로필 n-프로필 n-프로필 n-프로필 n-프로필 n-프로필 $CH_3O(CH$	[illegible] $CH_3O(CH_2)_2$ $HOCH_2CH_2$ [illegible]

화합물번호	실시예번호	R^4	R^5	Ar
808182838	[illegible]	[illegible]	[illegible]	[illegible]

화합물번호	실시예번호	R^4	R^5	Ar



화합물번호	실시예번호	R^1	R^2	R^3	Ar
464750	B.4B.4B.3		n-C_4H_9n-C_4H_9HNCH3-S-	CH_3CH_2O-	2,4-디클로로페닐2,4-디클로로페닐2,4-디클로로페닐

분석 데이터

화합물 번호	^{1}H NMR 데이터(CDCl$_3$)	MS M + 1
1	δ 0.45 (m,2H), 0.78 (m,2H), 1.20 (m,1H), 2.84 (s,3H), 3.40 (d,2H), 5.98 (s,1H), 7.41 (dd,1H), 7.52 (d,1H), 7.76 (d,1H), 8.32 (s,1H)	335
2	δ 0.88 (d,3H), 1.05 (d,3H), 1.74 (m,1H), 2.52 (s,3H), 3.20 (t,2H), 5.87 (s,1H), 6.40 (t,1H), 7.30 (dd,1H), 7.47 (d,1H), 7.99 (d,1H), 8.42 (s,1H)	349

화합물 번호	^{1}H NMR 데이터(CDCl$_3$)	MS M + 1
3	δ 1.57 (s,9H), 2.54 (s,3H), 6.05 (s,1H), 6.48 (s,1H), 7.31 (d,1H), 7.47 (s,1H), 7.99 (d,1H), 8.39 (s,1H)	349
4	δ 1.97 (m,2H), 2.43 (s,3H), 3.62 (m,2H), 3.75 (t,3H), 4,00 (brs, 1H), 6.18 (s,1H), 7.39 (dd,1H), 7.52 (d,1H), 8.19 (d,1H), 8.43 (s,1H)	351
5	δ 1.03 (t,6H), 1.60-1.85 (m,4H), 2.56 (s,3H), 3.49 (m,1H), 5.92 (s,1H), 6.19 (d,1H), 7.35 (dd,1H), 7.50 (dd,1H), 8.01 (d,1H), 8.44 (s,1H)	363
6	δ 2.02 (m,2H), 2.51 (s,3H), 3.40 (s,3H), 3.51 (m,4H), 5.91 (s,1H), 6.71 (t,1H), 7.31 (dd,1H), 7.47 (d,1H), 7.99 (d,1H), 8.42 (s,1H)	365
7	δ 1.23 (d,6H), 2.00 (m,2H), 2.52 (s,1H), 3.51 (dd,2H), 3.59 (m,2H), 5.90 (s,1H), 6.92 (t,1H), 7.31 (dd, 1H), 7.46 (d,1H), 8.00 (d,1H), 8.41 (s,1H)	393
8	δ 0.35 (m,2H), 0.68 (m,2H), 1.25 (m,1H), 2.52 (s,3H), 3.23 (dd,2H), 5.88 (s,1H), 6.40 (t,1H), 7.32 (d,1H), 7.48 (s,1H), 7.99 (s,1H), 8.43 (s,1H)	347
9	δ 1.03 (d,3H), 1.06 (d,3H), 1.31 (d,3H), 1.95 (m,1H), 2.52 (s,3H), 3.54 (m,1H), 5.88 (s,1H), 6.23 (d,1H), 7.32 (d,1H), 7.47 (s,1H), 7.98 (d,1H), 8.41 (s,1H)	363
10	δ 0.95 (d,3H), 0.97 (d,3H), 1.40-1.80 (m,3H), 2.53 (s,3H), 3.76 (m,1H), 5.89 (s,1H), 6.12 (d,1H), 7.32 (d,1H), 7.47 (s,1H), 7.97 (d,1H), 8.40 (s,1H)	377
11	δ 0.94 (d,3H), 0.99 (d,3H), 1.53 (m,1H), 1.76 (m,1H), 2.50 (s,3H), 2.93 (brs,1H), 3.48 (m,1H), 3.76 (m,1H), 5.97 (s,1H), 6.22 (d,1H), 7.35 (dd, 1H), 7.51 (d,1H), 7.95 (d,1H), 8.36 (s,	393
12	δ 0.92 (d,3H), 0.97 (d,3H), 1.52 (m,2H), 1.72 (m,1H), 2.47 (s,3H), 3.02 (brs,1H), 3.42 (m,1H), 3.72 (m,2H), 5.94 (s,1H), 6.20 (d,1H), 7.33 (d,1H), 7.49 (s,1H), 7.92 (d,1H), 8.33 (s,	393
13	δ 0.99 (d,6H), 1.98 (m,1H), 2.44 (s,3H), 3.22 (brs, 1H), 3.46 (m,2H), 3.73 (m,1H), 5.88 (s,1H), 6.31 (d,1H), 7.32 (d,1H), 7.48 (s,1H), 7.92 (d,1H), 8.32 (s, 1H)	379
14	δ 0.21 (m,2H), 0.54 (m,2H), 1.10 (m,1H), 2.53 (s,3H), 3.28 (s,3H), 3.91 (d,2H), 5.99 (s,1H), 7.32 (d,1H), 7.48 (s,1H), 7.97 (d,1H), 8.43 (s,1H)	379

화합물 번호	^{1}H NMR 데이터(CDCl$_3$)	MS M + 1
15	δ 0.96 (t,3H), 1.31 (t,3H), 1.38 (m,2H), 1.71 (m,2H), 2.49 (s,3H), 3.74 (t,2H), 3.65 (q,2H), 5.90 (s,1H), 7.30 (dd,1H), 7.46 (d,1H), 7.97 (d,1H), 8.40 (s,1H)	377
16	δ 0.96 (t,6H), 1.73 (m,4H), 2.49 (s,3H), 3.73 (t,4H), 5.88 (s,1H), 7.33 (dd,1H), 7.46 (d,1H), 7.98 (d,1H), 8.40 (s,1H)	377
17	δ 0.26 (m,2H), 0.58 (m,2H), 0.98 (t,3H), 1.18 (m,1H), 1.76 (m,2H), 2.53 (s,3H), 3.76 (d,2H), 3.81 (t,2H), 6.02 (s,1H), 7.34 (dd,1H), 7.49 (dd,1H), 8.44 (s,1H)	389
18	δ 1.04 (t,3H), 1.77 (m,2H), 2.53 (s,3H), 3.47 (t,2H), 3.98 (m,2H), 4.06 (m,2H), 5.52 (brs, 1H), 6.03 (s,1H), 7.33 (d,1H), 7.48 (s,1H), 7.93 (d, 1H), 8.39 (s, 1H)	379
19	δ 0.98 (t,3H), 1.76 (m,2H), 2.50 (s,3H), 3.35 (s,3H), 3.67 (t,2H), 3.72 (m,2H), 4.14 (m,2H), 5.95 (s,3H), 7.29 (d,1H), 7.47 (s,1H), 7.97 (d,1H), 8.39 (s,1H)	393
20	δ 0.96 (t,6H), 1.73 (m,4H), 2.55 (s,3H), 3.74 (t,4H), 5.90 (s,1H), 7.40 (d,2H), 8.04 (d,2H), 8.25 (s,1H)	343
21	δ 0.26 (m,2H), 0.51 (m,2H), 0.92 (t,3H), 1.10 (m,1H), 1.69 (m,2H), 2.72 (s,3H), 3.41 (d,2H), 3.47 (t,2H), 6.17 (s,1H), 7.18 (t,1H), 7.43 (d,2H), 7.99 (s,1H)	389
22	δ 0.93 (t,3H), 1.67 (m,2H), 2.71 (s,3H), 3.32 (s,3H), 3.44 (t,2H), 3.61 (m,2H), 3.68 (m,2H), 6.16 (s,1H), 7.17 (t,1H), 7.41 (d,2H), 7.99 (s,1H)	393
23	δ 0.24 (m,2H), 0.55 (m,2H), 0.95 (t,3H), 1.38 (m,2H), 1.69 (m,2H), 2.51 (s,3H), 3.74 (d,2H), 3.82 (t,2H), 6.00 (s,1H), 7.31 (dd,1H), 7.48 (dd,1H), 7.98 (d,1H), 8.42 (s,1H)	403
24	δ 0.28 (m,2H), 0.50 (m,2H), 0.94 (d,6H), 1.10 (m,1H), 2.05 (m,1H), 2.52 (s,3H), 3.62 (d,2H), 3.82 (d,2H), 6.03 (s,1H), 7.32 (d,1H), 7.47 (s,1H), 7.99 (d,1H), 8.43 (s,1H)	403
25	δ 0.17 (m,2H), 0.47 (m,2H), 0.97 (t,6H), 1.05 (m,1H), 1.67 (m,4H), 2.52 (s,3H), 2.43 (d,2H), 4.71 (m,1H), 6.13 (s,1H), 7.32 (dd,1H), 7.47 (d,1H), 8.02 (d,1H), 8.43 (s,1H)	417
26	δ 2.41 (s,3H), 4.01 (m,2H), 4.15 (m,2H), 4.79 (s,2H), 5.62 (brs, 1H), 6.02 (s,1H), 7.35 (m,6H), 7.48 (s,1H), 7.91 (d,1H), 8.41 (s,1H)	427
27	δ 1.91 (s,3H), 2.47 (s,3H), 4.20 (t,2H), 4.43 (t,2H), 4.96 (s,2H), 6.03 (s,1H), 7.34 (m,6H), 7.49 (s,1H), 7.94 (d,1H), 8.44 (s,1H)	469

28	δ 0.98 (t,3H), 1.74 (m,2H), 1.93 (s,3H), 2.49 (s,3H), 3.59 (m,2H), 4.84 (m,2H), 4.39 (m,2H), 5.95 (s,1H), 7.30 (dd,1H), 7.46 (d,1H), 7.92 (d,1H), 8.38 (s,1H)	421
29	δ 0.28 (m,2H), 0.60 (m,2H), 1.20 (m,1H), 2.51 (s,3H), 3.70 (d,2H), 4.50 (d,2H), 5.29 (d,1H), 5.30 (d,1H), 5.96 (m,1H), 6.05 (s,1H), 7.32 (dd,1H), 7.48 (d,1H), 7.96 (d,1H), 8.44 (s,1H)	387
30	δ 1.07 (t,3H), 1.80 (m,2H), 2.46 (s,3H), 2.55 (s,3H), 3.36 (dt,2H), 5.82 (s,1H), 6.29 (t,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	381
31	δ 1.41 (d,6H), 2.46 (s,3H), 2.55 (s,3H), 3.85 (m,1H), 5.82 (s,1H), 6.08 (d,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	381
32	δ 0.92 (t,3H), 1.01 (t,3H), 1.25-1.80 (m,8H), 2.45 (s,3H), 2.54 (s,3H), 3.48 (m,1H), 5.79 (s,1H), 6.02 (d,1H), 7.27 (d,1H), 7.39 (d,1H), 7.50 (s,1H)	437
33	δ 0.96 (t,3H), 1.20 (t,6H), 1.74 (m, 4H), 2.15 (s,3H), 2.34 (s,3H), 2.41 (s, 3H), 3.56 (t,4H), 3.79 (t,4H), 5.77 (s,1H), 6.41 (s,1H), 7.54 (s,1H)	-
34	δ 2.45 (s,3H), 2.56 (s,3H), 3.93 (s,3H), 4.60 (d,2H), 5.90 (s,1H), 6.70 (t,1H), 6.99 (t,2H), 7.27-7.41 (m,4H), 7.52 (s,1H)	459
35	δ 2.44 (s,3H), 2.60 (s,3H), 3.35 (s,6H), 5.00 (brs,1H), 5.84 (s,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	367
36	δ 1.36 (s,6H), 2.42 (s,3H), 2.59 (s,3H), 3.80 (m,4H), 5.80 (s,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	395
37	δ 0.98 (t,6H), 1.78 (m,4H), 2.40 (s,3H), 2.59 (s,3H), 3.69 (m,4H), 5.74 (s,1H), 7.28 (d,1H), 7.48 (d,1H)	423
38	δ 0.30 (m,2H), 0.62 (m,2H), 0.99 (t,3H), 1.20 (m,1H), 1.81 (m,2H), 2.49 (s,3H), 2.59 (s,3H), 3.65-3.90 (m,4H), 5.87 (s,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	435
39	δ 1.05 (d,3H), 1.38 (d,3H), 2.45 (s,3H), 2.56 (s,3H), 3.40 (m,1H), 5.80 (s,1H), 7.30 (d,1H), 7.37 (d,1H), 7.51 (s,1H)	423
40	δ 0.98 (t,6H), 1.40 (m,4H), 1.75 (m,4H), 2.42 (s,3H), 2.59 (s,3H), 3.71 (m,4H), 5.76 (s,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	451
41	δ 0.29 (m,2H), 0.61 (m,2H), 0.93 (t,3H), 1.20-1.56 (m,3H), 1.75 (m,2H), 2.43 (s,3H), 2.59 (s,3H), 3.65-3.90 (m,4H), 5.88 (s,1H), 7.30 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	449
42	δ 2.42 (s,3H), 2.59 (s,3H), 4.34 (d,4H), 5.30 (m,4H), 5.87 (s,1H), 6.05 (m,2H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	419

화합물 번호	^{1}H NMR 데이터(CDCl$_3$)	MS M + 1
43	δ 0.31 (m,2H), 0.62 (m,2H), 1.00 (t,3H), 1.23 (m,1H), 1.81 (m,1H), 2.49 (s,3H), 3.05 (brs,3H), 3.42-3.95 (m,4H), 6.04 (s,1H), 7.33 (d,1H), 7.50 (s,1H), 7.51 (d,1H)	451
44	δ 0.13 (m,2H), 0.48 (m,2H), 0.90 (t,3H), 1.05 (m,1H), 1.60 (m,2H), 2.64 (s,3H), 3.05 (brs,3H), 3.48 (d,2H), 3.71 (m,2H), 6.04 (s,1H), 7.37 (d,1H), 7.54 (s,1H), 7.60 (d,1H)	485 (+H_2O)
45	δ 0.95 (t,3H), 1.42 (m,2H), 1.98 (m,2H), 2.49 (s,3H), 3.33 (s,3H), 3.56 (m,2H), 3.75 (m,2H), 5.93 (m,1H), 7.31 (d,1H), 7.46 (s,1H), 7.96 (d,1H), 8.40 (s,1H)	407
46	δ 0.91 (t,3H), 0.95 (t,3H), 1.35-2.05 (m,8H), 2.70 (t,2H), 3.33 (s,3H), 3.40 (m,6H), 5.92 (s,1H), 7.30 (d,1H), 7.46 (s,1H), 8.02 (d,1H), 8.41 (s,1H)	449
47	δ 0.87 (t,3H), 1.25 (m,2H), 1.70 (m,2H), 2.04 (m,2H), 2.68 (m,2H), 3.41 (s,3H), 3.56 (m,4H), 5.86 (s,1H), 6.60 (t,1H), 7.31 (d,1H), 7.46 (s,1H), 8.14 (d,1H), 8.50 (s,1H)	407
48	δ 0.95 (t,6H), 1.71 (m,4H), 2.47 (s,3H), 2.55 (s,3H), 3.71 (t,4H), 5.82 (s,1H), 7.39 (d,2H), 7.70 (d,2H)	357
49	δ 0.24 (m,2H), 0.54 (m,2H), 0.96 (t,3H), 1.12 (m,1H), 1.74 (m,2H), 2.35 (s,3H), 2.44 (s,3H), 3.73 (d,2H), 3.76 (t,2H), 5.93 (s,1H), 7.29 (d,1H), 7.35 (d,1H), 7.51 (s,1H)	403
50	δ 1.64 (t,3H), 2.52 (s,3H), 2.60 (s,3H), 4.56 (q,2H), 6.02 (s,3H), 7.30 (d,1H), 7.37 (d,1H), 7.51 (s,1H)	368
52	δ 0.9 (t, 6H), 1.68 (m, 4H), 2.13 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.05 (s, 6H), 3.65 (m, 4H), 5.74 (s, 1H), 6.44 (s, 1H), 8.01 (s, 1H)	M^+ = 366
53	δ 0.9 (t, 6H), 1.70 (m, 4H), 2.35 (s, 3H), 2.45 (s, 3H), 3.05 (s, 6H), 3.65 (m, 4H), 5.74 (s, 1H), 6.44 (s, 1H), 8.01 (s, 1H)	M^+ = 380
54	δ 0.95 (t, 6H), 1.73 (m, 4H), 2.52 (s, 3H), 2.76 (s, 3H), 3.73 (t, 4H), 5.85 (s, 1H), 7.68 (dd, 1H), 8.45 (d, 1H), 8.57 (d, 1H)	-
55	δ 0.96 (t, 6H), 1.70 - 1.78 (m, 4H), 2.44 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 3.73 (t, 4H), 5.48 (s, 1H), 8.36 (d, 1H), 9.32 (d, 1H)	383
56	δ 0.93 (t, 6H), 1.66 - 1.73 (m, 4H), 2.19 (s, 3H), 2.36 (s, 3H), 2.42 (s, 3H), 3.71 (t, 4H), 5.79 (s, 1H), 6.39 (d, 1H), 8.05 (d, 1H)	353
57	δ 0.96 (t, 6H), 1.62 - 1.70 (m, 4H), 2.2 (s, 3H), 2.36 (s, 3H), 2.40 (s, 3H), 2.96 (s, 6H), 3.68 (t, 4H), 5.76 (s, 1H), 6.91 (d, 1H), 8.08 (d,1H)	381

화합물번호	질량스펙트럼데이터	화합물번호	질량스펙트럼데이터
58	409 [M+]	95	364 [MH+]
59	365 [M+]	96	395 [MH+]
60	394 [MH+]	97	407 [MH+]
61	380 [MH+]	98	372 [MH+] (Cl^{35})
62	381 [MH+]	99	464 [MH+]
63	381 [MH+]	100	356 [MH+]
64	393 [MH+]	101	426 [MH+] (Cl^{35})
65	350 [MH+]	102	458 [MH+] (Cl^{35})
66	366 [MH+]	103	392 [MH+] (Cl^{35})
67	381 [MH+]	104	408 [MH+] (Cl^{35})
68	399 [MH+]	105	404 [MH+] (Cl^{35})
69	415 [MH+]	106	368 [MH+]
70	411 [MH+]	107	409 [MH+]
71	399 [MH+]	108	421 [MH+]
72	371 [MH+]	109	383 [MH+]
73	397 [MH+]	110	353 [MH+]
74	388 [M+]	111	372 [MH+] (Cl^{35})
75	407 [MH+]	112	366 [MH+]
76	373 [MH+]	113	381 [MH+]
77	359 [MH+]	114	338 [MH+]
78	346 [M+]	115	377 [MH+]
79	373 [MH+]	116	383 [MH+]
80	397 [MH+]	117	399 [MH+]
81	381 [MH+]	118	395 [MH+]
82	393 [MH+]	119	415 [MH+]
83	429 [MH+]	120	385 [MH+]
84	377 [MH+]	121	367 [MH+]
85	409 [MH+]	122	383 [MH+]
86	367 [MH+]	123	383 [MH+]
87	339 [MH+]	124	399 [MH+]
88	381 [MH+]	125	338 [MH+]
89	367 [MH+]	126	353 [MH+]
90	381 [MH+]	127	365 [MH+]
91	393 [MH+]	128	370 [M+]

분석 데이터

화합물번호	질량 스펙트럼 데이터
929394129130131	381 [MH+]409 [MH+]352 [MH+]368 [M+]393 [MH+]379 [MH+]

C. 약물학적 실험

실시예 C.1: CRF 수용체 결합 활성을 갖는 대표적인 화합물

화합물을 DeSouza 등에 의한 문헌 [J. Neurosci. 7:88-100, 1987]에 일반적으로 기재된 표준 방사리간드 결합 분석에 의해 CRF 수용체에 대한 결합 활성에 대해 평가하였다. 여러 방사표지된 CRF 리간드를 분석에 사용하여 CRF 수용체 준타입(subtype)을 갖는 본 발명의 화합물의 결합 활성을 평가할 수 있다. 간단히 말해, 결합 분석은 CRF 수용체로부터 방사표지된 CRF 리간드를 대체시키는 것을 포함한다. 더욱 구체적으로, 결합 분석은 인간 CRF 수용체로 안정하게 형질감염된 튜브 하나당 약 $1x10^6$ 세포를 사용하여 1.5 ㎖의 에펜도르프(Eppendorf) 튜브중에서 수행한다. 각 튜브에 비특이적 결합을 결정하는 CRF(최종 농도, 1 μM), 유로텐신 I 또는 표지되지 않은 사우바긴(sauvagine)을 함유하거나 함유하지 않는 시험 완충액(예를 들어 둘베코(Dulbecco) 인산염 완충염수, 10 mM 의 염화마그네슘, 20 μM의 바시트라신) 약 0.1 ㎖ , [^{125}I]티로신 - 양의 CRF(최종 농도 200 pM 또는 대략 Scatchard 분석에 의해 측정된 K_D) 0.1 ㎖ 및 CRF 수용체를 함유하는 세포의 막 현탁액 0.1 ㎖를 도입한다. 혼합물을 22 ℃에서 2 시간동안 인큐베이션한 후, 원심분리하여 결합 및 유리된 방사리간드를 분리한다. 펠렛을 2회 세척하고, 튜브를 펠렛 바로 위에서 자른 후, 감마-카운터에서 약 80%의 효율로 방사활성에 대해 조사하였다. 비선형 리스트-스퀘어 커브-피팅(non-linear least-square curve-fitting) 프로그램을 사용하여 모든 방사리간드 결합 데이터를 분석하였다. 결합 활성은 수용체로부터 방사표지된 리간드의 50%를 대체시키는데 필요한 화합물의 농도(nM)에 상응한다. 표 2 내지 5에 기재된 바와 같이 화합물 5, 10, 12, 15-17, 19, 23, 24, 26, 27, 29, 31-33, 36-43, 48, 49, 51-54 및 57-130이 ≤250 nM의 K_i 값을 갖는다. 이 시험에서 화합물 17, 29, 38, 41, 42, 48, 49, 51-54, 57, 58, 70, 71, 81-85, 90-92, 101, 103-105, 115, 118, 121-123 및 125가 가장 좋은 점수를 갖는 것으로 확인되었다.

실시예 C.2

CRF 유도된 아데닐레이트 사이클라제 활성

본 발명의 화합물을 또한 각종 기능 시험에 의해 평가할 수 있다. 예를 들어, 본 발명의 화합물을 CRF 유도된 아데닐레이트 사이클라제 활성에 대해 스크리닝할 수 있다. CRF 유도된 아데닐레이트 사이클라제 활성의 측정 시험을 Battaglia 등에 의한 문헌 [Synapse 1:572, 1987]에 일반적으로 기재된 방법을 전체 세포 준비물 분석에 적합하도록 변형시켜 수행할 수 있다. 더욱 구체적으로, 표준 분석 혼합물은 2 mM L-글루타민, 20 mM의 HEPES 및 DMEM 완충액중의 1 mM IMBX를 최종 부피 0.5 ㎖로 함유할 수 있다. 유도 시험에서, 형질감염된 CRF 수용체를 갖는 전체 세포를 24 개의 웰 플레이트에 플레이팅하고, CRF-관련 및 비관련 펩타이드의 농도를 변화시키면서 37 ℃에서 1 시간동안 인큐베이션하여 특정 수용체 준타입의 약물학적 순위를 정한다. 인큐베이션후, 배지를 아스피레이션하고, 웰을 신선한 배지로 1회 부드럽게 행군후, 배지를 아스피레이션한다. 세포내 cAMP 의 양을 측정하기 위하여, 20 mM의 수성 염산 및 95% 에탄올의 용액 300 ㎕를 각 웰에 첨가하고, 생성된 현탁액을 -20 ℃에서 16 내지 18 시간동안 인큐베이션한다. 용액을 꺼내 1.5 ㎖의 에펜도르프 튜브에 도입하고, 웰을 추가의 에탄올/수성 염산 200 ㎕로 세척한 다음, 제 1 분획과 풀링한다(pool). 샘플을 동결건조시키고, 500 ㎕의 소듐 아세테이트 완충액으로 재현탁시킨다. 단일 항체 키트를 사용하여 샘플중의 cAMP 를 측정한다. 화합물의 기능성 측정을 위하여, cAMP 생산의 80%를 유도하는 단일 농도의 CRF 또는 관련 펩타이드를 다양한 농도의 경쟁 화합물(10^{-12} 내지 10^{-6} M)과 함께 인큐베이션한다.

실시예 C.3

플러스-미로(plus-maze) 및 방어적 후퇴 패러다임(defensive withdrawl paradigm)은 실험적 처리에 의한 불안 조장 및 불안 해소 효과에 민감한 탐험적 행위를 측정하기 위해 상호 보완 사용된다. 이들 동물 모델을 본 발명의 화합물의 불안 해소 및 항-스트레스 작용을 조사하기 위하여 사용하였다.

실시예 C.3-a: 고가 플러스-미로 패러다임

이 시험은 동물이 어떠한 방식으로 밝은 공간과 어두운 안전한 공간을 포함하는 접근-회피 상황에 응답할 수 있는지를 예견한다. 두 공간은 모두 지상으로부터 떨어져 있으며, 플러스 부호의 형태로 교차하는 두 개의 주로로 구성되어 있다. 이러한 형태의 접근-회피 상황은 "감정" 및 반응성을 조사하는 고전적인 시험방법이며, 탈억제(진정/최면과 같은) 및 스트레스를 형성하는 처리에 매우 민감하다. 움직임에 제한을 둘 필요는 없으며, 동물이 자유롭게 어둠속에 남아있거나 개방된 팔(open arm)로 탈출하도록 내버려 둔다. 플러스-미로 장치는 네 개의 팔(10 x 50 ㎝)을 90도 각도로 가지며, 바닥으로부터 50 ㎝ 떨어져 위치해 있다. 두 개의 팔은 벽(40 ㎝ 높이)으로 막혀 있고, 두 개의 팔은 장벽이 없다(개방 팔). 대상체를 미로의 중심부에 개별적으로 위치시키고, 5 분동안 네 개의 팔에 대해 자유롭게 접근하도록 한다. 대상체를 문에 있는 창을 통하여 관찰함과 동시에 컴퓨터 모니터상에 랫트의 위치가 온-라인 표시되록 함으로써 관찰한다. 각 팔에서 소비한 시간이 포토셀 빔 및 컴퓨터 프로그램에 의해 자동적으로 기록된다. 미로를 각 시험사이에 젖은 천으로 닦아낸다. 이 실험에서 불안 조장 행위는 개방된 팔에서 소비한 시간의 감소로 측정되고, 항-스트레스 효과는 개방된 팔에서 소비한 시간의 상보적인 증가로 측정된다.

CRF 펩타이드를 사용한 플러스-미로의 타당성

CRF의 중추 투여 및 수개의 실험적 스트레스 요인의 노출은 불안에 싸인 고가 플러스 미로 모델의 탐험성을 억제한다. 사회적인 좌절에 대한 행위적 반응을 측정하는 경우, 스트레스후[25 ㎍ ICV] 또는 스트레스전[1 ㎍ ICN]에 알파-나선형의 CRF (9-41)길항제를 중추 투여하게 되면 사회적인 좌절에 의한 불안 조장 효과가 반전된다. 이러한 CRF 길항제의 항-스트레스 작용은 또한 대뇌 도착후 소뇌편도의 중심핵으로 도달된다[250 ng IC].

랫트에 시험 화합물을 5 분시험 1 시간전에 경구 투여한다. 일부의 그룹을 플러스-미로에 도입시키기 바로 전에 90 초동안 물이 가득찬 풀에 놓고(스트레스 그룹), 대조군 그룹은 우리에서 직접 꺼낸다(비-스트레스 그룹). 비-처리 동물 그룹에 있어서 개방된 팔에서 소비하는 평균 시간 퍼센트가 상당히 감소하는 것으로 관찰되었다(약 36 내지 약 16%). 화합물 53을 2.5 또는 20 ㎎/㎏ 투여하였더니 개방된 팔에서의 소비 시간%가 오차 범위내에서 비처리 그룹과 마찬가지의 수준으로 되돌아 갔다.

실시예 C.3-b: 방어적 후퇴 패러다임

직경 10.2 ㎝이고, 길이 17.1 ㎝인 직류전기가 효르는 원통형의 스틸 챔버를 포함하는 플라스틱 유리의 개방 필드(106 x 92 x 77 ㎝)에서 시험을 수행하였다. 챔버를 한쪽 끝은 개방하고, 개방 필드의 코너로부터 15.0 ㎝ 떨어지고 세로로 정렬되도록 개방 필드의 벽과 나란히 위치시킨다. 개방 끝 부분은 코너와 직면한다. 형광빛을 천장으로 부터 개방 필드에 조명한다. 테스트를 위하여, 동물을 작은 챔버에 놓음으로써 친숙하지 않은 테스트 환경에 도입시킨다. 테스트 시간은 5분이고, 각 테스트후 장치를 연한 아세트산 용액으로 닦아 낸다. 시험 화합물을 5분 테스트 1 시간전에 경구 투여한다. 동물의 행동을 감시하고, 비디오 카메라로 기록한다. 챔버를 탈출하는 잠복기를 측정하고, 이는 개방 필드에 네 개의 모든 발이 놓이는 것으로 정의된다. 입구당 챔버내에서의 평균 시간 길이 및 챔버와 개방 필드사이에 만들어진 통로수를 또한 측정한다. 불안 해소 효과는 폐쇄된 챔버내에서 소비한 평균 시간의 감소로써 측정된다. 랫트에 화합물 53을 0.63, 2.5 및 20 ㎎/㎏ 경구 투여하였을때 챔버에서 평균시간은 약 80초에서 약 20 내지 40초로 감소하였다.

CRF 펩타이드를 사용한 방어적 후퇴의 타당성

알파-나선형 CRF(9-41) 및 CRF 둘 다를 ICV 주입하면 방어적 후퇴 패러다임에서의 행동에 변화가 생긴다. 특히, 이미 장치와 친숙해진 동물에 CRF를 ICV 투여하면 작은 챔버로 부터 나오는 잠복기 및 챔버내에서의 평균 소비시간 모두가 15분 이상으로 증가한다. 유사하게, CRF를 창반에 주사하면 방어적 후퇴 행동에 유사한 변화가 일어나고, 이것은 CRF와 노르아드레날린성 뉴론간의 상호작용이 랫트에서 방어적 후퇴 행동 동안에 동반됨을 의미하는 것이다. 반대로, 경쟁적인 CRF 수용체 길항제인 알파-나선형 CRF(9-14) 또는 d-Phe CRF(12-41)을 ICV 투여하면 친숙한 환경 상태의 구속 스트레스 요인에 대한 CRF 효과가 반전되며, 장치와 친숙하지 않은 동물에게서 챔버내의 평균 시간 및 탈출 잠복기가 상당히 감소된다.

D. 조성물 실시예

하기 실시예는 온혈동물에 전신적으로 또는 국소적으로 투여하기에 적합한 단위 복용형의 본 발명에 따른 대표적인 약제학적 조성물을 예시한다.

실시예에 사용된 "활성성분" (A.I.) 은 일반식 (I)의 화합물, 그의 N-옥사이드, 약제학적으로 허용되는 산 또는 염기 부가염, 입체화학적 이성체에 관한 것이다.

실시예 D.1: 경구용 용액제

메틸 4-하이드록시벤조에이트 9 g 및 프로필 4-하이드록시벤조에이트 1 g 을 비등 정제수 4 ℓ 에 용해시킨다. 이 용액 3 ℓ 에 우선 2,3-디하이드록시부타노산 10 g 을 용해시킨 후, A.I. 20 g 을 용해시킨다. 후자의 용액을 전자의 남아 있는 용액과 합치고, 여기에 1,2,3-프로판트리올 12 ℓ 및 소르비톨 70% 용액 3 ℓ 를 가한다. 사카린 나트륨 40 g 을 물 0.5 ℓ 에 용해시키고, 라즈베리 2 ㎖ 및 구즈베리 에센스 2 ㎖ 를 가한다. 후자의 용액을 전자와 합치고, 용적을 20 ℓ 로 만들기에 적합한 적당량의 물을 가하여 티스푼당(5 ㎖) 당 A.I. 5 ㎎ 을 함유하는 경구용 용액을 수득한다. 생성 용액을 적당한 용기에 충전한다.

실시예 D.2: 캅셀제

A.I. 20 g, 소듐 라우릴설페이트 6 g, 전분 56 g, 락토오스 56 g, 콜로이드성 이산화규소 0.8 g 및 마그네슘 스테아레이트 1.2 g 을 함께 격렬하게 교반한다. 생성된 혼합물을 계속해서 각각 활성성분 20 ㎎ 씩을 함유하는 1000 개의 적합한 경질 젤라틴 캅셀에 충전시킨다.

실시예 D.3: 필름-코팅 정제

정제핵의 제조

A.I. 100 g, 락토오스 570 g 및 전분 200 g 의 혼합물을 잘 혼합한 후에 물 약 200 ㎖ 중의 소듐 도데실설페이트 5 g 및 폴리비닐피롤리돈 10 g 의 용액으로 습윤시킨다. 습윤된 분말 혼합물을 체로 치고 건조시킨 후에 다시 체로 친다. 그후에 미세결정성 셀룰로오스 100 g 및 수소화 식물유 15 g 을 가한다. 전체 혼합물을 잘 혼합시키고, 타정하여 각각 활성성분 10 ㎎ 씩을 함유하는 정제 10,000 정을 수득한다.

코팅(coating)

변성 에탄올 75 ㎖ 중의 메틸셀룰로오스 10 g 의 용액에 디클로로메탄 150 ㎖ 중의 에틸 셀룰로오스 5 g 의 용액을 가한다. 그후, 여기에 디클로로메탄 75 ㎖ 및 1,2,3-프로판트리올 2.5 ㎖ 를 가한다. 폴리에틸렌글리콜 10 g 을 용융시키고 디클로로메탄 75 ㎖ 에 용해시킨다. 후자의 용액을 전자의 용액에 가한 다음, 여기에 마그네슘 옥타데카노에이트 2.5 g, 폴리비닐피롤리돈 5 g 및 농축된

색소 현탁액 30 ㎖ 를 가하고 전체 혼합물을 균질화시킨다. 이렇게 하여 수득한 혼합물로 코팅 장치내에서 정제핵을 코팅한다.

실시예 D.4 : 주사용 용액제

메틸 4-하이드록시벤조에이트 1.8 g 및 프로필 4-하이드록시벤조에이트 0.2 g 을 주사용 비등수 약 0.5 ℓ 에 용해시킨다. 약 50 ℃ 로 냉각시킨 후, 교반하면서 락트산 4 g, 프로필렌 글리콜 0.05 g 및 A.I. 4 g 을 가한다. 용액을 실온으로 냉각시키고, 용적을 1 ℓ 로 만들기에 적합한 적당량의 주사용수를 보충하여 ㎖ 당 4 ㎎ 의 A.I. 용액을 수득한다. 용액을 여과에 의해 멸균시키고, 무균 용기에 충전한다.

실시예 D.5: 좌제

A.I. 3 g 을 폴리에틸렌 글리콜 400 25 ㎖중의 2,3-디하이드록시부탄디오산 3 g 의 용액에 용해시킨다. 계면활성제 12 g 및 트리글리세라이드 300 g을 함께 용융시킨다. 후자의 혼합물을 전자의 용액과 잘 혼합한다. 수득한 혼합물을 37 내지 38 ℃ 온도의 주형에 부어 각각 ㎖당 A.I. 30 ㎎을 함유하는 좌제 100 개를 수득한다.

PATENT
Attorney Docket No. 50535-710.306

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Alexis Howerton et al. Application No.: 19/043,264 Filing Date: January 31, 2025 Title: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS	Confirmation No.: 6961 Art Unit: 1627 Examiner: Pihonak, Sarah Customer No.: 21971 Certificate of Electronic Filing I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office's electronic filing system to the USPTO on July 25, 2025. By: / Colleen Mensching / Colleen Mensching

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Dear Commissioner:

In response to the Non-Final Office Action mailed April 25, 2025, setting an initial due date of July 25, 2025, Applicant respectfully requests reconsideration of the above-referenced application in view of the following amendments and remarks.

Amendments to the Specification begin on page **2** of this paper.
Amendments to the Claims begin on page **3** of this paper.
Remarks begin on page **7** of this paper.
Conclusion begins on page **11** of this paper.

AMENDMENTS TO THE SPECIFICATION

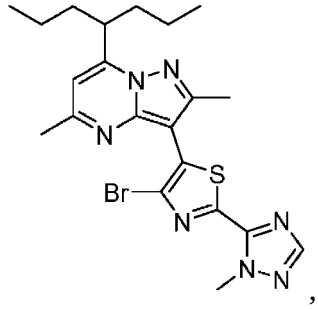
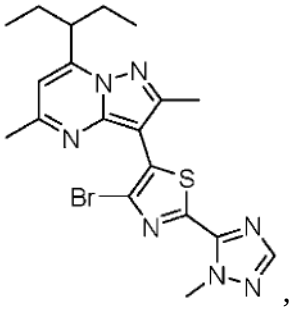
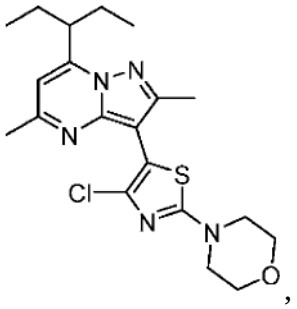
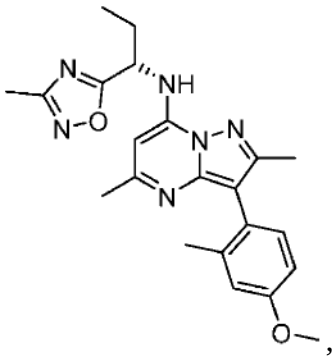
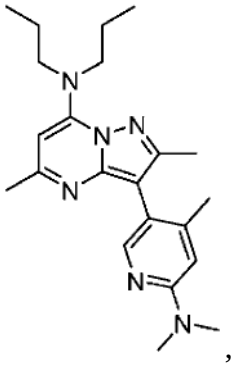
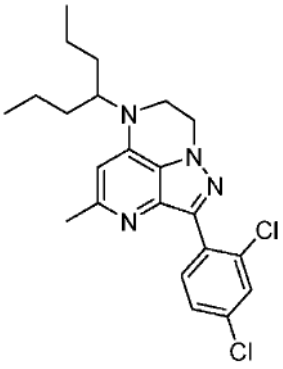
Applicant provides herewith both a clean copy and a marked copy of a substitute specification, excluding claims, in compliance with 37 C.F.R. §§ 1.52, 1.121, and 1.125. The amendments follow the Certificate of Correction (submitted on March 12, 2025, and accepted by the US Patent Office on June 17, 2025) corresponding to US Pat. No. 11,304,950.

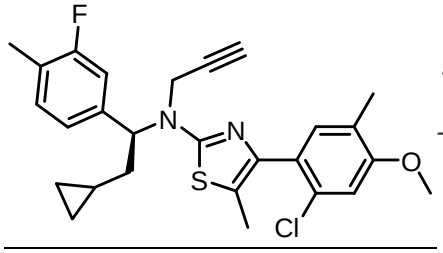
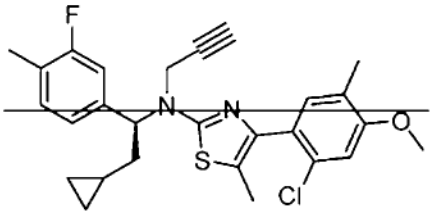
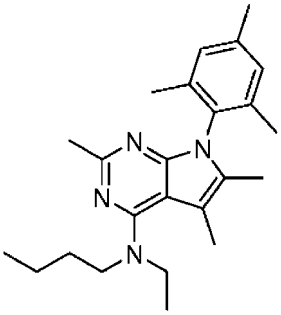
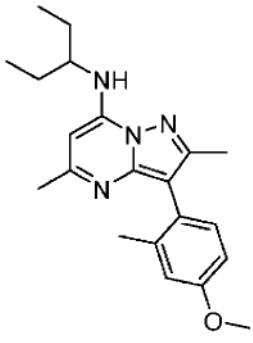
Applicant respectfully requests that the specification of record be replaced with the substitute specification filed herewith.

AMENDMENTS TO THE CLAIMS

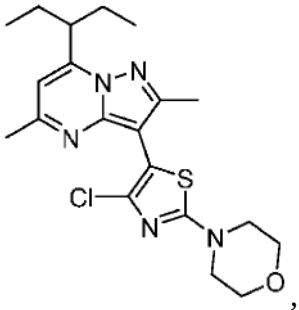
Listing of the Claims

1. (**Currently Amended**) A method of treating ovarian adrenal rest tumors (OART) and menstrual irregularity in a subject, comprising administering to the subject a small molecule corticotropin-releasing factor type-1 (CRF_1) antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF_1 antagonist is:

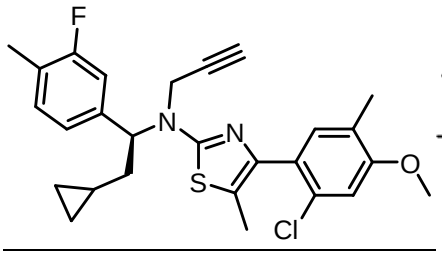
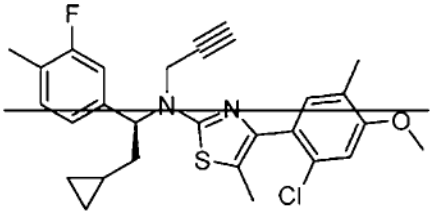

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, or a pharmaceutically acceptable salt thereof.

2. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is:


, or a pharmaceutically acceptable salt thereof.

3. (**Currently Amended**) The method of claim 1, wherein the small molecule CRF_1 antagonist is:



, or a pharmaceutically acceptable salt thereof.

4. (**Currently Amended**) The method of claim 1, ~~wherein the metabolic parameter is insulin sensitivity~~ further comprising treating ovulatory dysfunction or infertility.
5. (Original) The method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).
6. (Original) The method of claim 1, wherein the subject is an adolescent.
7. (Original) The method of claim 1, wherein the subject is at least 18 years or older.
8. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.
9. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 50 mg.
10. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 100 mg.
11. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 200 mg.
12. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 400 mg.
13. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered to the subject once per day.
14. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered to the subject twice per day.
15. (Original) The method of claim 13, wherein the subject is in a fed state.
16. (Original) The method of claim 14, wherein the subject is in a fed state.
17. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered orally.
18. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is formulated as a capsule or tablet.
19. (Original) The method of claim 1, wherein the administering reduces a plasma concentration of a biomarker comprising 17α-hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, androstenedione (A4), luteinizing hormone (LH), follicle-

stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, or aldosterone, or a combination thereof.

20. (Original) The method of claim 19, wherein the biomarker is selected from the group consisting of 17-OHP, ACTH, and A4.

21. (Original) The method of claim 19, wherein the plasma concentration of the biomarker is reduced by at least 10% from baseline.

REMARKS

Claims 1-21 were pending prior to entry of the amendments presented in this response. Claims 1, 3, and 4 are herein amended, support for which can be found in the as-filed application, at least at ¶¶ [0181] and [0208]. No new matter is added by any of these amendments. Reconsideration and allowance are respectfully requested based on the amendments and the following remarks.

Indefiniteness 35 U.S.C. § 112

Claim 4 is rejected under 35 U.S.C. § 112(b) as allegedly being indefinite. Without conceding to the basis of the rejection and for the purpose of compact prosecution, Applicant herein amends claim 4 and requests withdrawal of the indefiniteness rejection.

Anticipation Under 35 U.S.C. § 102

Claim(s) 1-2 and 5-21 is/are rejected under 35 U.S.C. § 102(a)(1) and § 102(a)(2) as being anticipated by Howerton et. al., WO 2019036503 A1, publ. 2/21/2019, international filing date 8/14/2018, cited in an IDS.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP § 2131.

Applicant submits amended claim 1 is novel over Howerton et al., which Applicant submits does not describe "treating ovarian adrenal rest tumors (OART)." Therefore, Applicant respectfully requests withdrawal of the anticipation rejection and favorable reconsideration. By virtue of their dependencies, claims 2 and 5-21 are also novel, as they depend from amended claim 1, which is novel for at least the reason above.

Obviousness Under 35 U.S.C. § 103

To establish a *prima facie* case of obviousness, all of the claim limitations must be taught by the prior art. "A prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on the

applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2141(III).

Grigoriadis

Claim(s) 1, 3-14, and 17-21 is/are rejected under 35 U.S.C. § 103 as being unpatentable over Grigoriadis, WO 2015112642 A1, publ. 7/30/2015, cited in an IDS (hereafter "Grigoriadis").

Applicant submits amended claim 1 is nonobvious over Grigoriadis. For instance, Grigoriadis does not appear to teach or suggest treating "treating ovarian adrenal rest tumors (OART) and menstrual irregularity in a subject" as in amended claim 1. As such, a person of ordinary skill in the art would not find a teaching or suggestion in Grigoriadis to arrive at amended claim 1. Therefore, amended claim 1 is nonobvious over Grigoriadis for at least this reason, and withdrawal of the obviousness rejection is respectfully requested.

By virtue of their dependencies, claims 3-14 and 17-21 are also nonobvious over the cited references, as they depend from amended claim 1, which is nonobvious for the reasons above.

Chen in view of Grigoriadis

Claim(s) 1-2, 5-14, and 17-21 is/are rejected under 35 U.S.C. § 103 as being unpatentable over Chen et. al., WO 2008036579 A1, publ. 3/27/2008, cited in an IDS (hereafter "Chen") in view of Grigoriadis.

Applicant submits amended claim 1 is nonobvious over Chen in view of Grigoriadis. Chen does not appear to teach or suggest treating "treating ovarian adrenal rest tumors (OART) and menstrual irregularity in a subject" as in amended claim 1. As such, a person of ordinary skill in the art would not find a teaching or suggestion in Chen to arrive at amended claim 1. Therefore, amended claim 1 is nonobvious over Chen for at least this reason.

Grigoriadis does not cure the deficiencies of Chen for the same reasons as above. As such, a person of ordinary skill in the art would not find a teaching or suggestion in Chen or Grigoriadis, alone or in combination, to arrive at amended claim 1. Therefore, amended claim 1 is nonobvious over the cited references for at least this reason, and withdrawal of the obviousness rejection is respectfully requested.

By virtue of their dependencies, claims 2, 5-14, and 17-21 are also nonobvious over the cited references, as they depend from amended claim 1, which is nonobvious for the reasons above.

Obviousness-Type Double Patenting

Pending claims 1-3, 5, 8-14, and 17-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over:

- Claims 1-4, 7-8, 11-14, 17-18, and 21-22 of U.S. Patent No. 10,849,908 B2 in view of Grigoriadis, WO 2015112642 A1, publ. 7/30/2015;
- Claims 1-4, 7-8, and 11-16 of U.S. Patent No. 11,007,201 B2 in view of Grigoriadis, WO 2015112642 A1, publ. 7/30/2015;
- Claims 1-4, 7-8, 11-16, and 19-24 of U.S. Patent No. 11,344,557 B2 in view of Grigoriadis, WO 2015112642 A1, publ. 7/30/2015; and
- Claims 1-15 and 19 of U.S. Patent No. 11,304,950 B2 in view of Stikkelbroeck et. al., *Fertility & Sterility*, vol. 80(4), pp. 1030-1036, publ. 2003; and Grigoriadis, WO 2015112642 A1, publ. 7/30/2015.

Pending claims 1-2, 5, 8-14, and 17-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over:

- Claims 1-4, 7-8, and 14-19 of U.S. Patent No. 11,351,177 B2 in view of Grigoriadis, WO 2015112642 A1, publ. 7/30/2015.
- Claims 1-4, 7-8, and 11-16 of U.S. Patent No. 11,311,549 B2 in view of Grigoriadis, WO 2015112642 A1, publ. 7/30/2015.

Pending claims 1-3, and 5-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over:

- Pending claims 72-91 of copending application 18941832 in view of Stikkelbroeck et. al., *Fertility & Sterility*, vol. 80(4), pp. 1030-1036, publ. 2003; and
- Pending claims 1-5 and 9-21 of copending application 19043275 in view of Stikkelbroeck et. al., *Fertility & Sterility*, vol. 80(4), pp. 1030-1036, publ. 2003.

Claims 1-3, 5-13, and 17-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending application 19043303 in view of Stikkelbroeck et. al., *Fertility & Sterility*, vol. 80(4), pp. 1030-1036, publ. 2003.

Without conceding in the basis of the rejection, Applicant submits the amended claims are patentably distinct from the cited patents, cited patent applications, and cited references above. Accordingly, Applicant respectfully requests the withdrawal of the nonstatutory double patenting rejections.

***

It shall be understood herein that any instance in which Applicant has addressed certain comments set forth by the Office shall not be construed as a concession to other comments or arguments advanced by the Office. Any circumstance in which Applicant has amended or cancelled a claim also does not mean that Applicant concedes to the arguments or positions advanced by the Office with respect to that claim or other claims pending herein.

CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858) 350-2240.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 50535-710.306).

Respectfully submitted,

Date: July 25, 2025 By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79,641

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone: (650) 493-9300
Customer No. 21971

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**07/25/2025 02:04:48 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Colleen Mensching
PATENT CENTER #	71528969	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 7

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710.306 - Internet Comms Auth.pdf		2	Internet Communications Authorization	209 KB
Spruce 50535-710.306 - Office Action Response.pdf		11	-	288 KB
Spruce 50535-710.306 - Office Action Response-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	108 KB
Spruce 50535-710.306 - Office Action Response-SPEC.pdf	(2-2)	1	Specification	107 KB
Spruce 50535-710.306 - Office Action Response-CLM.pdf	(3-6)	4	Claims	218 KB

Spruce 50535-710.306 - Office Action Response-REM.pdf	(7-11)	5	Applicant Arguments/Remarks Made in an Amendment	168 KB
Spruce 50535-710.306 - Substitute Specification - Marked.pdf		114	Specification	1120 KB
Spruce 50535-710.306 - Substitute Specification - Clean.pdf		113	Specification	1110 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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Spruce 50535-710.306 - Substitute Specification - Marked.pdf	F3774E93C3F6DF3D8D4A7AC5AA46113F741DCB80BD01AFA178ED0942D776CEC63405FAF6EA6FE3D7885AFDF0CBE35AF52E1A82E02BA24E2235EA6CD2E3B2AB78
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT
Attorney Docket No. 50535-710.306

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Alexis Howerton et al. Application No.: 19/043,264 Filing Date: January 31, 2025 Title: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS	Confirmation No.: 6961 Art Unit: 1627 Examiner: Pihonak, Sarah Customer No.: 21971 Certificate of Electronic Filing I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office's electronic filing system to the USPTO on July 25, 2025. By: / Colleen Mensching / Colleen Mensching

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Dear Commissioner:

In response to the Non-Final Office Action mailed April 25, 2025, setting an initial due date of July 25, 2025, Applicant respectfully requests reconsideration of the above-referenced application in view of the following amendments and remarks.

Amendments to the Specification begin on page **2** of this paper.
Amendments to the Claims begin on page **3** of this paper.
Remarks begin on page **7** of this paper.
Conclusion begins on page **11** of this paper.

AMENDMENTS TO THE SPECIFICATION

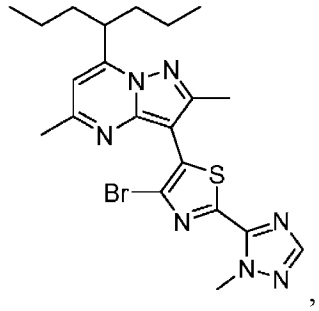
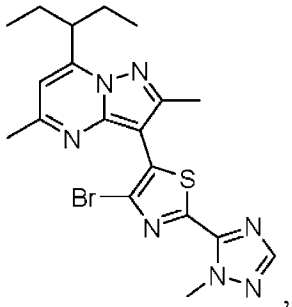
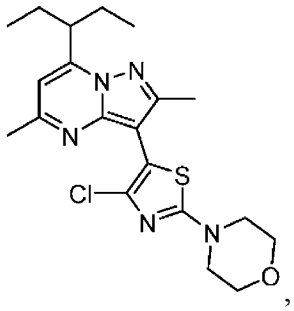
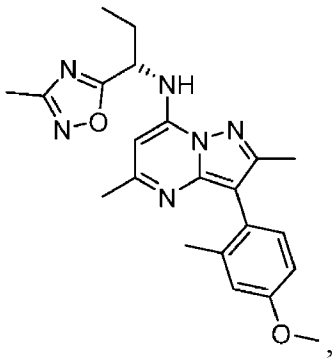
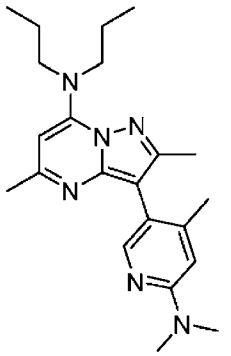
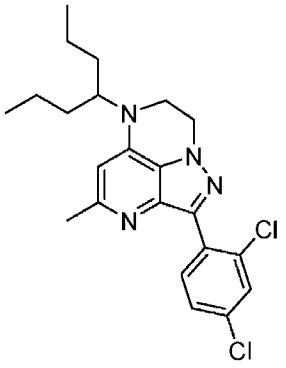
Applicant provides herewith both a clean copy and a marked copy of a substitute specification, excluding claims, in compliance with 37 C.F.R. §§ 1.52, 1.121, and 1.125. The amendments follow the Certificate of Correction (submitted on March 12, 2025, and accepted by the US Patent Office on June 17, 2025) corresponding to US Pat. No. 11,304,950.

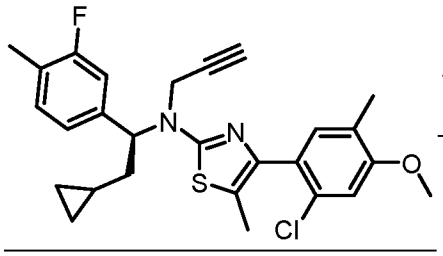
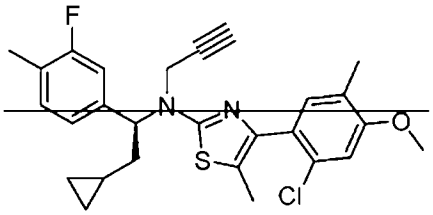
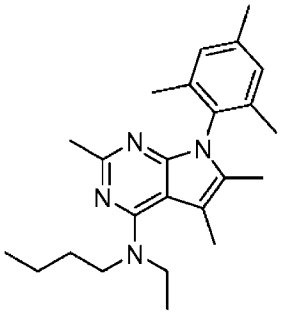
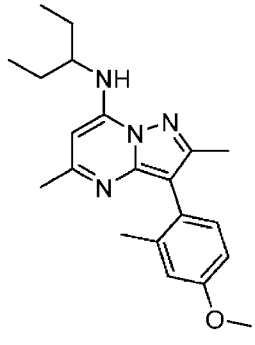
Applicant respectfully requests that the specification of record be replaced with the substitute specification filed herewith.

AMENDMENTS TO THE CLAIMS

Listing of the Claims

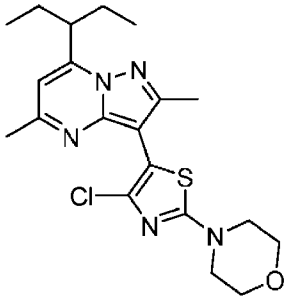
1. (**Currently Amended**) A method of treating ovarian adrenal rest tumors (OART) and menstrual irregularity in a subject, comprising administering to the subject a small molecule corticotropin-releasing factor type-1 (CRF_1) antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF_1 antagonist is:


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, SSR-126374,

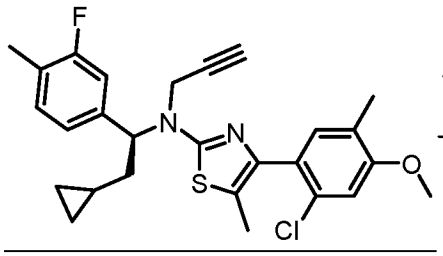
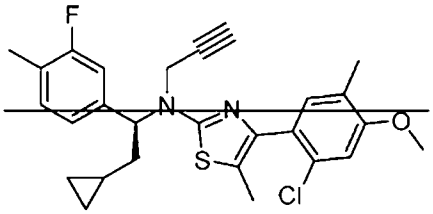
, or a pharmaceutically acceptable salt thereof.

2. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is:



, or a pharmaceutically acceptable salt thereof.

3. (**Currently Amended**) The method of claim 1, wherein the small molecule CRF_1 antagonist is:

, or a pharmaceutically acceptable salt thereof.

4. (**Currently Amended**) The method of claim 1, ~~wherein the metabolic parameter is insulin sensitivity~~ further comprising treating ovulatory dysfunction or infertility.
5. (Original) The method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).
6. (Original) The method of claim 1, wherein the subject is an adolescent.
7. (Original) The method of claim 1, wherein the subject is at least 18 years or older.
8. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.
9. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 50 mg.
10. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 100 mg.
11. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 200 mg.
12. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 400 mg.
13. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered to the subject once per day.
14. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered to the subject twice per day.
15. (Original) The method of claim 13, wherein the subject is in a fed state.
16. (Original) The method of claim 14, wherein the subject is in a fed state.
17. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered orally.
18. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is formulated as a capsule or tablet.
19. (Original) The method of claim 1, wherein the administering reduces a plasma concentration of a biomarker comprising 17α-hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, androstenedione (A4), luteinizing hormone (LH), follicle-

stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, or aldosterone, or a combination thereof.

20. (Original) The method of claim 19, wherein the biomarker is selected from the group consisting of 17-OHP, ACTH, and A4.

21. (Original) The method of claim 19, wherein the plasma concentration of the biomarker is reduced by at least 10% from baseline.

REMARKS

Claims 1-21 were pending prior to entry of the amendments presented in this response. Claims 1, 3, and 4 are herein amended, support for which can be found in the as-filed application, at least at ¶¶ [0181] and [0208]. No new matter is added by any of these amendments. Reconsideration and allowance are respectfully requested based on the amendments and the following remarks.

Indefiniteness 35 U.S.C. § 112

Claim 4 is rejected under 35 U.S.C. § 112(b) as allegedly being indefinite. Without conceding to the basis of the rejection and for the purpose of compact prosecution, Applicant herein amends claim 4 and requests withdrawal of the indefiniteness rejection.

Anticipation Under 35 U.S.C. § 102

Claim(s) 1-2 and 5-21 is/are rejected under 35 U.S.C. § 102(a)(1) and § 102(a)(2) as being anticipated by Howerton et. al., WO 2019036503 A1, publ. 2/21/2019, international filing date 8/14/2018, cited in an IDS.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP § 2131.

Applicant submits amended claim 1 is novel over Howerton et al., which Applicant submits does not describe "treating ovarian adrenal rest tumors (OART)." Therefore, Applicant respectfully requests withdrawal of the anticipation rejection and favorable reconsideration. By virtue of their dependencies, claims 2 and 5-21 are also novel, as they depend from amended claim 1, which is novel for at least the reason above.

Obviousness Under 35 U.S.C. § 103

To establish a *prima facie* case of obviousness, all of the claim limitations must be taught by the prior art. "A prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on the

applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2141(III).

Grigoriadis

Claim(s) 1, 3-14, and 17-21 is/are rejected under 35 U.S.C. § 103 as being unpatentable over Grigoriadis, WO 2015112642 A1, publ. 7/30/2015, cited in an IDS (hereafter "Grigoriadis").

Applicant submits amended claim 1 is nonobvious over Grigoriadis. For instance, Grigoriadis does not appear to teach or suggest treating "treating ovarian adrenal rest tumors (OART) and menstrual irregularity in a subject" as in amended claim 1. As such, a person of ordinary skill in the art would not find a teaching or suggestion in Grigoriadis to arrive at amended claim 1. Therefore, amended claim 1 is nonobvious over Grigoriadis for at least this reason, and withdrawal of the obviousness rejection is respectfully requested.

By virtue of their dependencies, claims 3-14 and 17-21 are also nonobvious over the cited references, as they depend from amended claim 1, which is nonobvious for the reasons above.

Chen in view of Grigoriadis

Claim(s) 1-2, 5-14, and 17-21 is/are rejected under 35 U.S.C. § 103 as being unpatentable over Chen et. al., WO 2008036579 A1, publ. 3/27/2008, cited in an IDS (hereafter "Chen") in view of Grigoriadis.

Applicant submits amended claim 1 is nonobvious over Chen in view of Grigoriadis. Chen does not appear to teach or suggest treating "treating ovarian adrenal rest tumors (OART) and menstrual irregularity in a subject" as in amended claim 1. As such, a person of ordinary skill in the art would not find a teaching or suggestion in Chen to arrive at amended claim 1. Therefore, amended claim 1 is nonobvious over Chen for at least this reason.

Grigoriadis does not cure the deficiencies of Chen for the same reasons as above. As such, a person of ordinary skill in the art would not find a teaching or suggestion in Chen or Grigoriadis, alone or in combination, to arrive at amended claim 1. Therefore, amended claim 1 is nonobvious over the cited references for at least this reason, and withdrawal of the obviousness rejection is respectfully requested.

By virtue of their dependencies, claims 2, 5-14, and 17-21 are also nonobvious over the cited references, as they depend from amended claim 1, which is nonobvious for the reasons above.

Obviousness-Type Double Patenting

Pending claims 1-3, 5, 8-14, and 17-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over:

- Claims 1-4, 7-8, 11-14, 17-18, and 21-22 of U.S. Patent No. 10,849,908 B2 in view of Grigoriadis, WO 2015112642 A1, publ. 7/30/2015;
- Claims 1-4, 7-8, and 11-16 of U.S. Patent No. 11,007,201 B2 in view of Grigoriadis, WO 2015112642 A1, publ. 7/30/2015;
- Claims 1-4, 7-8, 11-16, and 19-24 of U.S. Patent No. 11,344,557 B2 in view of Grigoriadis, WO 2015112642 A1, publ. 7/30/2015; and
- Claims 1-15 and 19 of U.S. Patent No. 11,304,950 B2 in view of Stikkelbroeck et. al., *Fertility & Sterility*, vol. 80(4), pp. 1030-1036, publ. 2003; and Grigoriadis, WO 2015112642 A1, publ. 7/30/2015.

Pending claims 1-2, 5, 8-14, and 17-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over:

- Claims 1-4, 7-8, and 14-19 of U.S. Patent No. 11,351,177 B2 in view of Grigoriadis, WO 2015112642 A1, publ. 7/30/2015.
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Pending claims 1-3, and 5-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over:

- Pending claims 72-91 of copending application 18941832 in view of Stikkelbroeck et. al., *Fertility & Sterility*, vol. 80(4), pp. 1030-1036, publ. 2003; and
- Pending claims 1-5 and 9-21 of copending application 19043275 in view of Stikkelbroeck et. al., *Fertility & Sterility*, vol. 80(4), pp. 1030-1036, publ. 2003.

Claims 1-3, 5-13, and 17-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending application 19043303 in view of Stikkelbroeck et. al., *Fertility & Sterility*, vol. 80(4), pp. 1030-1036, publ. 2003.

Without conceding in the basis of the rejection, Applicant submits the amended claims are patentably distinct from the cited patents, cited patent applications, and cited references above. Accordingly, Applicant respectfully requests the withdrawal of the nonstatutory double patenting rejections.

***

It shall be understood herein that any instance in which Applicant has addressed certain comments set forth by the Office shall not be construed as a concession to other comments or arguments advanced by the Office. Any circumstance in which Applicant has amended or cancelled a claim also does not mean that Applicant concedes to the arguments or positions advanced by the Office with respect to that claim or other claims pending herein.

CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858) 350-2240.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 50535-710.306).

Respectfully submitted,

Date: July 25, 2025

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79,641

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone: (650) 493-9300
Customer No. 21971

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

CROSS-REFERENCE

[0001] This application is a continuation of U.S. Application No. 18/941,832, filed November 8, 2024, which is a continuation of U.S. Application No. 17/667,285, filed on February 8, 2022, which is a continuation of U.S. Application No. 17/081,694 filed on October 27, 2020, which issued as U.S. Pat. No. 11,304,950 on April 19, 2022, and which is a continuation of International Application No. PCT/US2019/029486 filed on April 26, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019, each of which is entirely incorporated herein by reference.

BACKGROUND

[0002] Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

[0003] CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

[0004] Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, *inter alia*, are solutions to these and other problems in the art.

SUMMARY

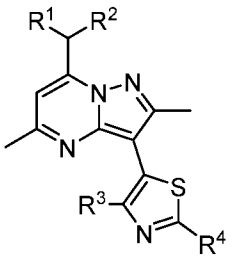
[0005] Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

[0006] Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

[0007] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0008] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

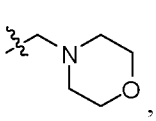
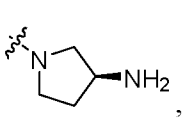
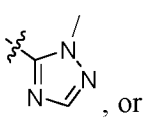
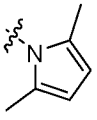
[0009] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):


(I), or a pharmaceutically acceptable salt thereof,

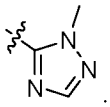
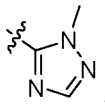
wherein:

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

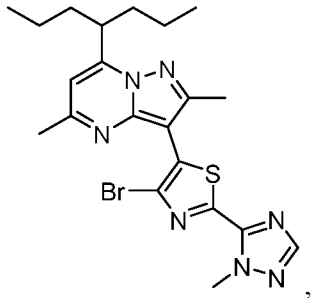
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ;

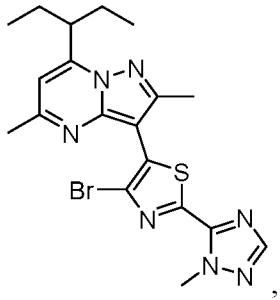
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0010] In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl. In some embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or  .

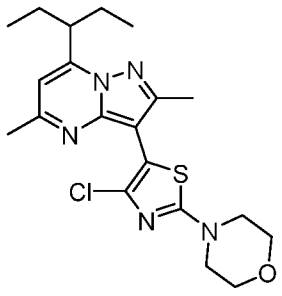
[0011] In some embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl. In some embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0012] In some embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0013] In some embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0014] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

[0015] In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically

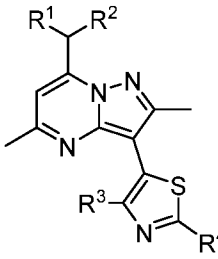
acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0016] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

[0017] In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

[0018] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

[0019] One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:

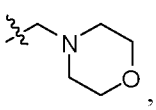
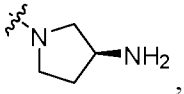
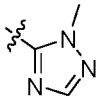
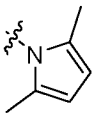


(I), or a pharmaceutically acceptable salt thereof,

wherein:

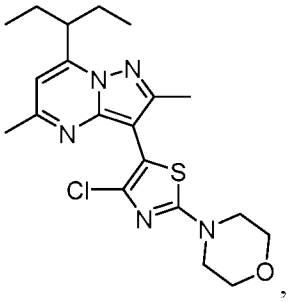
R^1 and R^2 are independently ethyl or n-propyl;

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

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0020] In some embodiments, the compound of Formula (I) has the structure:



, or a pharmaceutically acceptable salt thereof.

[0021] In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0022] In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265

mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

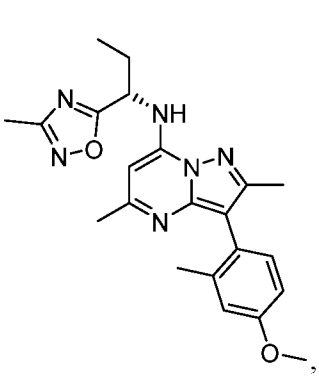
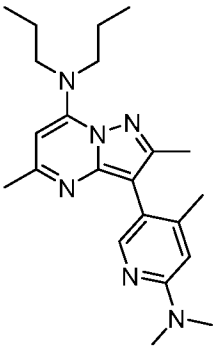
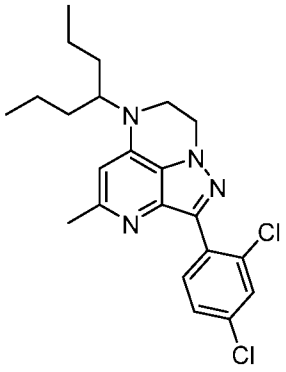
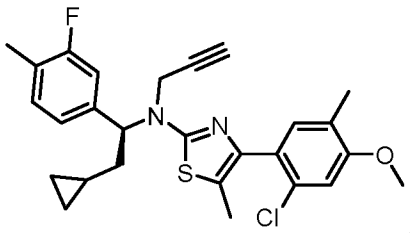
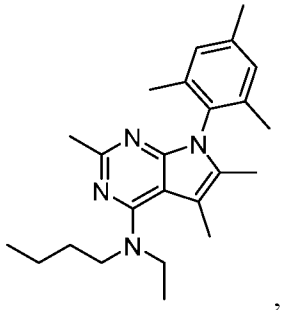
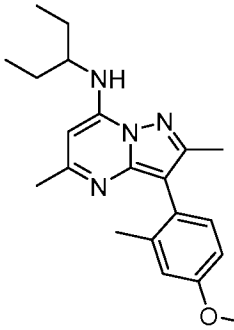
[0023] In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0024] In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

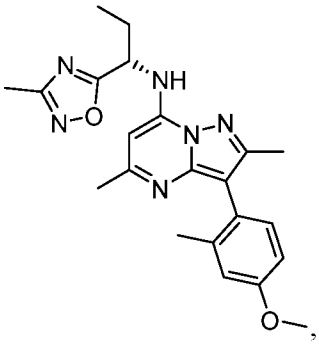
[0025] In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

[0026] In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

[0027] In some embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In some embodiments, the CRF_1 antagonist is




, SSR-126374,


, or

, or a pharmaceutically acceptable salt thereof.

[0028] In some embodiments, the CRF_1 antagonist is


, or a pharmaceutically acceptable salt thereof.

[0029] In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

[0030] In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

[0031] In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with

administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0032] In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0033] In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0034] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0035] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

[0037] FIG. 1A-1B. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics **(A).** A schematic representation of inhibition of CRF_1 with a CRF_1 antagonist (Compound 1) **(B)**.

[0038] FIG. 2. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

[0039] FIG. 3. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

[0040] FIG. 4. Graphic representation of patient-level response (measuring ACTH levels) to a CRF_1 antagonist (Compound 1).

[0041] FIG. 5A-5B. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a CRF_1 antagonist [Patient 10 **(A)**; Patient 8 **(B)**].

[0042] FIG. 6. Graphic representation of patient-level response (measuring 17-OHP levels) to a CRF_1 antagonist (Compound 1).

[0043] FIG. 7A-7B. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a CRF_1 antagonist [Patient 10 **(A)**; Patient 8 **(B)**].

[0044] FIG. 8. Graphic representation of patient-level response (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1).

[0045] FIG. 9A-9B. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1) [Patient 10 **(A)**; Patient 8 **(B)**].

[0046] FIG. 10A-10B. Images of a patient with TART pre-treatment with a CRF_1 antagonist (Compound 1) **(A)** and 6-weeks post-treatment with a CRF_1 antagonist (Compound 1) **(B)**.

[0047] FIG. 11A-11B. Graphic representation of an *in vitro* binding assay of a CRF_1 antagonist (Compound 1); ^{125}I-sauvagine binding to rat cerebellar membranes one hour after oral administration of increasing Compound 1 doses **(A)** and *in vivo* inhibition of CRF-induced activity after treatment with a CRF_1 antagonist; Compound 1 (oral, 10 mg/kg) **(B)**.

[0048] FIG. 12A-12B. Graphic representation of ACTH levels (A) and 17-OHP levels (B) after treatment with a CRF_1 antagonist.

[0049] FIG. 13. Graphic representation of hormone responses after treatment with a CRF_1 antagonist (Compound 1).

[0050] FIG. 14 depicts the proof of concept and escalating QD dosing at 10 pm for Cohort A and the single dose level and BID dosing at 10 am and 10 pm for Cohort B.

[0051] FIG. 15A-15D are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

[0052] FIG. 16A-16D are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

[0053] FIG. 17A-17D are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

DETAILED DESCRIPTION

[0054] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

I. Definitions

[0055] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0056] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0057] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

[0058] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms,

with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0059] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

[0060] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0061] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

[0062] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0063] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0064] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and

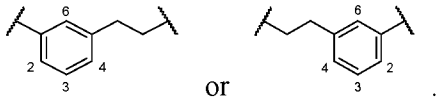
the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

[0065] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0066] The symbol "  " denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0067] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0068] The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



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[0069] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -CHO, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2CH_3$ $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0070] Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0071] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', $-NR''C(O)_2R'$, -NR-C(NR'R''R''')=NR'''', -NR-C(NR'R'')=NR''', $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R''$, $-NRSO_2R'$, –NR'NR''R''', –ONR'R'', –NR'C(O)NR''NR'''R'''', -CN, $-NO_2$, $-NR'SO_2R''$, -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R'', R''', and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' group when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include

groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0072] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", $-NR"C(O)_2R'$, -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'", $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, –NR'NR"R'", –ONR'R", –NR'C(O)NR"NR'"R"", -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

[0073] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the

heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0074] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0075] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C"R"R"')_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R", and R"' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0076] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0077] A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

[0078] A “size-limited substituent” or “ size-limited substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0079] A “lower substituent” or “ lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each

substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0080] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0081] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0082] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some

embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0083] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0084] As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0085] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0086] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0087] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0088] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a

deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0089] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0090] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0091] "Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0092] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0093] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R^{13} substituents are present, each R^{13} substituent may be distinguished as R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc. is defined within the scope of the definition of R^{13} and optionally differently.

[0094] A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

[0095] Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0096] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic,

methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0097] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0098] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

[0099] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0100] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In

general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0101] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0102] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0103] A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

[0104] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and

homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

[0105] A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.*, in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0106] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

[0107] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

[0108] As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

[0109] The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

[0110] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

[0111] The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

[0112] The terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms include any recombinant or naturally-occurring form of CRF_1 variants thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of CRF_1 variants (e.g., frameshift mutations) thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF_1). In embodiments, the

CRF_1 protein encoded by the *CRHR1* gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

[0113] The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

[0114] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

[0115] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer,

premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0116] The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

[0117] "Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

[0118] "Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

[0119] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic

leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[0120] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[0121] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

[0122] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma,

comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

[0123] The terms “treating” or “treatment” refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term “treating” and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

[0124] “Treating” or “treatment” as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject’s condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent

of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (*e.g.*, ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

[0125] "Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

[0126] The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

[0127] "Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0128] An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a

"therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see*, *e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

[0129] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0130] Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based

on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0131] The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

[0132] The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

[0133] The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

[0134] The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

[0135] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0136] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.,* buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.,* intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is

administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.,* by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0137] By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0138] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0139] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

[0140] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

[0141] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

[0142] The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered

either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

[0143] The compounds disclosed herein may be co-administered with an agonist or antagonist of CRF_1 function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

[0144] "Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (*e.g.,* cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (*e.g.,* 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (*e.g.,* vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (*e.g.,* irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.,* doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin,

tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins;

iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate;

sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan;

menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A,

Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, lnanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, lsoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (*e.g.,* dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (*e.g.,* Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (*e.g.,* anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (*e.g.,* anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (*e.g.,* anti-CD20 monoclonal antibody conjugated to ^{111}In, ^{90}Y, or ^{131}I, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa ™), erlotinib (Tarceva ™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-

380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0145] "Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0146] The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoli- n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli- n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family; (v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a

compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin .alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

[0147] In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax I1-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

[0148] In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

[0149] In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{89}Sr, ^{86}Y, ^{87}Y, ^{90}Y, ^{105}Rh, ^{111}Ag, ^{111}In, ^{117m}Sn, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi, optionally conjugated to antibodies directed against tumor antigens.

[0150] In addition, a CRF_1 inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

[0151] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

[0152] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

[0153] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered once daily until study reached endpoint. The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

[0154] The methods disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

[0155] A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaroytic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, spodoptera) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

[0156] "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

[0157] The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a CRF1 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with CRF_1 (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A CRF_1 modulator is a compound that increases or decreases the activity or function or level of activity or level of function of CRF_1. A modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

[0158] The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of CRF_1, either directly or indirectly, relative to the absence of the molecule.

[0159] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with CRF_1 activity, a CRF_1 associated disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in

whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with CRF_1 activity or function may be an endocrine disorder that results (entirely or partially) from aberrant CRF_1 function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant CRF_1 activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., CRF_1 modulator, CRF_1 inhibitor, or CRF_1 antagonist), in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated endocrine disorder, may be treated with an CRF_1 modulator or CRF_1 inhibitor, in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease.

[0160] The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

[0161] The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a CRF_1 with a compound as described herein may reduce the level of a product of the CRF_1 catalyzed reaction or the level of a downstream derivative of the product or binding may reduce the interactions between the CRF_1 or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

[0162] As used herein, the terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the CRF_1 receptor in an *in vitro* assay, an *in vivo* model, and/or other

means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

[0163] The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

[0164] The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

[0165] "Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

[0166] The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In embodiments, the antibody will have an affinity that is greater than about 10^9 liters/mol, as determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

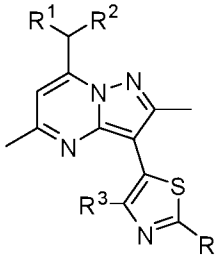
[0167] The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA), complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

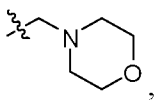
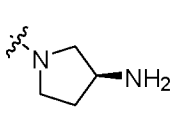
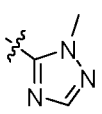
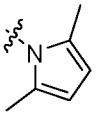
[0168] As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

[0169] The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

II. Compounds

[0170] In an aspect provided herein, is a compound of Formula (I):

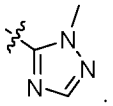


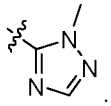
, or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . R^a and R^b are independently hydrogen, C_1-C_3alkyl,

$H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

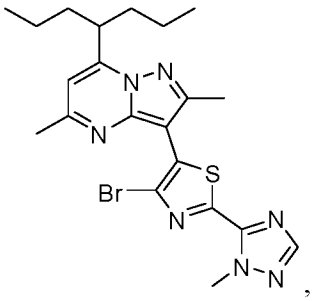
[0171] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

[0172] In certain embodiments, R^3 is Cl, Br, or methyl.

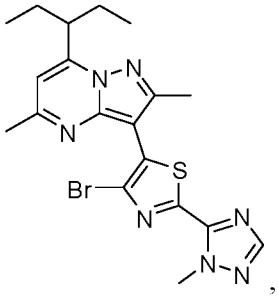
[0173] In certain embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

[0174] In certain embodiments, R^4 is morpholin-4-yl or  .

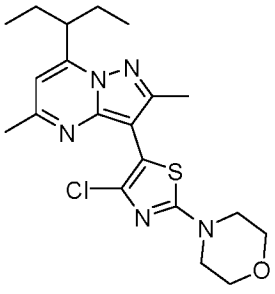
[0175] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

[0176] In certain embodiments, the compound is  , or a pharmaceutically acceptable salt thereof.

[0177] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0178] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0179] In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof.

An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

[0180] In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

[0181] In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

[0182] In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

III. Pharmaceutical Compositions

[0183] In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

[0184] The compounds (e.g., CRF_1 inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., CRF_1 inhibitor(s)/ antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., CRF_1 inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the

pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

[0185] In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

[0186] The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

[0187] The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of CRF_1 function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[0188] The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use

of hydroxymethylcellulose or gelatin-microcapsules or poly(methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

[0189] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0190] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

[0191] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

[0192] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

[0193] The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from

fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

[0194] The pharmaceutical compositions typically comprise a therapeutically effective amount of a CRF_1 inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

[0195] After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

[0196] Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a CRF_1

inhibitor/antagonist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

[0197] Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., CRF_1 inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

[0198] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

[0199] The present disclosure contemplates the administration of the compound (e.g., CRF_1 inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

[0200] The compound (e.g., CRF_1 inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

IV. Methods

[0201] In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0202] In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0203] In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0204] In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix,

uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

[0205] In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinemia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, aligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal

cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcorna; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but not limited to, renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (*See* Fishman *et al.*, 1985, *Medicine*, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy *et al.*, 1997, *Informed Decisions:*

The Complete Book of Cancer Diagnosis, Treatment, and Recovery, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

[0206] Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

[0207] The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

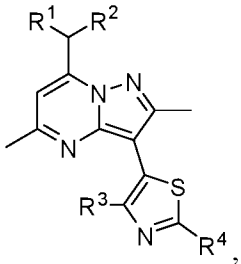
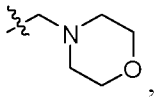
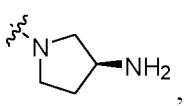
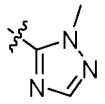
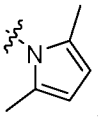
[0208] In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

[0209] In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

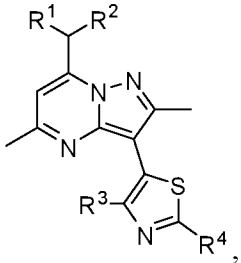
[0210] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0211] In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

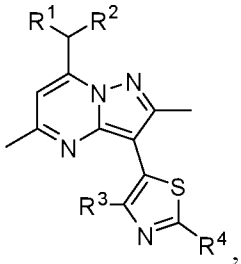
[0212] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):

 , or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0213] In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):

 , or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments.

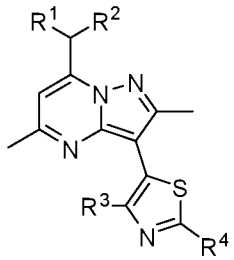
[0214] In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):

 , or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 70% of the subjects demonstrate reduction in

ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

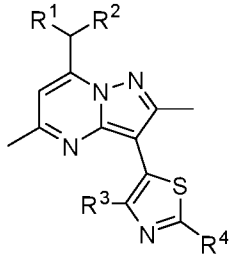
[0215] In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

[0216] In an aspect provided herein, is a method of decreasing or reducing 17α-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):



, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least about 30% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

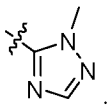
[0217] In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

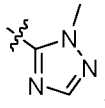


, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

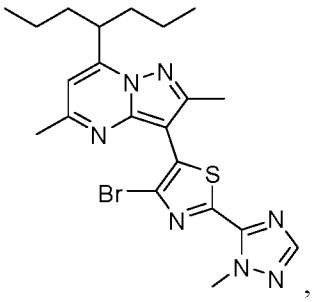
[0218] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

[0219] In certain embodiments, R^3 is Cl, Br, or methyl.

[0220] In certain embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

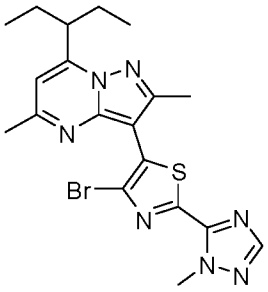
[0221] In certain embodiments, R^4 is morpholin-4-yl or  .

[0222] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.



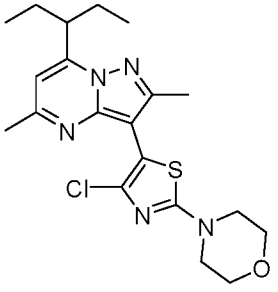
[0223] In certain embodiments, the compound is , or a pharmaceutically acceptable salt thereof.

[0224] In certain embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0225] In certain embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0226] In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is cyclically administered to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

[0227] In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg,

from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

[0228] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

[0229] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

[0230] For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about

350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about

310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg,

about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

[0231] In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate,

hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

[0232] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

[0233] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least

about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

[0234] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily

for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily

for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

[0235] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330

mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

[0236] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula

(I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

[0237] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230

mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

[0238] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula

(I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

[0239] In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200

mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

[0240] In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0241] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

[0242] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

[0243] In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

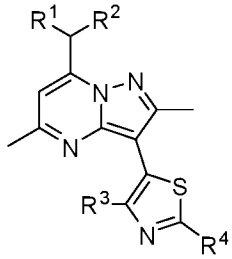
[0244] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject.In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0245] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

[0246] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

[0247] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

[0248] In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I): and a pharmaceutically acceptable excipientcomprising with a compound as described herein, including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3, and R^4 are as described herein, including embodiments.

[0249] In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments,

the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0250] In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0251] In certain embodiments, the pharmaceutical composition is administered orally.

[0252] In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0253] In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically

acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0254] In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0255] In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

[0256] In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

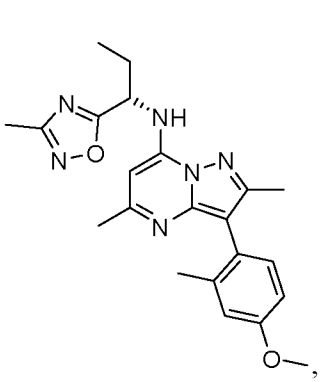
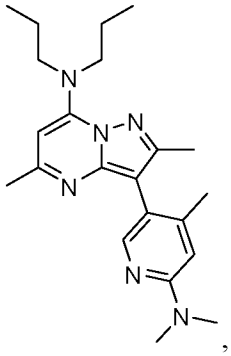
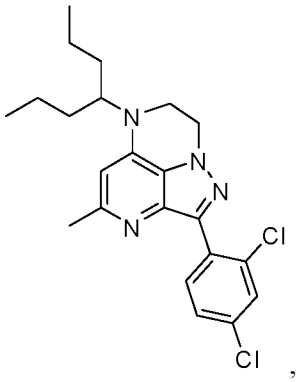
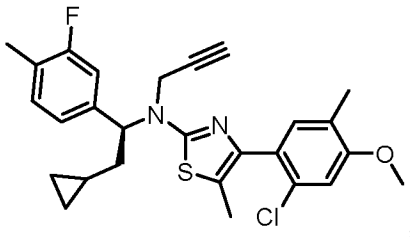
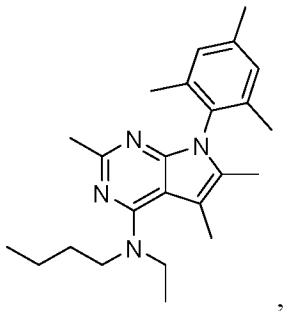
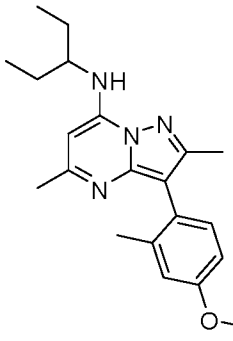
[0257] In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

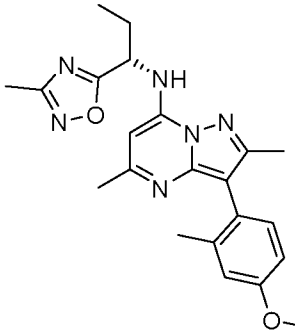
[0258] In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

[0259] In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

[0260] In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

[0261] In certain embodiments, the the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In certain embodiments, the CRF_1 antagonist is:


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, SSR-126374,

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, or

, or a pharmaceutically acceptable salt thereof. In certain embodiments, the CRF_1 antagonist is


, or a pharmaceutically acceptable salt thereof.

[0262] In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior

to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0263] In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0264] In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

[0265] In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

[0266] In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

[0267] The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, 2nd Edition, Rathbone *et al.*, Eds., Marcel Dekker, Inc.: New York, NY, 2008).

[0268] The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

[0269] The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

[0270] In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

[0271] The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage

forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[0272] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[0273] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[0274] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange

resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[0275] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[0276] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add,

sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[0277] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[0278] The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[0279] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0280] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a

preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[0281] Coloring and flavoring agents can be used in all of the above dosage forms.

[0282] The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

[0283] The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[0284] The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[0285] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[0286] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil,

hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methy1-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[0287] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl-and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[0288] When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[0289] In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[0290] The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[0291] The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[0292] Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and metliacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[0293] Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

V. Examples

[0294] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

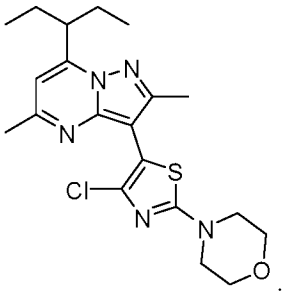
Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

[0295] Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)–driven

overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

[0296] Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 (CRF_1) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH (FIG. 12A-12B). Compound 1 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

[0297] The structure of Compound 1 is:



[0298] Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will

receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

[0299] The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

[0300] The specification of study drug dosing at 10pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma C_{max} (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. (**FIGS. 1A-1B**).

Objectives	Endpoints
Primary	
• To assess the efficacy of Compound 1 in subjects with TART	• Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12
Secondary	
• To evaluate the safety of Compound 1 in subjects with TART	• Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs) • Physical examination findings • Vital signs • Changes in electrocardiogram (ECG) • Changes in clinical laboratory values
• To assess the pharmacodynamic (PD) biomarker effects of Compound 1	• Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH),

	follicle-stimulating hormone (FSH), inhibin B, sex hormone–binding globulin (SHBG), renin, and aldosterone from baseline to Week 12
• To assess changes on semen analysis	• Changes in sperm count, morphology, and motility from baseline to Week 12
• To assess changes in metabolism	• Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12 • Changes in body weight, body mass index (BMI), waist circumference, and blood pressure
• To evaluate changes in quality of life (QoL) and mood	• Changes in QoL measured using the Short Form 36 (SF-36) • Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS)

Study Population

[0301] Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

Eligibility Criteria

Inclusion Criteria

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with ≥1 lesion(s) measuring ≥2 cm in diameter
- On a stable regimen of GC replacement for ≥30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria

- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:

- A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
- Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2
- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
- Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)

- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months
- HADS score >12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at screening and baseline (eg, C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:
  - Clinically meaningful abnormal ECG results, in the opinion of the Investigator
  - Fridericia-corrected QT interval (QTcF) >450 msec
  - Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
  - Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be

withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.

- Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

Study Duration

[0302] The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of ≤4 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

Study Design

[0303] This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks.In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

Dose, Route, Regimen

[0304] All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

[0305] On mornings of study visits with 8am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6am and 8am).

[0306] If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

Investigational Drug

[0307] Compound 1 is a small-molecule CRF_1 receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

Example 2.

[0308] Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a small-molecule antagonist of the CRF_1 receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been

validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B). The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

Nonclinical Toxicology of Compound 1

[0309] The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

[0310] Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70 days before mating, during mating, and ≤4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

[0311] In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

Clinical Experience with Compound 1

[0312] To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

[0313] An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (**FIGS. 2-3**).

Known Potential Risks

[0314] Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to monitor the risk of testicular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

[0315] Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

[0316] Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

Known Potential Benefits

[0317] Early clinical studies suggests that Compound 1 is effective as a CRF_1 receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B).

Assessment of Potential Risks and Benefits

[0318] The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a CRF_1 receptor antagonist, Compound 1 is intended to reduce

abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

[0319] Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

Example 3. Congenital Andrenal Hyperplasia (CAH)

[0320] CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks CRF_1 receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

[0321] As shown in **FIGS. 4** and **5A-5B**, the attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated > 25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a CRF_1 receptor antagonist.

[0322] **FIGS. 6** and **7A-7B** demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated > 25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a CRF_1 receptor antagonist.

[0323] **FIGS. 8** and **9A-9B** demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess andreogen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated > 25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a CRF_1 receptor antagonist.

[0324] FIGS. 10A-10B show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF_1 receptor antagonist.

[0325] FIGS. 11A-11B demonstrate Compound 1 is a potent, selective, and functional CRF_1 receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective CRF_1 receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity (CRF_1 receptor-mediated downstream cascade), demonstrating in vitro efficacy as a CRF_1 receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.c.v. administration of CRF (**FIG. 11B**).

[0326] FIGS. 12A-12B demonstrate single pill of CRF_1 receptor antagonist (i.e., as described in US 2017/0020877 A1) improves ACTH and 17-OHP in CAH patients.

[0327] FIG. 13 shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a CRF_1 receptor antagonist.

Example 4. Assess reduction in excess ACTH and adrenal steroid production

[0328] The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and tolerability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

ELIGIBILITY CRITERIA

[0329] Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP ≥800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for ≥30 days before enrollment

[0330] Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

STUDY DESIGN

[0331] FIG. 14 depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

BASELINE CHARACTERISTICS

[0332] Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 partcipants were enrolled and received at least 1 dose of Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

Table 1 – Baseline characteristics of each cohort

Parameter	Cohort A (n=10)	Cohort B (n=8)
Demographics		
Age (years), mean (range)	39.3 (24-66)	36.8 (19-66)
Sex	5M, 5F	1M, 7F
Bmi (kg/m^2), mean ± SD	31.5 ± 12.0	31.1 ± 6.7
Daily GC dose (mg HC equivalents), mean range	28 (13-40)	35 (20-50)
Types of GCs	4 JC, 3 pred, 3 dex	2HC, 4 pred, 3 dex
17OHP at screening[a] (ng/dl), mean ± SD	5,985 ± 6,347	4,592 ±4,624

Abbreviations: 17OHP: 17-hydroxyprogesterone; BMI: body mass index; dex: dexamethasone; F: female; GC: glucocorticoid; HC: hydrocortisone; M: male; pred: prednisone; SD: standard deviation.
a 17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females.

SAFETY

[0333] Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

PHARMACOKINETICS

[0334] Over a wide range of doses (200 to 1000 mg QD), Compound 1exhibited a predictable, dose-dependent PK profile.

EFFICACY

[0335] FIG. 15A-15D show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

[0336] FIG. 16A-16D show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

[0337] FIG. 17A-17D show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at ≥1 dose level for 8 out of 10 participants in

Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and fucntional CRF_1 receptor antagonism.

Table 2 – Percentage change from baseline in ACTH, 17OHP and A4.

	Cohort A			Cohort B
	200 mg QD (Week 2)	600 mg QD (Week 4)	1000 mg QD (Week 6)	200 mg BID (Weed 2)
ACTH	-25.7 (±51.6)	-60.1 (±37.5)	-32.7 (±47.0)	-36.5 (±58.0)
17OHP	+22.2 (±172.3)	-23.7 (±64.2)	-13.8 (±74.7)	-47.8 (±63.3)
A4	-12.1 (±47.4)	-33.2 (±36.5)	-28.6 (±44.6)	-16.0 (±81.4)

CONCLUSIONS

[0338] Compound 1, a potent and selective CRF_1 receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAH. Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

[0339] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

ABSTRACT OF THE DISCLOSURE

Provided herein are compounds and pharmaceutical compositions for the prevention and treatment of testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART).

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

CROSS-REFERENCE

[0001] This application is a continuation of U.S. Application No. 18/941,832, filed November 8, 2024, which is a continuation of U.S. Application No. 17/667,285, filed on February 8, 2022, which is a continuation of U.S. Application No. 17/081,694 filed on October 27, 2020, which issued as U.S. Pat. No. 11,304,950 on April 19, 2022, and which is a continuation of International Application No. PCT/US2019/029486 filed on April 26, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019, each of which is entirely incorporated herein by reference.

BACKGROUND

[0002] Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

[0003] CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

[0004] Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, *inter alia*, are solutions to these and other problems in the art.

SUMMARY

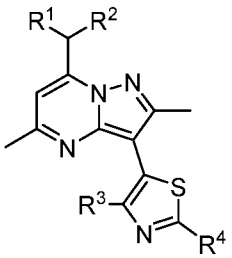
[0005] Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

[0006] Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

[0007] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0008] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

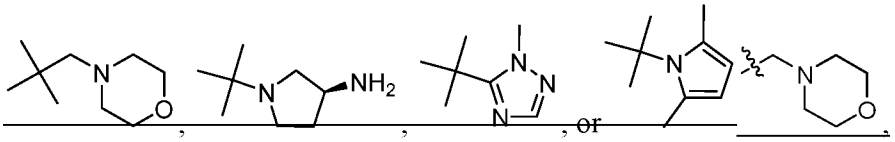
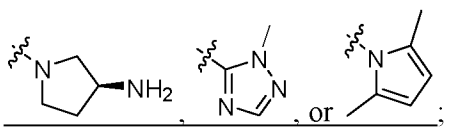
[0009] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):


(I), or a pharmaceutically acceptable salt thereof,

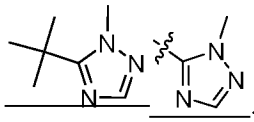
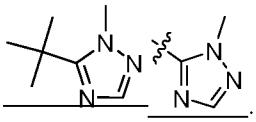
wherein:

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

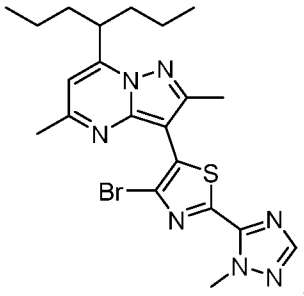
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  , or  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

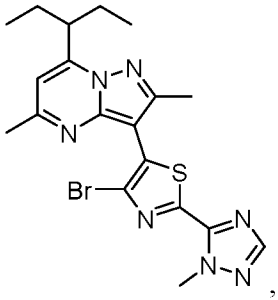
[0010] In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl. In some embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or  .

[0011] In some embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl. In some embodiments, the compound is



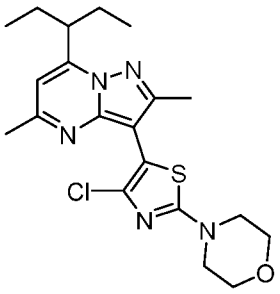
, or a pharmaceutically acceptable salt thereof.

[0012] In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0013] In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0014] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

[0015] In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a

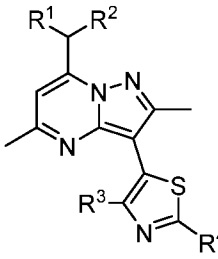
pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0016] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

[0017] In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

[0018] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

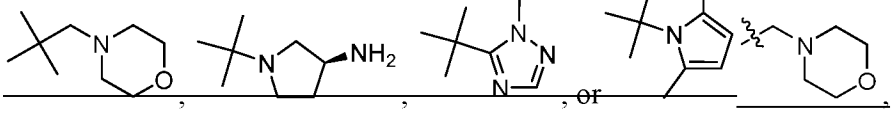
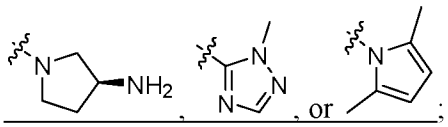
[0019] One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:


(I), or a pharmaceutically acceptable salt thereof,

wherein:

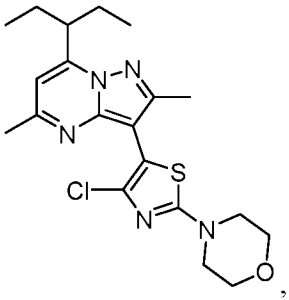
R^1 and R^2 are independently ethyl or n-propyl;

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

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  , or  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0020] In some embodiments, the compound of Formula (I) has the structure:


, or a pharmaceutically acceptable salt thereof.

[0021] In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0022] In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

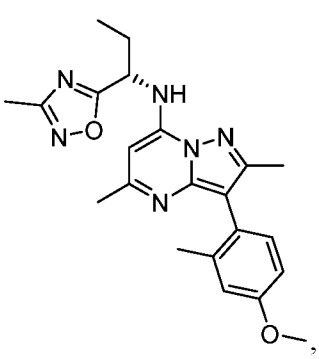
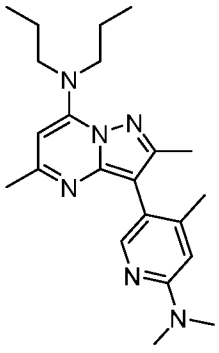
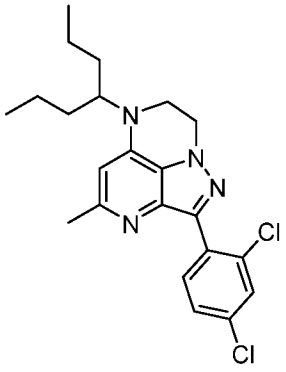
[0023] In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

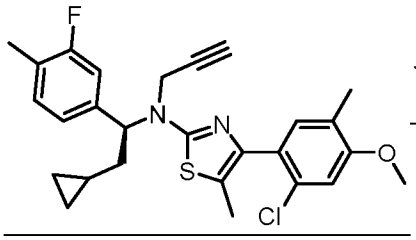
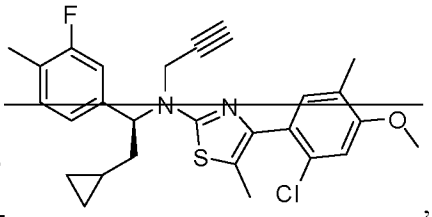
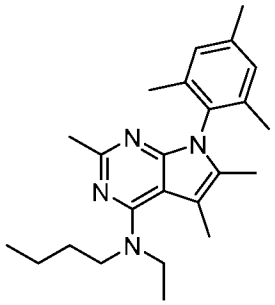
[0024] In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

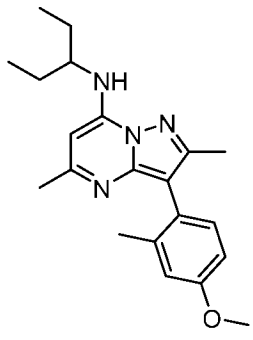
[0025] In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

[0026] In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

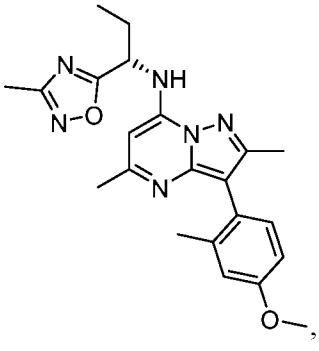
[0027] In some embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In some embodiments, the CRF_1 antagonist is




, SSR-126374,




, or


, or a pharmaceutically acceptable salt thereof.

[0028] In some embodiments, the CRF_1 antagonist is


, or a pharmaceutically acceptable salt thereof.

[0029] In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

[0030] In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural

Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

[0031] In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0032] In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0033] In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0034] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0035] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

[0037] FIG. 1A-1B. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics **(A).** A schematic representation of inhibition of CRF_1 with a CRF_1 antagonist (Compound 1) **(B)**.

[0038] FIG. 2. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

[0039] FIG. 3. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

[0040] FIG. 4. Graphic representation of patient-level response (measuring ACTH levels) to a CRF_1 antagonist (Compound 1).

[0041] FIG. 5A-5B. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a CRF_1 antagonist [~~Subject 003001~~Patient 10 **(A)**; ~~Subject 007002~~ Patient 8 **(B)**].

[0042] FIG. 6. Graphic representation of patient-level response (measuring 17-OHP levels) to a CRF_1 antagonist (Compound 1).

[0043] FIG. 7A-7B. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a CRF_1 antagonist [~~Subject 003001~~Patient 10 **(A)**; ~~Subject 007002~~ Patient 8 **(B)**].

[0044] FIG. 8. Graphic representation of patient-level response (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1).

[0045] FIG. 9A-9B. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1) [~~Subject 003001~~Patient 10 **(A)**; ~~Subject 007002~~ Patient 8 **(B)**].

[0046] FIG. 10A-10B. Images of a patient with TART pre-treatment with a CRF_1 antagonist (Compound 1) **(A)** and 6-weeks post-treatment with a CRF_1 antagonist (Compound 1) **(B)**.

[0047] FIG. 11A-11B. Graphic representation of an *in vitro* binding assay of a CRF_1 antagonist (Compound 1); ^{125}I-sauvagine binding to rat cerebellar membranes one hour after oral

administration of increasing Compound 1 doses **(A)** and *in vivo* inhibition of CRF-induced activity after treatment with a CRF_1 antagonist; Compound 1 (oral, 10 mg/kg) **(B)**.

[0048] FIG. 12A-12B. ~~Graphic representation of ACTH levels **(A)** and 17-OHP levels **(B)** after treatment with a CRF_1 antagonist (Compound 1)~~ Graphic representation of ACTH levels (A) and 17-OHP levels (B) after treatment with a CRF_1 antagonist.

[0049] FIG. 13. Graphic representation of hormone responses after treatment with a CRF_1 antagonist (Compound 1).

[0050] FIG. 14 depicts the proof of concept and escalating QD dosing at 10 pm for Cohort A and the single dose level and BID dosing at 10 am and 10 pm for Cohort B.

[0051] FIG. 15A-15D are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

[0052] FIG. 16A-16D are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

[0053] FIG. 17A-17D are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

DETAILED DESCRIPTION

[0054] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

I. Definitions

[0055] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0056] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0057] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl,

sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

[0058] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -$CH_2CH_2CH_2CH_2$-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0059] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -CH_2-CH_2-O-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-CH_2-N(CH_3)-CH_3, -CH_2-S-CH_2-CH_3, -CH_2-CH_2, -S(O)-CH_3, -CH_2-CH_2-S(O)$_2$-CH_3, -CH=CH-O-CH_3, -Si(CH_3)$_3$, -CH_2-CH=N-OCH_3, -CH=CH-N(CH_3)-CH_3, -O-CH_3, -O-CH_2-CH_3, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3 and -CH_2-O-Si(CH_3)$_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

[0060] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH_2-CH_2-S-CH_2-CH_2- and -CH_2-S-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and

heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0061] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

[0062] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0063] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0064] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term

"heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

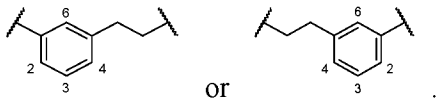
[0065] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted

heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0066] The symbol "" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0067] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0068] The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



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[0069] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -CHO, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2CH_3$ $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $–NHNH_2$, $–ONH_2$, $–NHC(O)NHNH_2$, substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0070] Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0071] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', $-NR"C(O)_2R'$, -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, –NR'NR"R"', –ONR'R", –NR'C(O)NR"NR"'R"", -CN, $-NO_2$, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R"', and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or

unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0072] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", $-NR"C(O)_2R'$, -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'", -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, –NR'NR"R'", –ONR'R", –NR'C(O)NR"NR'"R"", -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

[0073] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic

ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0074] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0075] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C''R''R''')_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R'', and R''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0076] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0077] A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

[0078] A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or

unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0079] A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0080] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0081] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0082] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0083] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0084] As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0085] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0086] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0087] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0088] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0089] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0090] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0091] "Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0092] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0093] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one

R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R^{13} substituents are present, each R^{13} substituent may be distinguished as R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc. is defined within the scope of the definition of R^{13} and optionally differently.

[0094] A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

[0095] Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0096] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of

pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0097] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0098] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

[0099] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present

invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0100] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0101] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0102] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0103] A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

[0104] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and

"protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

[0105] A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.*, in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0106] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

[0107] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

[0108] As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

[0109] The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity

is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

[0110] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

[0111] The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

[0112] The terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms include any recombinant or naturally-occurring form of CRF_1 variants thereof that maintain

CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of CRF_1 variants (e.g., frameshift mutations) thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF_1). In embodiments, the CRF_1 protein encoded by the *CRHR1* gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

[0113] The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

[0114] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

[0115] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung

adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0116] The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

[0117] "Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

[0118] "Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

[0119] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia,

hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[0120] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[0121] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

[0122] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma,

carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

[0123] The terms “treating” or “treatment” refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term “treating” and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

[0124] "Treating" or "treatment" as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (*e.g.*, ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

[0125] "Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

[0126] The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

[0127] "Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0128] An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is

administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see*, *e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

[0129] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0130] Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above.

Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0131] The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

[0132] The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

[0133] The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

[0134] The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

[0135] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0136] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.,* buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.,* intravenous, intramuscular, intra-arteriole,

intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.,* by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.*

46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0137] By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0138] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0139] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

[0140] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

[0141] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

[0142] The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

[0143] The compounds disclosed herein may be co-administered with an agonist or antagonist of CRF_1 function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

[0144] "Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (*e.g.,* cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (*e.g.,* 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (*e.g.,* vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (*e.g.,* irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.,* doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-

9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene;

idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence

derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole

hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e.

LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, lnanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, lsoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (*e.g.,* dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (*e.g.,* Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (*e.g.,* anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (*e.g.,* anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (*e.g.,* anti-CD20 monoclonal antibody conjugated to ^{111}In, ^{90}Y, or ^{131}I, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa ™), erlotinib (Tarceva ™), cetuximab (Erbitux™), lapatinib

(Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0145] "Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0146] The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoli- n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli- n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family; (v)

an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin .alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

[0147] In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax I1-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

[0148] In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

[0149] In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{89}Sr, ^{86}Y, ^{87}Y, ^{90}Y, ^{105}Rh, ^{111}Ag, ^{111}In, ^{117m}Sn, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi, optionally conjugated to antibodies directed against tumor antigens.

[0150] In addition, a CRF_1 inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the

above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

[0151] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

[0152] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

[0153] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered once daily until study reached endpoint. The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

[0154] The methods disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

[0155] A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaroytic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, spodoptera) and

human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

[0156] "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

[0157] The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a CRF1 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with CRF_1 (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A CRF_1 modulator is a compound that increases or decreases the activity or function or level of activity or level of function of CRF_1. A modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

[0158] The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of CRF_1, either directly or indirectly, relative to the absence of the molecule.

[0159] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with CRF_1 activity, a CRF_1 associated disease (e.g., testicular

adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with CRF_1 activity or function may be an endocrine disorder that results (entirely or partially) from aberrant CRF_1 function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant CRF_1 activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., CRF_1 modulator, CRF_1 inhibitor, or CRF_1 antagonist), in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated endocrine disorder, may be treated with an CRF_1 modulator or CRF_1 inhibitor, in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease.

[0160] The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

[0161] The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a CRF_1 with a compound as described herein may reduce the level of a product of the CRF_1 catalyzed reaction or the level of a downstream derivative of the product or binding may reduce the interactions between the CRF_1 or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

[0162] As used herein, the terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted

terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the CRF_1 receptor in an *in vitro* assay, an *in vivo* model, and/or other means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

[0163] The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

[0164] The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

[0165] "Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

[0166] The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In embodiments, the antibody will have an affinity that is greater than about 10^9 liters/mol, as determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

[0167] The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA),

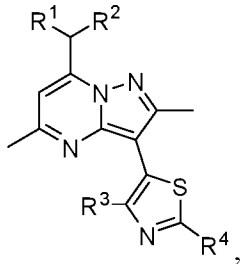
complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

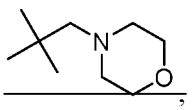
[0168] As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

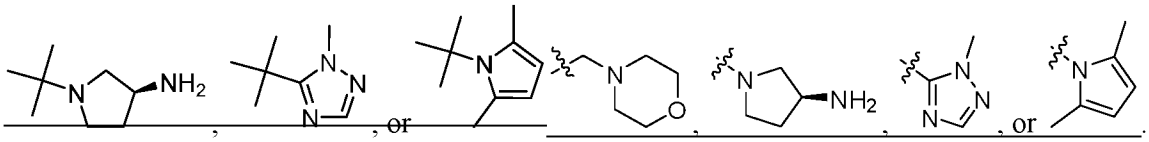
[0169] The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

II. Compounds

[0170] In an aspect provided herein, is a compound of Formula (I):



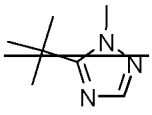
, or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,

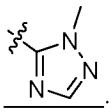


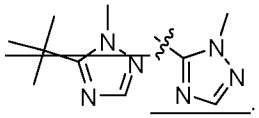
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

[0171] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

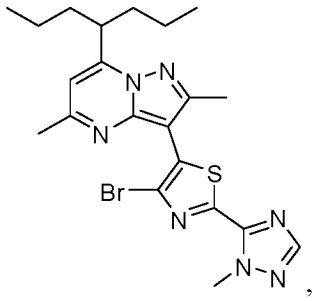
[0172] In certain embodiments, R^3 is Cl, Br, or methyl.

[0173] In certain embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or 

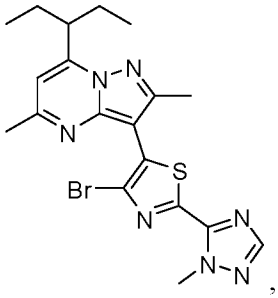


[0174] In certain embodiments, R^4 is morpholin-4-yl or  .

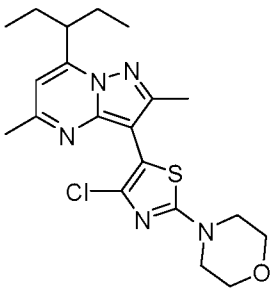
[0175] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

[0176] In certain embodiments, the compound is  , or a pharmaceutically acceptable salt thereof.

[0177] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0178] In certain embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0179] In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

[0180] In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

[0181] In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

[0182] In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

III. Pharmaceutical Compositions

[0183] In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

[0184] The compounds (e.g., CRF_1 inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., CRF_1 inhibitor(s)/ antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., CRF_1 inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

[0185] In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

[0186] The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

[0187] The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of CRF_1 function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[0188] The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for

controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly(methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

[0189] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0190] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

[0191] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

[0192] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting

agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

[0193] The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

[0194] The pharmaceutical compositions typically comprise a therapeutically effective amount of a CRF_1 inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

[0195] After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container

(e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

[0196] Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a CRF_1 inhibitor/antagonist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

[0197] Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., CRF_1 inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

[0198] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

[0199] The present disclosure contemplates the administration of the compound (e.g., CRF_1 inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

[0200] The compound (e.g., CRF_1 inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

IV. Methods

[0201] In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0202] In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0203] In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are

methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0204] In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix, uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

[0205] In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinemia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, aligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and

inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonserninoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcorna; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but not limited to, renal cell

cancer, adenocarcinoma, hypernephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (*See* Fishman *et al.*, 1985, *Medicine*, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy *et al.*, 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

[0206] Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

[0207] The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

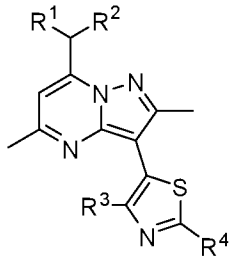
[0208] In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

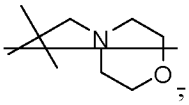
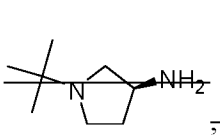
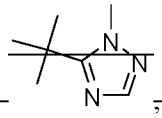
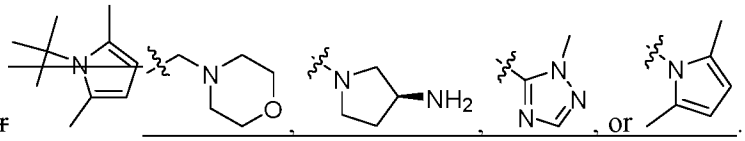
[0209] In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

[0210] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0211] In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

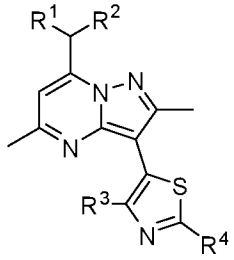
[0212] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):



, or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , ~~or~~  .

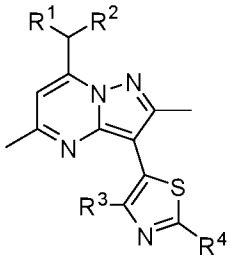
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0213] In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



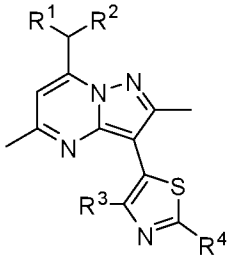
, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments.

[0214] In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):

 , or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 70% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

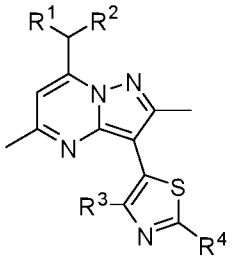
[0215] In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

[0216] In an aspect provided herein, is a method of decreasing or reducing 17α-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

 , or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least about 30% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 40% of subjects were in the standard

or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

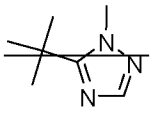
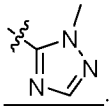
[0217] In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

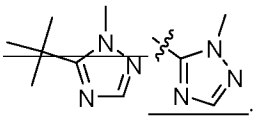


, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

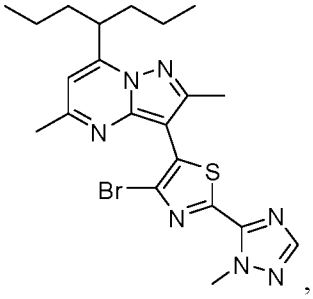
[0218] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

[0219] In certain embodiments, R^3 is Cl, Br, or methyl.

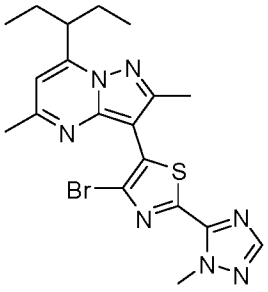
[0220] In certain embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or   .

[0221] In certain embodiments, R^4 is morpholin-4-yl or  .

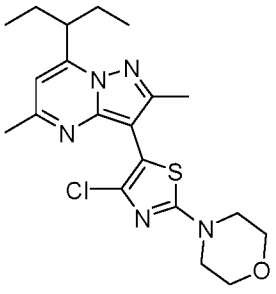
[0222] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

[0223] In certain embodiments, the compound is  , or a pharmaceutically acceptable salt thereof.

[0224] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0225] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0226] In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is cyclically administered

to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

[0227] In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg, from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55

mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

[0228] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic

variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

[0229] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

[0230] For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the

pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In

certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg,

about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg,

about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

[0231] In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In

some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the

compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

[0232] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

[0233] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the

compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

[0234] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug

thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain

embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or

prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

[0235] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt,

solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28

days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

[0236] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at

least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

[0237] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for

a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for

a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

[0238] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330

mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

[0239] In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

[0240] In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0241] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

[0242] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

[0243] In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0244] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of

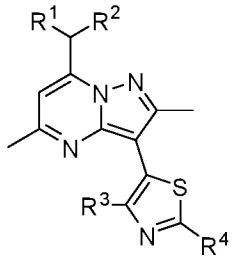
Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject.In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0245] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

[0246] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

[0247] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

[0248] In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I): and a pharmaceutically acceptable excipientcomprising with a compound as described herein, including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3, and R^4 are as described herein, including embodiments.

[0249] In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0250] In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0251] In certain embodiments, the pharmaceutical composition is administered orally.

[0252] In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360

mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0253] In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0254] In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0255] In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

[0256] In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the

pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

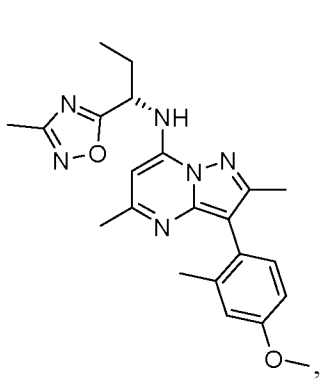
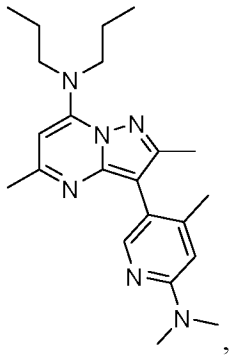
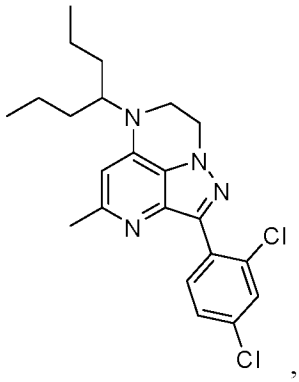
[0257] In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

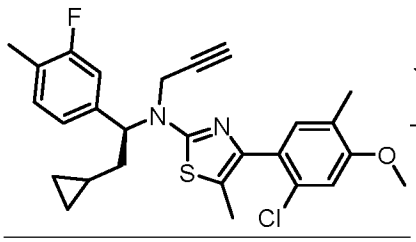
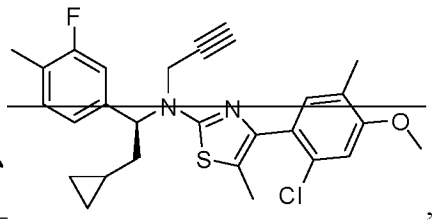
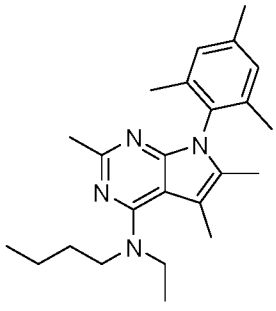
[0258] In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

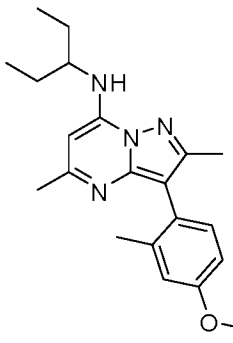
[0259] In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

[0260] In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

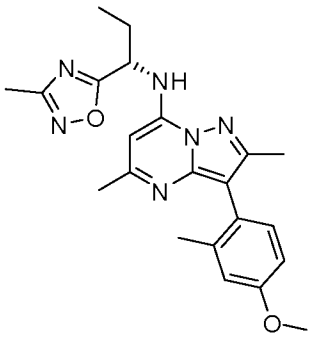
[0261] In certain embodiments, the the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In certain embodiments, the CRF_1 antagonist is:




, SSR-126374,




, or



, or a pharmaceutically acceptable salt thereof. In certain embodiments, the CRF_1 antagonist is



, or a pharmaceutically acceptable salt thereof.

[0262] In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0263] In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is

concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0264] In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

[0265] In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

[0266] In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

[0267] The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, 2nd Edition, Rathbone *et al.*, Eds., Marcel Dekker, Inc.: New York, NY, 2008).

[0268] The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s)

sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

[0269] The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

[0270] In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

[0271] The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[0272] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage

of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[0273] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[0274] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[0275] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil,

including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[0276] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[0277] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[0278] The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients

from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[0279] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0280] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[0281] Coloring and flavoring agents can be used in all of the above dosage forms.

[0282] The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

[0283] The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral

administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[0284] The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[0285] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[0286] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methy1-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[0287] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl-and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable

emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[0288] When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[0289] In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[0290] The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[0291] The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[0292] Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and metliacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[0293] Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

V. Examples

[0294] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

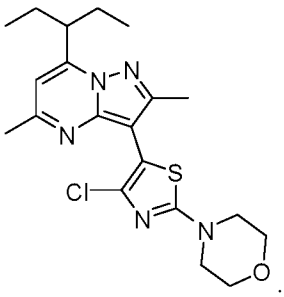
Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

[0295] Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)–driven overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

[0296] Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 (CRF_1) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH (FIG. 12A-12B). Compound 1 has been

shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

[0297] The structure of Compound 1 is:



[0298] Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

[0299] The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

[0300] The specification of study drug dosing at 10pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma C_{max} (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. (**FIGS. 1A-1B**).

Objectives	Endpoints
Primary	
• To assess the efficacy of Compound 1 in subjects with TART	• Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12
Secondary	
• To evaluate the safety of Compound 1 in subjects with TART	• Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs) • Physical examination findings • Vital signs • Changes in electrocardiogram (ECG) • Changes in clinical laboratory values
• To assess the pharmacodynamic (PD) biomarker effects of Compound 1	• Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone–binding globulin (SHBG), renin, and aldosterone from baseline to Week 12
• To assess changes on semen analysis	• Changes in sperm count, morphology, and motility from baseline to Week 12
• To assess changes in metabolism	• Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12 • Changes in body weight, body mass index (BMI), waist circumference, and blood pressure
• To evaluate changes in quality of life (QoL) and mood	• Changes in QoL measured using the Short Form 36 (SF-36) • Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS)

Study Population

[0301] Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

Eligibility Criteria

Inclusion Criteria

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with ≥1 lesion(s) measuring ≥2 cm in diameter
- On a stable regimen of GC replacement for ≥30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria

- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
  - A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
  - Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2
  - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
  - Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months
- HADS score >12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at screening and baseline (eg,

C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)

- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:
  - Clinically meaningful abnormal ECG results, in the opinion of the Investigator
  - Fridericia-corrected QT interval (QTcF) >450 msec
  - Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
  - Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
- Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

Study Duration

[0302] The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of ≤4 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

Study Design

[0303] This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks.In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

Dose, Route, Regimen

[0304] All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

[0305] On mornings of study visits with 8am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6am and 8am).

[0306] If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

Investigational Drug

[0307] Compound 1 is a small-molecule CRF_1 receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

Example 2.

[0308] Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a small-molecule antagonist of the CRF_1 receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B). The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

Nonclinical Toxicology of Compound 1

[0309] The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

[0310] Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70

days before mating, during mating, and ≤4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

[0311] In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

Clinical Experience with Compound 1

[0312] To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

[0313] An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (**FIGS. 2-3**).

Known Potential Risks

[0314] Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to

monitor the risk of testicular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

[0315] Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

[0316] Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

Known Potential Benefits

[0317] Early clinical studies suggests that Compound 1 is effective as a CRF_1 receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B).

Assessment of Potential Risks and Benefits

[0318] The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a CRF_1 receptor antagonist, Compound 1 is intended to reduce abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

[0319] Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

Example 3. Congenital Andrenal Hyperplasia (CAH)

[0320] CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks CRF_1 receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

[0321] As shown in **FIGS. 4** and **5A-5B**, the attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated > 25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a CRF_1 receptor antagonist.

[0322] **FIGS. 6** and **7A-7B** demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated > 25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a CRF_1 receptor antagonist.

[0323] **FIGS. 8** and **9A-9B** demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess andreogen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated > 25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a CRF_1 receptor antagonist.

[0324] **FIGS. 10A-10B** show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF_1 receptor antagonist.

[0325] **FIGS. 11A-11B** demonstrate Compound 1 is a potent, selective, and functional CRF_1 receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective CRF_1 receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity (CRF_1 receptor-mediated downstream cascade), demonstrating in vitro efficacy as a CRF_1 receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.c.v. administration of CRF (**FIG. 11B**).

[0326] ~~**FIGS. 12A-12B** demonstrate single pill of CRF_1 receptor antagonist improves ACTH and 17-OHP in CAH patients.~~ **FIGS. 12A-12B** demonstrate single pill of CRF_1 receptor antagonist (i.e., as described in US 2017/0020877 A1) improves ACTH and 17-OHP in CAH patients.

[0327] FIG. 13 shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a CRF_1 receptor antagonist.

Example 4. Assess reduction in excess ACTH and adrenal steroid production

[0328] The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and tolerability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

ELIGIBILITY CRITERIA

[0329] Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP ≥800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for ≥30 days before enrollment

[0330] Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

STUDY DESIGN

[0331] FIG. 14 depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

BASELINE CHARACTERISTICS

[0332] Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 partcipants were enrolled and received at least 1 dose of Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

Table 1 – Baseline characteristics of each cohort

Parameter	**Cohort A (n=10)**	**Cohort B (n=8)**
Demographics		
Age (years), mean (range)	39.3 (24-66)	36.8 (19-66)
Sex	5M, 5F	1M, 7F
Bmi (kg/m^2), mean ± SD	31.5 ± 12.0	31.1 ± 6.7

Daily GC dose (mg HC equivalents), mean range Types of GCs	28 (13-40) 4 JC, 3 pred, 3 dex	35 (20-50) 2HC, 4 pred, 3 dex
17OHP at screening[a] (ng/dl), mean ± SD	5,985 ± 6,347	4,592 ±4,624

Abbreviations: 17OHP: 17-hydroxyprogesterone; BMI: body mass index; dex: dexamethasone; F: female; GC: glucocorticoid; HC: hydrocortisone; M: male; pred: prednisone; SD: standard deviation.
a 17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females.

SAFETY

[0333] Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

PHARMACOKINETICS

[0334] Over a wide range of doses (200 to 1000 mg QD), Compound 1exhibited a predictable, dose-dependent PK profile.

EFFICACY

[0335] FIG. 15A-15D show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

[0336] FIG. 16A-16D show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

[0337] FIG. 17A-17D show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and fucntional CRF_1 receptor antagonism.

Table 2 – Percentage change from baseline in ACTH, 17OHP and A4.

	Cohort A			Cohort B
	200 mg QD (Week 2)	600 mg QD (Week 4)	1000 mg QD (Week 6)	200 mg BID (Weed 2)
ACTH	-25.7 (±51.6)	-60.1 (±37.5)	-32.7 (±47.0)	-36.5 (±58.0)
17OHP	+22.2 (±172.3)	-23.7 (±64.2)	-13.8 (±74.7)	-47.8 (±63.3)
A4	-12.1 (±47.4)	-33.2 (±36.5)	-28.6 (±44.6)	-16.0 (±81.4)

CONCLUSIONS

[0338] Compound 1, a potent and selective CRF_1 receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAH.

Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

[0339] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

ABSTRACT OF THE DISCLOSURE

Provided herein are compounds and pharmaceutical compositions for the prevention and treatment of testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART).

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorization/Internet Communications Authorization Withdrawal

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	19/043,264
	Filing Date	January 31, 2025
	First Named Inventor	Alexis Howerton
	Art Unit	1627
	Examiner Name	Pihonak, Sarah
	Practitioner Docket No.	50535-710.306

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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☒ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☐ attorney or agent of record. Registration number _____.

☒ attorney or agent acting under 37 CFR 1.34. Registration number 79,641.

/Victoria Cheng/ — Signature

07/24/2025 — Date

Victoria Cheng — Typed or printed name

(858) 350-2240 — Telephone Number

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☒ * Total of 1 forms are submitted.

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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 19/043,264	Filing Date 01/31/2025	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $200 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $600 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	07/25/2025	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 21	= 0		x $200 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $600 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/DEIDRE C KING-WOODWARD/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

21971 7590 07/29/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
PIHONAK, SARAH	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
07/29/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Applicant-Initiated Interview Summary	**Application No.** 19/043,264	**Applicant(s)** HOWERTON et al.		
	Examiner SARAH PIHONAK	**Art Unit** 1627	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
SARAH PIHONAK	Primary Examiner	Telephonic
Victoria Cheng	Attorney of Record	

Date of Interview: 24 July 2025

Issues Discussed:

Other

Atty. Cheng contacted the examiner to discuss the submission of a response to the 4/25/25 office action, with claim amendments, as well as several other related track one applications. Atty. Cheng intends to file an authorization form to permit email communications.

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,264	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**6961**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: August 13, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: August 13, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	9	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	EP-3784233-B1	06-05-2024	SPRUCE BIOSCIENCES INC [US]		☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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				Examiner Name	PIHONAK, SARAH
Sheet	2	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	AUCHUS, Richard J. et al. Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	002	AUCHUS, Richard J. et al. Supplemental Information: Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	003	AUCHUS, Richard J. Management Considerations for the Adult With Congenital Adrenal Hyperplasia. Molecular and Cellular Endocrinology 408:190-197 (2015).	☐
	004	AVILA, N. A. et al. Testicular adrenal rest tissue in congenital adrenal hyperplasia: serial sonographic and clinical findings. AJR. American journal of roentgenology 172(5):1235-1238 (1999).	☐
	005	AYCAN, Zehra et al. Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia. Clinical endocrinology 78(5):667-672 (2013).	☐
	006	CLAAHSEN-VAN DER GRINTEN, H. L. et al. Testicular adrenal rest tumours in congenital adrenal hyperplasia. International Journal of pediatric endocrinology 2009:624823, 1-8 (2009).	☐
	007	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Prevalence of testicular adrenal rest tumours in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. European journal of endocrinology 157(3):339-344 (2007).	☐
	008	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Repeated successful induction of fertility after replacing hydrocortisone with dexamethasone in a patient with congenital adrenal hyperplasia and testicular adrenal rest tumors. Fertility and Sterility 88(3):705.e5-705.e8 (2007).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	3	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	009	ClinicalTrials.gov Identifier: NCT04457336. A Ph2b to Evaluate Clinical Efficacy and Safety of Tildacerfont in Adult CAH, Record created June 25, 2020. pp. 1-17. [retrieved on 2025-08-12] Available at URL: https://clinicaltrials.gov/study/NCT04457336.	☐
	010	DELFINO, Michele et al. Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia: prevalence and sonographic, hormonal, and seminal characteristics. Journal of ultrasound in medicine 31(3):383-388 (2012).	☐
	011	ENGELS, Manon et al. Testicular adrenal rest tumors: current insights on prevalence, characteristics, origin, and treatment. Endocrine Reviews 40(4):973-987 (2019).	☐
	012	EP19793181.9 Brief Communication - Opposition Proceedings dated August 5, 2025.	☐
	013	EP19793181.9 Reply from the opponent to submission of proprietor dated July 18, 2025.	☐
	014	EP19793181.9 Reply of the Patent Proprietor to the notice(s) of opposition dated June 18, 2025.	☐
	015	FLECK, Beth A. et al. Binding Kinetics Redefine the Antagonist Pharmacology of the Corticotropin-releasing Factor Type 1 Receptor. The Journal of Pharmacology and Experimental Therapeutics 341(2):518-531 (2012).	☐
	016	JOSEPH, Dana N., and Shannon Whirledge. Stress and the HPA axis: balancing homeostasis and fertility. International journal of molecular sciences 18(10):2224, 1-15 (2017).	☐
	017	MA, Li et al. Sonographic features of the testicular adrenal rests tumors in patients with congenital adrenal hyperplasia: a single-center experience and literature review. Orphanet Journal of Rare Diseases 14(1):242, 1-8 (2019).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
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	018	MAZZILLI, Rossella et al. The High Prevalence of Testicular Adrenal Rest Tumors in Adult Men With Congenital Adrenal Hyperplasia Is Correlated With ACTH Levels. Front Endocrinol (Lausanne) 10:335 (2019).	☐
	019	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Defence dated March 13, 2025 (Claim No. HP-2025-000005) (pp. 1-3).	☐
	020	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Grounds of Invalidity dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	021	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Particulars of Claim dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	022	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Patent Owner's Response in U.S. Patent No. 12,115,166 dated July 8, 2025 (pp 1-6) (PGR-2025-00032).	☐
	023	Neurocrine Biosciences, Inc. (Plaintiff) v. Spruce Biosciences, Inc. (Defendant). Memorandum dated June 9, 2025 (Case No. 1:25-cv-00059-JDW (pp. 1-10).	☐
	024	NISSEN, Trygve et al. The clinical case report: a review of its merits and limitations. BMC Research Notes 7:264, 1-7 (2014).	☐
	025	REISCH, Nicole et al. High prevalence of reduced fecundity in men with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 94(5):1665-1670 (2009).	☐
	026	Spruce Biosciences announces topline results from CAHMELIA-203 in adult classic CAH and CAHPTAIN-205 in pediatric classic CAH. Spruce Biosciences :1-7 (2024).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	5	of	9	Attorney Docket Number	50535-710.306

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	027	Spruce Biosciences announces topline results from CAHMELIA-204 in adult CAH and CAHPTAIN-205 in adult and pediatric CAH. Spruce Biosciences :1-4 (2024).	☐
	028	STIKKELBROECK, Nike M. M. L. et al. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 86(12):5721-5728 (2001).	☐
	029	The Journal of Clinical Endocrinology and Metabolism Author Guidelines. Oxford Academic (2025); [retrieved on 2025-06-09]. Available at URL: https://academic.oup.com/jcem/pages/author_guidelines.	☐
	030	TURCU, Adina F. and Richard J. Auchus. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinology and Metabolism Clinics 44(2):275-296 (2015).	☐
	031	TURCU, Adina F., and Richard J. Auchus. Novel treatment strategies in congenital adrenal hyperplasia. Current Opinion in Endocrinology, Diabetes and Obesity 23(3):225-232 (2016).	☐
	032	TURCU, Adina F. et al. Supplemental Information: Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016).	☐
	033	U.S. Provisional Application No. 62/822,815 filed on March 23, 2019.	☐
	034	WALDRON, James. Spruce saws off only drug after 2nd hyperplasia fail, leaving biotech's direction in doubt. Fierce Biotech :1-2 (2024).	☐
	035	WANG, Zhu et al. Diagnosis of testicular adrenal rest tumors on ultrasound: a retrospective study of 15 cases report. Medicine 94(36):e1471, 1-6 (2015).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	6	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	036	World Health Organization Drug Information, 32(2):369-370 (2018).	☐
	037	YAMADA, Yasuki et al. New class of corticotropin-releasing factor (CRF) antagonists: small peptides having high binding affinity for CRF receptor. Journal of medicinal chemistry 47(5):1075-1078 (2004).	☐
	038	YASIR, Muhammad et al. Corticosteroid Adverse Effects. StatPearls, July 3, 2023; [retrieved on 2025-06-17]. Available at URL: https://www.ncbi.nlm.nih.gov/books/NBK531462/ pp. 1-14.	☐
	039	YU, Min Kyung et al. Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia. Annals of pediatric endocrinology and metabolism 20(3):155-161 (2015).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	7	of	9	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☐ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☒ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-08-13
Name/Print	Kaia R. Parenti	Registration Number	81050

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
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Sheet	8	of	9	Attorney Docket Number	50535-710.306

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,264	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**6961**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: August 13, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: August 13, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
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PTO/SB/08 (01-25)
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				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	9	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	EP-3784233-B1	06-05-2024	SPRUCE BIOSCIENCES INC [US]		☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Sheet	2	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
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	001	AUCHUS, Richard J. et al. Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	002	AUCHUS, Richard J. et al. Supplemental Information: Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	003	AUCHUS, Richard J. Management Considerations for the Adult With Congenital Adrenal Hyperplasia. Molecular and Cellular Endocrinology 408:190-197 (2015).	☐
	004	AVILA, N. A. et al. Testicular adrenal rest tissue in congenital adrenal hyperplasia: serial sonographic and clinical findings. AJR. American journal of roentgenology 172(5):1235-1238 (1999).	☐
	005	AYCAN, Zehra et al. Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia. Clinical endocrinology 78(5):667-672 (2013).	☐
	006	CLAAHSEN-VAN DER GRINTEN, H. L. et al. Testicular adrenal rest tumours in congenital adrenal hyperplasia. International Journal of pediatric endocrinology 2009:624823, 1-8 (2009).	☐
	007	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Prevalence of testicular adrenal rest tumours in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. European journal of endocrinology 157(3):339-344 (2007).	☐
	008	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Repeated successful induction of fertility after replacing hydrocortisone with dexamethasone in a patient with congenital adrenal hyperplasia and testicular adrenal rest tumors. Fertility and Sterility 88(3):705.e5-705.e8 (2007).	☐

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Sheet	3	of	9	Attorney Docket Number	50535-710.306

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	009	ClinicalTrials.gov Identifier: NCT04457336. A Ph2b to Evaluate Clinical Efficacy and Safety of Tildacerfont in Adult CAH, Record created June 25, 2020. pp. 1-17. [retrieved on 2025-08-12] Available at URL: https://clinicaltrials.gov/study/NCT04457336.	☐
	010	DELFINO, Michele et al. Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia: prevalence and sonographic, hormonal, and seminal characteristics. Journal of ultrasound in medicine 31(3):383-388 (2012).	☐
	011	ENGELS, Manon et al. Testicular adrenal rest tumors: current insights on prevalence, characteristics, origin, and treatment. Endocrine Reviews 40(4):973-987 (2019).	☐
	012	EP19793181.9 Brief Communication - Opposition Proceedings dated August 5, 2025.	☐
	013	EP19793181.9 Reply from the opponent to submission of proprietor dated July 18, 2025.	☐
	014	EP19793181.9 Reply of the Patent Proprietor to the notice(s) of opposition dated June 18, 2025.	☐
	015	FLECK, Beth A. et al. Binding Kinetics Redefine the Antagonist Pharmacology of the Corticotropin-releasing Factor Type 1 Receptor. The Journal of Pharmacology and Experimental Therapeutics 341(2):518-531 (2012).	☐
	016	JOSEPH, Dana N., and Shannon Whirledge. Stress and the HPA axis: balancing homeostasis and fertility. International journal of molecular sciences 18(10):2224, 1-15 (2017).	☐
	017	MA, Li et al. Sonographic features of the testicular adrenal rests tumors in patients with congenital adrenal hyperplasia: a single-center experience and literature review. Orphanet Journal of Rare Diseases 14(1):242, 1-8 (2019).	☐

EXAMINER SIGNATURE			
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	018	MAZZILLI, Rossella et al. The High Prevalence of Testicular Adrenal Rest Tumors in Adult Men With Congenital Adrenal Hyperplasia Is Correlated With ACTH Levels. Front Endocrinol (Lausanne) 10:335 (2019).	☐
	019	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Defence dated March 13, 2025 (Claim No. HP-2025-000005) (pp. 1-3).	☐
	020	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Grounds of Invalidity dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	021	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Particulars of Claim dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	022	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Patent Owner's Response in U.S. Patent No. 12,115,166 dated July 8, 2025 (pp 1-6) (PGR-2025-00032).	☐
	023	Neurocrine Biosciences, Inc. (Plaintiff) v. Spruce Biosciences, Inc. (Defendant). Memorandum dated June 9, 2025 (Case No. 1:25-cv-00059-JDW (pp. 1-10).	☐
	024	NISSEN, Trygve et al. The clinical case report: a review of its merits and limitations. BMC Research Notes 7:264, 1-7 (2014).	☐
	025	REISCH, Nicole et al. High prevalence of reduced fecundity in men with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 94(5):1665-1670 (2009).	☐
	026	Spruce Biosciences announces topline results from CAHMELIA-203 in adult classic CAH and CAHPTAIN-205 in pediatric classic CAH. Spruce Biosciences :1-7 (2024).	☐

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				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	5	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	027	Spruce Biosciences announces topline results from CAHMELIA-204 in adult CAH and CAHPTAIN-205 in adult and pediatric CAH. Spruce Biosciences :1-4 (2024).	☐
	028	STIKKELBROECK, Nike M. M. L. et al. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 86(12):5721-5728 (2001).	☐
	029	The Journal of Clinical Endocrinology and Metabolism Author Guidelines. Oxford Academic (2025); [retrieved on 2025-06-09]. Available at URL: https://academic.oup.com/jcem/pages/author_guidelines.	☐
	030	TURCU, Adina F. and Richard J. Auchus. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinology and Metabolism Clinics 44(2):275-296 (2015).	☐
	031	TURCU, Adina F., and Richard J. Auchus. Novel treatment strategies in congenital adrenal hyperplasia. Current Opinion in Endocrinology, Diabetes and Obesity 23(3):225-232 (2016).	☐
	032	TURCU, Adina F. et al. Supplemental Information: Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016).	☐
	033	U.S. Provisional Application No. 62/822,815 filed on March 23, 2019.	☐
	034	WALDRON, James. Spruce saws off only drug after 2nd hyperplasia fail, leaving biotech's direction in doubt. Fierce Biotech :1-2 (2024).	☐
	035	WANG, Zhu et al. Diagnosis of testicular adrenal rest tumors on ultrasound: a retrospective study of 15 cases report. Medicine 94(36):e1471, 1-6 (2015).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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				Application Number	19/043,264
				Filing Date	01-31-2025
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	036	World Health Organization Drug Information, 32(2):369-370 (2018).	☐
	037	YAMADA, Yasuki et al. New class of corticotropin-releasing factor (CRF) antagonists: small peptides having high binding affinity for CRF receptor. Journal of medicinal chemistry 47(5):1075-1078 (2004).	☐
	038	YASIR, Muhammad et al. Corticosteroid Adverse Effects. StatPearls, July 3, 2023; [retrieved on 2025-06-17]. Available at URL: https://www.ncbi.nlm.nih.gov/books/NBK531462/ pp. 1-14.	☐
	039	YU, Min Kyung et al. Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia. Annals of pediatric endocrinology and metabolism 20(3):155-161 (2015).	☐

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				Application Number	19/043,264
				Filing Date	01-31-2025
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				Examiner Name	PIHONAK, SARAH
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TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

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☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

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☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

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SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

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A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-08-13
Name/Print	Kaia R. Parenti	Registration Number	81050

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	8	of	9	Attorney Docket Number	50535-710.306

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(11) EP 3 784 233 B1

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05.06.2024 Bulletin 2024/23

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(51) International Patent Classification (IPC):
A61K 31/4162 *(2006.01)* ***A61K 31/505*** *(2006.01)*
A61K 31/519 *(2006.01)* ***C07D 231/54*** *(2006.01)*
C07D 233/70 *(2006.01)* ***C07D 247/02*** *(2006.01)*
A61K 9/20 *(2006.01)* ***A61P 35/00*** *(2006.01)*

(52) Cooperative Patent Classification (CPC):
(C-Sets available)
A61K 31/519; A61K 31/5377; A61K 45/06; A61P 35/00; A61K 9/2004; A61K 9/4841 (Cont.)

(86) International application number:
PCT/US2019/029486

(87) International publication number:
WO 2019/210266 (31.10.2019 Gazette 2019/44)

(54) **METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS**

VERFAHREN ZUR BEHANDLUNG VON HODEN-UND EIERSTOCK-NEBENNIERENTUMOREN

MÉTHODES DE TRAITEMENT DE TUMEURS DES VERTIGES SURRÉNALIENS DES TESTICULES ET DES OVAIRES

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **27.04.2018 US 201862663951 P**
23.03.2019 US 201962822815 P

(43) Date of publication of application:
03.03.2021 Bulletin 2021/09

(73) Proprietor: **Spruce Biosciences, Inc.**
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(56) References cited:
WO-A1-2008/036579 **WO-A1-2015/112642**
WO-A1-2019/036472 **WO-A1-2019/036503**
US-A1- 2010 196 389 **US-A1- 2010 222 339**
US-A1- 2017 020 877

- **CHEN HUA-DONG ET AL: "Ovarian Adrenal Rest Tumors Undetected by Imaging Studies and Identified at Surgery in Three Females with Congenital Adrenal Hyperplasia Unresponsive to Increased Hormone Therapy Dosage", ENDOCRINE PATHOLOGY, HUMANA PRESS, TOTOWA, NJ, US, vol. 28, no. 2, 28 December 2016 (2016-12-28), pages 146-151, XP036564071, ISSN: 1046-3976, DOI: 10.1007/S12022-016-9461-4 [retrieved on 2016-12-28]**

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(52) Cooperative Patent Classification (CPC): (Cont.)

C-Sets
A61K 31/5377, A61K 2300/00

Description

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019.

BACKGROUND

[0002] Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

[0003] CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

[0004] Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, *inter alia*, are solutions to these and other problems in the art. Document CHEN HUA-DONG ET AL: "Ovarian Adrenal Rest Tumors Undetected by Imaging Studies and Identified at Surgery in Three Females with Congenital Adrenal Hyperplasia Unresponsive to Increased Hormone Therapy Dosage",ENDOCRINE PATHOLOGY, HUMANA PRESS, TOTOWA, NJ, US, vol. 28, no. 2, 28 December 2016 (2016-12-28), pages 146-151
discloses how patients with congenital adrenal hyperplasia have a predisposition for developing adrenal rest tumors. In contrast to testicular adrenal rest tumors, ovarian adrenal rest tumors are less common, and only a few cases have been reported in the literature. The preferred treatment for this type of tumors, which are also presently claimed, is said to be adrenal hormone replacement therapy.

SUMMARY

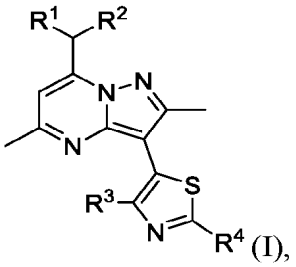
[0005] The references to methods of treatment in the summary and detailed description of the invention in this description are to be interpreted as references to the compounds, pharmaceutical compositions and medicaments of the present invention for use in a method for treatment of the human (or animal) body by therapy. Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

[0006] Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

[0007] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0008] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

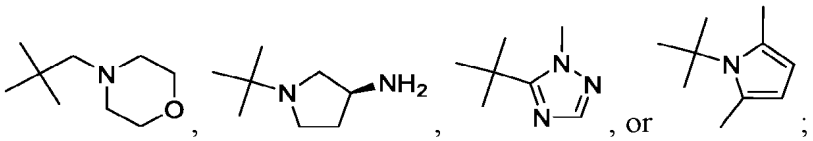
[0009] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,
wherein:

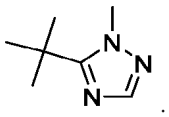
R^1 and R^2 are independently ethyl or n-propyl;
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and
R^4 is hydrogen, Br, R^aR^bN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



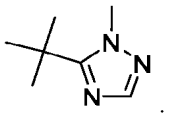
;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-.

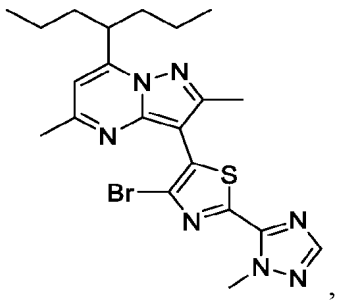
[0010] In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl. In some embodiments, R^4 is Br, R^aR^bN-, pyridin-4-yl, morpholin-4-yl, or



In some embodiments, R^4 is morpholin-4-yl or



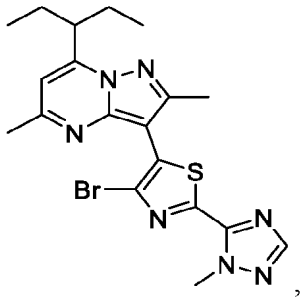
[0011] In some embodiments, R^4 is hydrogen, Br, R^aR^bN- and R^a and R^b are independently C_1-C_3alkyl. In some embodiments, the compound is



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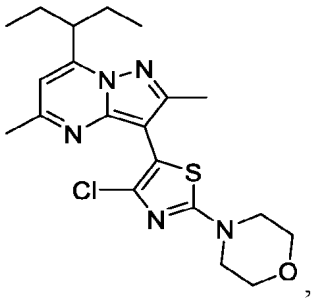
or a pharmaceutically acceptable salt thereof.

[0012] In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0013] In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

[0014] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

[0015] In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

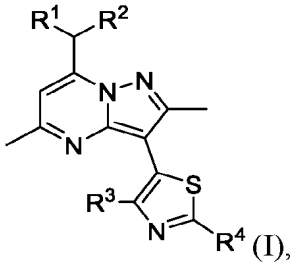
[0016] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

[0017] In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

[0018] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically

acceptable salt thereof, is administered at about 10 pm at night.

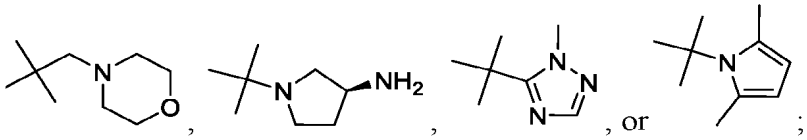
[0019] One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:



(I),

or a pharmaceutically acceptable salt thereof,
wherein:

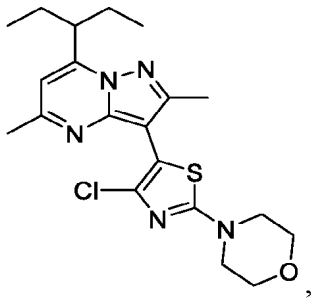
R^1 and R^2 are independently ethyl or n-propyl;
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and
R^4 is hydrogen, Br, R^aR^bN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-.

[0020] In some embodiments, the compound of Formula (I) has the structure:



,

or a pharmaceutically acceptable salt thereof.

[0021] In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0022] In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about

295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

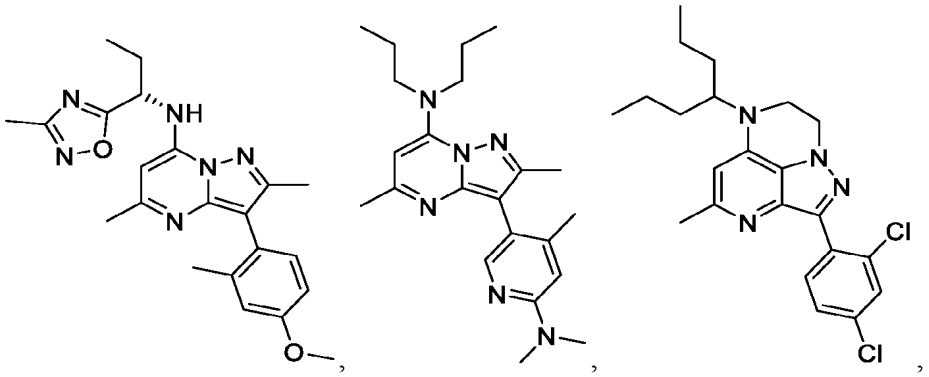
[0023] In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0024] In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

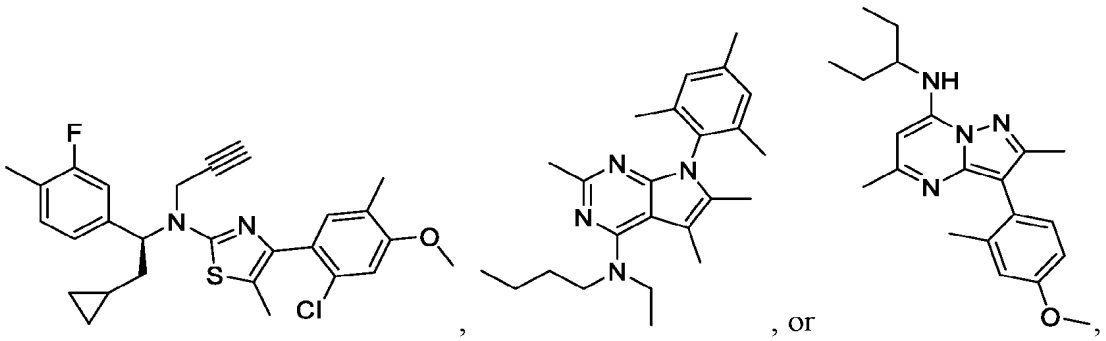
[0025] In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

[0026] In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

[0027] In some embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In some embodiments, the CRF_1 antagonist is

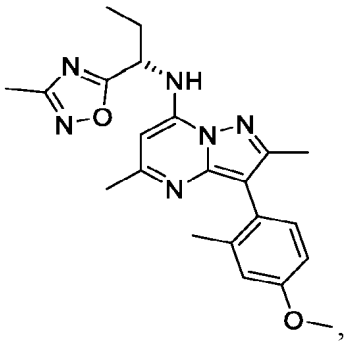


S SR-126374,



or a pharmaceutically acceptable salt thereof.

[0028] In some embodiments, the CRF_1 antagonist is



or a pharmaceutically acceptable salt thereof.

[0029] In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

[0030] In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

[0031] In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0032] In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural

[0033] Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0034] In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0035] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. Accordingly, the drawings and description are to be regarded as illustrative.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

FIG. 1A-1B. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics **(A)**. A schematic representation of inhibition of CRF_1 with a CRF_1 antagonist (Compound 1) **(B)**.

FIG. 2. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

FIG. 3. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

FIG. 4. Graphic representation of patient-level response (measuring ACTH levels) to a CRF_1 antagonist (Compound 1).

FIG. 5A-5B. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a CRF_1 antagonist [Subject 003001 **(A)**; Subject 007002 **(B)**].

FIG. 6. Graphic representation of patient-level response (measuring 17-OHP levels) to a CRF_1 antagonist (Compound 1).

FIG. 7A-7B. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to

a CRF_1 antagonist [Subject 003001 **(A)**; Subject 007002 **(B)**].

FIG. 8. Graphic representation of patient-level response (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1).

FIG. 9A-9B. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1) [Subject 003001 **(A)**; Subject 007002 **(B)**].

FIG. 10A-10B. Images of a patient with TART pre-treatment with a CRF_1 antagonist (Compound 1) **(A)** and 6-weeks post-treatment with a CRF_1 antagonist (Compound 1) **(B)**.

FIG. 11A-11B. Graphic representation of an *in vitro* binding assay of a CRF_1 antagonist (Compound 1); ^{125}I-sauvagine binding to rat cerebellar membranes one hour after oral administration of increasing Compound 1 doses **(A)** and *in vivo* inhibition of CRF-induced activity after treatment with a CRF_1 antagonist; Compound 1 (oral, 10 mg/kg) **(B)**.

FIG. 12A-12B. Graphic representation of ACTH levels **(A)** and 17-OHP levels **(B)** after treatment with a CRF_1 antagonist (Compound 1).

FIG. 13. Graphic representation of hormone responses after treatment with a CRF_1 antagonist (Compound 1).

FIG. 14 depicts the proof of concept and escalating QD dosing at 10 pm.

FIG. 15A-15D are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

FIG. 16A-16D are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

FIG. 17A-17D are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

DETAILED DESCRIPTION

[0037] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only.

I. Definitions

[0038] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0039] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0040] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

[0041] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0042] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be

consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

[0043] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as - C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0044] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

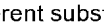
[0045] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0046] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0047] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

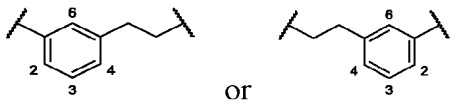
[0048] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual

rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0049] The symbol "  " denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0050] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0051] The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



[0052] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -CHO, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2CH_3$ $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0053] Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0054] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R‴, -OC(O)R', - C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R‴, $-NR"C(O)_2R'$, - NR-C(NR'R"R‴)=NR"", -NR-C(NR'R")=NR‴, -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -NR'NR"R‴, -ONR'R", -NR'C(O)NR"NR‴R"", -CN, $-NO_2$, $-NR'SO_2R"$, -NR'C(O)R", - NR'C(O)-OR", -NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R‴, and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R‴, and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0055] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, - SiR'R"R‴, -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R‴, $-NR"C(O)_2R'$, -NR-C(NR'R"R‴)=NR"", -NR-C(NR'R")=NR‴, $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -NR'NR"R‴, -ONR'R", -NR'C(O)NR"NR‴R"", -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R‴, and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R‴, and R"" groups when more than one of these

groups is present.

[0056] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0057] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0058] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula $-T-C(O)-(CRR')_q-U-$, wherein T and U are independently -NR-, -O-, - CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, $-S(O)_2-$, $-S(O)_2NR'-$, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C"R"R'")_d-$, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R, R', R", and R‴ are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0059] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0060] A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC= (O)H, - NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, un-

substituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)\ NH_2$, $-NHSO_2H$, -NHC= (O)H, - NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

[0061] A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0062] A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0063] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0064] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0065] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0066] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to

include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0067] As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0068] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0069] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0070] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0071] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0072] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0073] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0074] "Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0075] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0076] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R^{13} substituents are present, each R^{13} substituent may be distinguished as R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc. is defined within the scope of the definition of R^{13} and optionally differently.

[0077] A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

[0078] Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0079] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared

with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see,* for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0080] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0081] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

[0082] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0083] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0084] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0085] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0086] A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

[0087] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino

acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

[0088] A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.,* in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0089] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

[0090] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

[0091] As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

[0092] The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

[0093] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

[0094] The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

[0095] The terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and

"CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms include any recombinant or naturally-occurring form of CRF_1 variants thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of CRF_1 variants (e.g., frameshift mutations) thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF_1). In embodiments, the CRF_1 protein encoded by the *CRHR1* gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

[0096] The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.).*

[0097] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

[0098] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0099] The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

[0100] "Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

[0101] "Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

[0102] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leuke-

mia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[0103] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[0104] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

[0105] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

[0106] The terms "treating" or "treatment" refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing In embodiments, treating does not include preventing.

[0107] "Treating" or "treatment" as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical

results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (*e.g.*, ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

[0108] "Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

[0109] The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

[0110] "Patient" or "subject in need thereof' refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0111] An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Lieberman, Pharmaceutical Dosage Forms (vols. 1-3, 1992); Lloyd, The Art, Science and Technology of Pharmaceutical Compounding (1999); Pickar, Dosage Calculations (1999); and Remington: The Science and Practice of Pharmacy, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

[0112] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0113] Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0114] The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

[0115] The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

[0116] The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

[0117] The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

[0118] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0119] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, J. Biomater Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao Pharm. Res. 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. Pharm. Pharmacol. 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.,* Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, Curr. Opin. Biotechnol. 6:698-708, 1995; Ostro, Am. J. Hosp. Pharm. 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0120] By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions,

emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0121] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0122] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

[0123] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

[0124] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

[0125] The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

[0126] The compounds disclosed herein may be co-administered with an agonist or antagonist of CRF_1 function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

[0127] "Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (*e.g.*, cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (*e.g.*, 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (*e.g.*, vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.),* topoisomerase inhibitors (*e.g.,* irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.,* doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins;

benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-aminotriazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflomithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bize-

lesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rIL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levam-

isole, interleukin-2, alpha-interferon, *etc.),* monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In, ^{90}Y, or ^{131}I, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa ™), erlotinib (Tarceva ™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0128] "Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0129] The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoli- n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli- n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family; (v) an anti angiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin .alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme prodrug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

[0130] In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax 11-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

[0131] In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

[0132] In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{89}Sr, ^{86}Y, ^{87}Y, ^{90}Y, ^{105}Rh, ^{111}Ag,

^{111}In, ^{117m}Sn, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi, optionally conjugated to antibodies directed against tumor antigens.

[0133] In addition, a CRF_1 inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

[0134] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

[0135] The CRF_1 inhibitors/CRF, antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

[0136] The CRF_1 inhibitors/CRF, antagonists disclosed herein may be administered once daily until study reached endpoint. The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

[0137] The compositions disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

[0138] A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaroytic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (e.g., spodoptera) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

[0139] "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

[0140] The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a CRF_1 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with CRF_1 (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A CRF_1 modulator is a compound that increases or decreases the activity or function or level of activity or level of function of CRF_1. A modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

[0141] The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of CRF_1, either directly or indirectly, relative to the absence of the molecule.

[0142] The term "associated" or "associated with" in the context of a substance or substance activity or function

associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with CRF_1 activity, a CRF_1 associated disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with CRF_1 activity or function may be an endocrine disorder that results (entirely or partially) from aberrant CRF_1 function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant CRF_1 activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., CRF_1 modulator, CRF_1 inhibitor, or CRF_1 antagonist), in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated endocrine disorder, may be treated with an CRF_1 modulator or CRF_1 inhibitor, in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease.

[0143] The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

[0144] The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a CRF_1 with a compound as described herein may reduce the level of a product of the CRF_1 catalyzed reaction or the level of a downstream derivative of the product or binding may reduce the interactions between the CRF_1 or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

[0145] As used herein, the terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the CRF_1 receptor in an *in vitro* assay, an *in vivo* model, and/or other means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

[0146] The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

[0147] The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

[0148] "Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

[0149] The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In embodiments, the antibody will have an affinity that is greater than about 10^9 liters/mol, as determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

[0150] The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA),

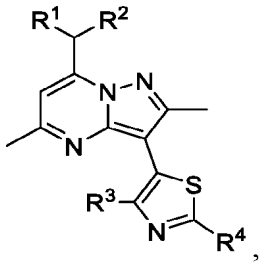
complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

[0151] As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

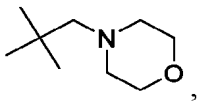
[0152] The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

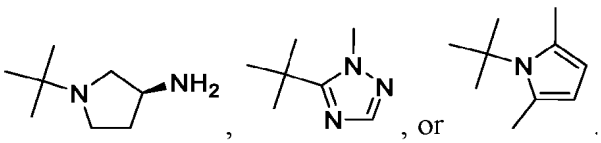
II. Compounds

[0153] In an aspect provided herein, is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



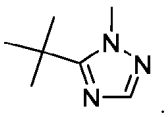


R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

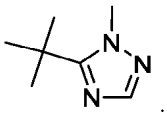
[0154] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

[0155] In certain embodiments, R^3 is Cl, Br, or methyl.

[0156] In certain embodiments, R^4 is Br, R^aR^bN-, pyridin-4-yl, morpholin-4-yl, or

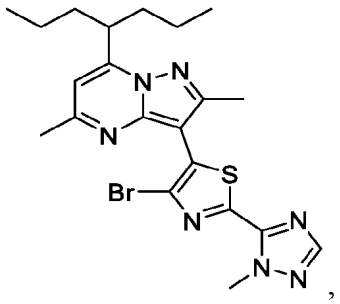


[0157] In certain embodiments, R^4 is morpholin-4-yl or



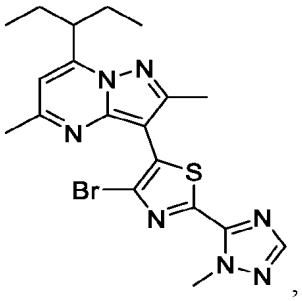
[0158] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN- and R^a and R^b are independently C_1-C_3alkyl.

[0159] In certain embodiments, the compound is



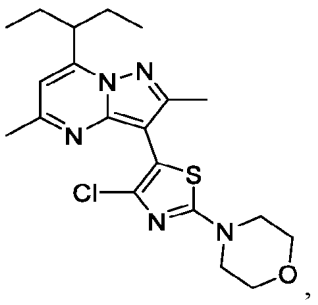
or a pharmaceutically acceptable salt thereof.

[0160] In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

[0161] In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

[0162] The invention is defined by the claims. Any subject-matter falling outside the scope of the claims is provided for information purposes only. The following paragraphs are part of the disclosure but are not claimed.

[0163] In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

[0164] In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

[0165] In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

[0166] In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

III. Pharmaceutical Compositions

[0167] In an aspect, there is provided a pharmaceutical composition, for the claimed use, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

[0168] The compounds (e.g., CRF_1 inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., CRF_1 inhibitor(s)/ antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., CRF_1 inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

[0169] In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

[0170] The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

[0171] The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of CRF_1 function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[0172] The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered compo-

sition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly(methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

[0173] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0174] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

[0175] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

[0176] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

[0177] The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

[0178] The pharmaceutical compositions typically comprise a therapeutically effective amount of a CRF_1 inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

[0179] After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

[0180] Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a CRF_1 inhibitor/antag-

onist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

[0181] Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., CRF_1 inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

[0182] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

[0183] The present disclosure contemplates the administration of the compound (e.g., CRF_1 inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

[0184] The compound (e.g., CRF_1 inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

IV. Methods

[0185] In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0186] In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0187] In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0188] In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder according to the claims, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix, uterus, ovary,

testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

[0189] In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinernia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, aligodendrogliorna, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but not limited to, renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (*See* Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy et al., 1997, Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

[0190] Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal,

intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

[0191] The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

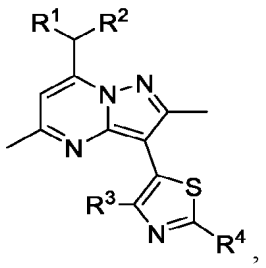
[0192] In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

[0193] In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

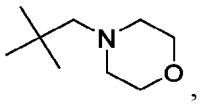
[0194] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

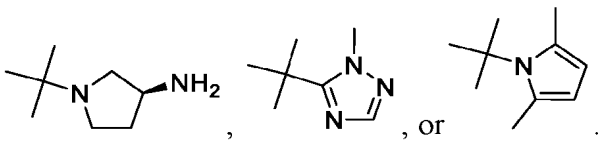
[0195] In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0196] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):



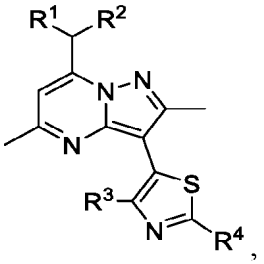
or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,





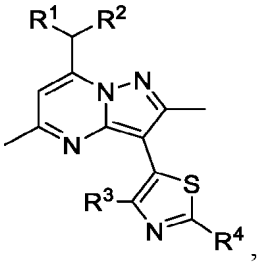
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-.

[0197] In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments.

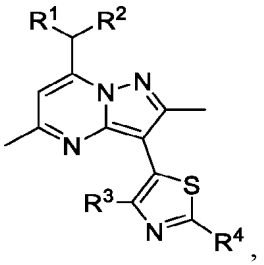
[0198] In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 70% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

[0199] In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

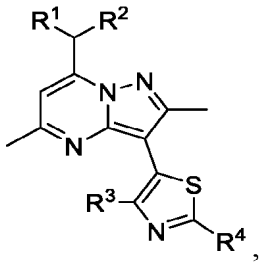
[0200] In an aspect provided herein, is a method of decreasing or reducing 17α-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least

about 30% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

[0201] In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

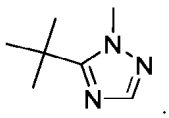


or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

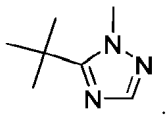
[0202] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

[0203] In certain embodiments, R^3 is Cl, Br, or methyl.

[0204] In certain embodiments, R^4 is Br, R^aR^bN-, pyridin-4-yl, morpholin-4-yl, or

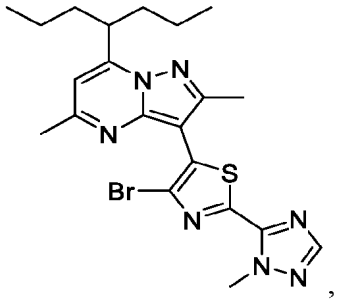


[0205] In certain embodiments, R^4 is morpholin-4-yl or



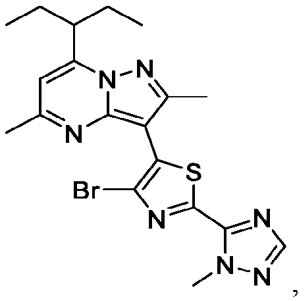
[0206] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN- and R^a and R^b are independently C_1-C_3alkyl.

[0207] In certain embodiments, the compound is



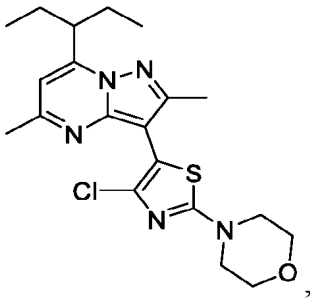
or a pharmaceutically acceptable salt thereof.

[0208] In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

[0209] In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

[0210] In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate thereof is cyclically administered to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment. Prodrugs of the present compounds are not part of the claimed invention.

[0211] In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg, from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I),

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

[0212] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

[0213] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

[0214] For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about

680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about

305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

[0215] In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate,

hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

[0216] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

[0217] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or

prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

[0218] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or

prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to

at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

[0219] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In

certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

[0220] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a phar-

maceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

[0221] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or

a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily

for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

[0222] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of

Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

[0223] In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

[0224] In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subj ect.

[0225] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

[0226] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formu-

lated as a capsule or tablet.

[0227] In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

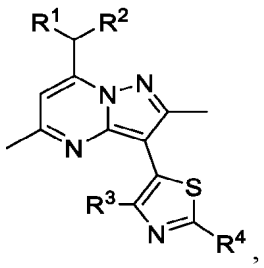
[0228] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject.In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0229] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

[0230] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

[0231] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

[0232] In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I): and a pharmaceutically acceptable excipientcomprising with a compound as described herein, including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3, and R^4 are as described herein, including embodiments.

[0233] In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0234] In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about

270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0235] In certain embodiments, the pharmaceutical composition is administered orally.

[0236] In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0237] In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subj ect.

[0238] In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0239] In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

[0240] In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

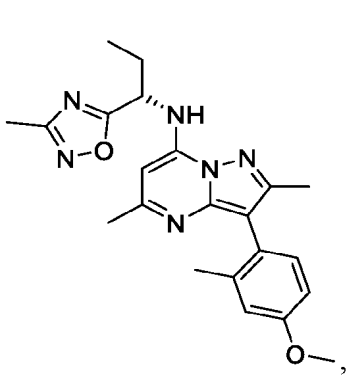
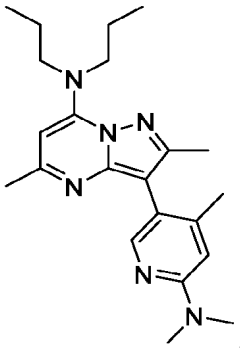
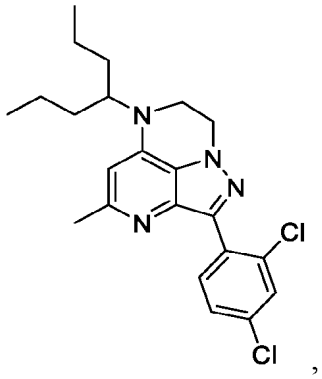
[0241] In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

[0242] In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

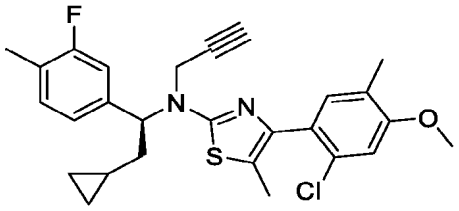
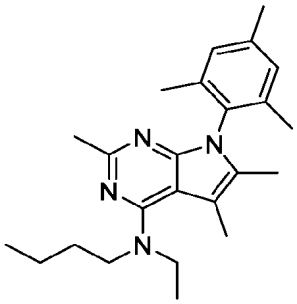
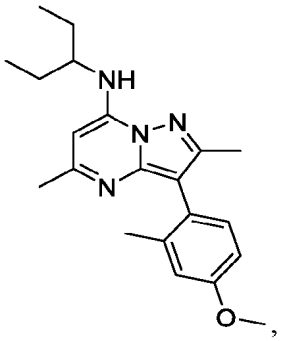
[0243] In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

[0244] In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

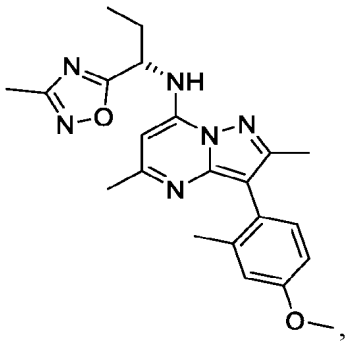
[0245] In certain embodiments, the the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In certain embodiments, the CRF_1 antagonist is:

S SR-126374,

or a pharmaceutically acceptable salt thereof. In certain embodiments, the CRF_1 antagonist is



or a pharmaceutically acceptable salt thereof.

[0246] In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0247] In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy

is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0248] In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

[0249] In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

[0250] In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

[0251] The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy,* supra; Modified-Release Drug Delivery Technology, 2nd Edition, Rathbone et al., Eds., Marcel Dekker, Inc.: New York, NY, 2008).

[0252] The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

[0253] The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

[0254] In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

[0255] The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[0256] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression.

Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[0257] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[0258] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[0259] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[0260] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[0261] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[0262] The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that

resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[0263] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0264] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[0265] Coloring and flavoring agents can be used in all of the above dosage forms.

[0266] The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

[0267] The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[0268] The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy,* supra).

[0269] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[0270] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*'-methy1-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[0271] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl-and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate.

Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[0272] When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[0273] In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[0274] The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[0275] The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[0276] Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[0277] Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

V. Examples

[0278] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only.

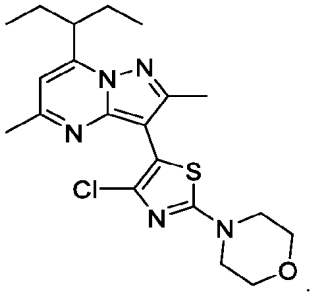
Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

[0279] Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)-driven overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

[0280] Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 (CRF_1) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a

similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH. Compound 1 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

[0281] The structure of Compound 1 is:



[0282] Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

[0283] The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

[0284] The specification of study drug dosing at 10pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma C_{max} (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. **(FIGS. 1A-1B)**

Objectives	Endpoints
Primary	
• To assess the efficacy of Compound 1 in subjects with TART	• Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12
Secondary	
• To evaluate the safety of Compound 1 in subjects with TART	• Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs) • Physical examination findings • Vital signs • Changes in electrocardiogram (ECG) • Changes in clinical laboratory values
• To assess the pharmacodynamic (PD) biomarker effects of Compound 1	• Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH),

(continued)

Secondary	
	follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, and aldosterone from baseline to Week 12
• To assess changes on semen analysis	• Changes in sperm count, morphology, and motility from baseline to Week 12
• To assess changes in metabolism	• Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12
	• Changes in body weight, body mass index (BMI), waist circumference, and blood pressure
• To evaluate changes in quality of life (QoL) and mood	• Changes in QoL measured using the Short Form 36 (SF-36)
	• Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS)

Study Population

[0285] Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

Eligibility Criteria

Inclusion Criteria

[0286]

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with ≥1 lesion(s) measuring ≥2 cm in diameter
- On a stable regimen of GC replacement for ≥30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol Exclusion Criteria
- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
    - o A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
    - o Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2
    - o Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
    - o Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months

- HADS score >12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at screening and baseline (eg, C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:

    o Clinically meaningful abnormal ECG results, in the opinion of the Investigator
    o Fridericia-corrected QT interval (QTcF) >450 msec
    o Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
    o Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)

- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
- Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

Study Duration

[0287] The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of ≤4 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

Study Design

[0288] This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks.In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

Dose, Route, Regimen

[0289] All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

[0290] On mornings of study visits with 8am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6am and 8am).

[0291] If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

Investigational Drug

[0292] Compound 1 is a small-molecule CRF_1 receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

Example 2.

[0293] Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a

small-molecule antagonist of the CRF_1 receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH. The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

Nonclinical Toxicology of Compound 1

[0294] The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

[0295] Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70 days before mating, during mating, and ≤4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

[0296] In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

Clinical Experience with Compound 1

[0297] To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

[0298] An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (FIGS. 2-3).

Known Potential Risks

[0299] Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to monitor the risk of testicular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

[0300] Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

[0301] Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

Known Potential Benefits

[0302] Early clinical studies suggests that Compound 1 is effective as a CRF_1 receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH.

Assessment of Potential Risks and Benefits

[0303] The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a CRF_1 receptor antagonist, Compound 1 is intended to reduce abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

[0304] Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

Example 3. Congenital Andrenal Hyperplasia (CAH)

[0305] CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks CRF_1 receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

[0306] As shown in **FIGS. *4*** and **5A-5B,** the attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated > 25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a CRF_1 receptor antagonist.

[0307] **FIGS. *6*** and **7A-7B** demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated > 25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a CRF_1 receptor antagonist.

[0308] **FIGS. *8*** and **9A-9B** demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess andreogen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated > 25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a CRF_1 receptor antagonist.

[0309] ***FIGS. 10A-10B*** show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF_1 receptor antagonist.

[0310] ***FIGS. 11A-11B*** demonstrate Compound 1 is a potent, selective, and functional CRF_1 receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective CRF_1 receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity (CRF_1 receptor-mediated downstream cascade), demonstrating in vitro efficacy as a CRF_1 receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.c.v. administration of CRF (**FIG. 11B**).

[0311] ***FIGS. 12A-12B*** demonstrate single pill of CRF_1 receptor antagonist improves ACTH and 17-OHP in CAH patients.

[0312] ***FIG. 13*** shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a CRF_1 receptor antagonist.

Example 4. Assess reduction in excess ACTH and adrenal steroid production

[0313] The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and tolerability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

ELIGIBILITY CRITERIA

[0314] Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP ≥800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for ≥30 days before enrollment

[0315] Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

STUDY DESIGN

[0316] FIG. 14 depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

BASELINE CHARACTERISTICS

[0317] Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 partcipants were enrolled and received at least 1 dose of Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

Table - 1 Baseline characteristics of each cohort

Parameter		Cohort A (n=10)	Cohort B (n=8)
Demographics			
	Age (years), mean (range)	39.3 (24-66)	36.8 (19-66)
	Sex	5M, 5F	1M, 7F
	Bmi (kg/m^2), mean ± SD	31.5 ± 12.0	31.1 ± 6.7
Daily GC dose (mg HC equivalents), mean range		28 (13-40)	35 (20-50)
Types of GCs		4 JC, 3 pred, 3 dex	2HC, 4 pred, 3 dex
17OHP at screening[a] (ng/dl), mean ± SD		5,985 ± 6,347	4,592 ±4,624
Abbreviations: 17OHP: 17-hydroxyprogesterone; BMI: body mass index; dex: dexamethasone; F: female; GC: glucocorticoid; HC: hydrocortisone; M: male; pred: prednisone; SD: standard deviation a 17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females.			

SAFETY

[0318] Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

PHARMACOKINETICS

[0319] Over a wide range of doses (200 to 1000 mg QD), Compound 1 exhibited a predictable, dose-dependent PK profile.

EFFICACY

[0320] ***FIG.*** **15A-15D** show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

[0321] **FIG. 16A-16D** show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

[0322] **FIG. 17A-17D** show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and fucntional CRF_1 receptor antagonism.

Table 2 - Percentage change from baseline in ACTH, 17OHP *and A4.*

	Cohort A			Cohort B
	200 mg QD (Week 2)	600 mg QD (Week 4)	1000 mg QD (Week 6)	200 mg BID (Weed 2)
ACTH	-25.7 (±51.6)	-60.1 (±37.5)	-32.7 (±47.0)	-36.5 (±58.0)
17OHP	+22.2 (±172.3)	-23.7 (±64.2)	-13.8 (±74.7)	-47.8 (±63.3)
A4	-12.1 (⊥47.4)	-33.2 (⊥36.5)	-28.6 (⊥44.6)	-16.0 (⊥81.4)

CONCLUSIONS

[0323] Compound 1, a potent and selective CRF_1 receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAH. Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

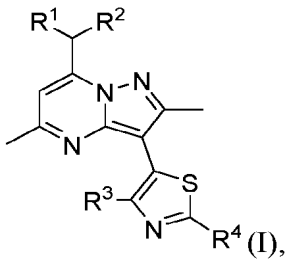
Claims

1. A corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof.

2. The CRF_1 antagonist for use according to claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).

3. The CRF_1 antagonist for use according to claim 1, wherein the treatment is a reduction in the size and/or the number of the tumors.

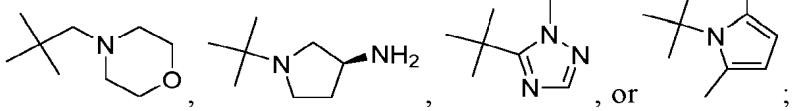
4. The CRF_1 antagonist for use according to claim 1, wherein the CRF_1 antagonist comprises a compound having structural Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,
wherein:

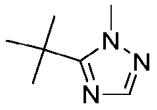
R^1 and R^2 are independently ethyl or n-propyl;
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and
R^4 is hydrogen, Br, R^aR^bN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



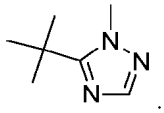
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-.

5. The CRF_1 antagonist for use according to claim 4, wherein R^3 is Cl, Br, or methyl.

6. The CRF_1 antagonist for use according to claim 4, wherein R^4 is Br, R^aR^bN-, pyridin-4-yl, morpholin-4-yl, or

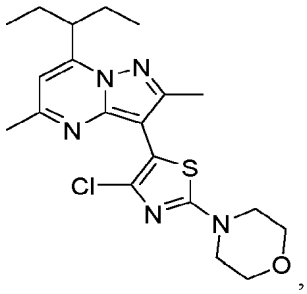


7. The CRF_1 antagonist for use according to claim 4, wherein R^4 is morpholin-4-yl or



8. The CRF_1 antagonist for use according to claim 4, wherein R^4 is hydrogen, Br, R^aR^bN- and R^a and R^b are independently C_1-C_3alkyl.

9. The CRF_1 antagonist for use according to claim 4, wherein the compound is



or a pharmaceutically acceptable salt thereof.

10. The CRF_1 antagonist for use according to claim 1, wherein a dosage regime of the CRF_1 antagonist, or a pharmaceutically acceptable salt thereof, is about 5 mg/day to about 400 mg/day to the subject.

11. The CRF_1 antagonist or a pharmaceutically acceptable salt thereof for use according to claim 1, for use in oral administration.

12. The CRF_1 antagonist for use according to claim 1, wherein the CRF_1 antagonist, or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

13. The CRF_1 antagonist of claim 1 and an additional chemotherapeutic agent, for use in the treatment or prevention of testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, wherein

the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen.

14. The CRF_1 antagonist and the additional chemotherapeutic agent for use according to claim 13, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.

15. The CRF_1 antagonist for use according to claim 4, wherein R^3 is Cl, Br, methyl, or trifluoromethyl.

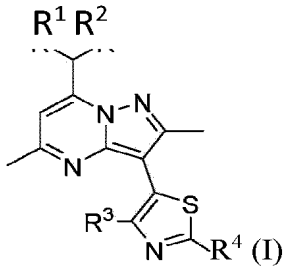
Patentansprüche

1. Corticotropin-releasing-Faktor-Typ-1 (CRF_1)-Antagonist oder ein pharmazeutisch verträgliches Salz davon zur Verwendung bei der Behandlung oder Vorbeugung von testikulären adrenalen Resttumoren (TART) oder ovariellen adrenalen Resttumoren (OART) bei einem Subjekt, das dessen bedarf.

2. CRF_1-Antagonist zur Verwendung nach Anspruch 1, wobei der Patient eine kongenitale Nebennierenhyperplasie (CAH) hat.

3. CRF_1-Antagonist zur Verwendung nach Anspruch 1, wobei die Behandlung in einer Verringerung der Größe und/oder der Anzahl der Tumore besteht.

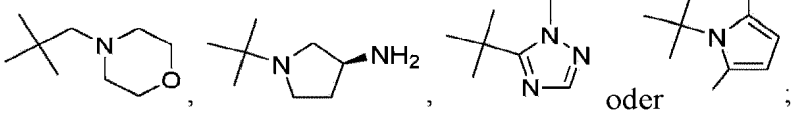
4. CRF_1-Antagonist zur Verwendung nach Anspruch 1, wobei der CRF_1-Antagonist eine Verbindung 10 mit der Strukturformel (I) umfasst:



(I)

oder ein pharmazeutisch verträgliches Salz davon, wobei:

R^1 und R^2 unabhängig voneinander Ethyl oder n-Propyl sind;
R^3 Wasserstoff, Cl, Br, Methyl, Trifluormethyl oder Methoxy ist; und
R^4 Wasserstoff, Br, R^aR^bN-, Methoxymethyl, n-Butyl, Acetamido, Pyridin-4-yl, Morpholin-4-yl,

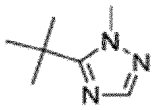


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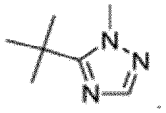
ist
R^a und R^b unabhängig voneinander Wasserstoff, C_1-C_3-Alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$- oder $CH_3CH_2CH_2NHCH_2CH_2$- sind.

5. CRF_1-Antagonist zur Verwendung nach Anspruch 4, wobei R^3 Cl, Br oder Methyl ist.

6. CRF_1-Antagonist zur Verwendung nach Anspruch 4, wobei R^4 Br, R^aR^bN-, Pyridin-4-yl, Morpholin-4-yl oder Folgendes ist:

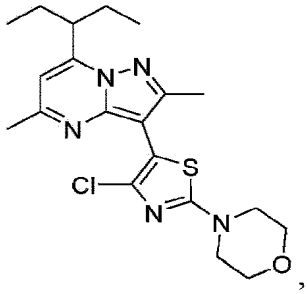


7. CRF_1-Antagonist zur Verwendung nach Anspruch 4, wobei R^4 Morpholin-4-yl oder Folgendes ist:



8. CRF_1-Antagonist zur Verwendung nach Anspruch 4, wobei R^4 Wasserstoff, Br, R^aR^bN-ist und R^a und R^b unabhängig voneinander C_1-C_3-Alkyl sind.

9. CRF_1-Antagonist zur Verwendung nach Anspruch 4, wobei die Verbindung



oder ein pharmazeutisch verträgliches Salz davon ist.

10. CRF_1-Antagonist zur Verwendung nach Anspruch 1, wobei das Dosierungsschema des CRF_1-Antagonisten oder eines pharmazeutisch verträglichen Salzes davon etwa 5 mg/Tag bis etwa 400 mg/Tag für das Subjekt beträgt.

11. CRF_1-Antagonist oder ein pharmazeutisch verträgliches Salz davon zur Verwendung nach Anspruch 1 zur Verwendung bei oraler Verabreichung.

12. CRF_1-Antagonist zur Verwendung nach Anspruch 1, wobei der CRF_1-Antagonist oder ein pharmazeutisch verträgliches Salz davon als Kapsel oder Tablette formuliert ist.

13. CRF_1-Antagonist nach Anspruch 1 und zusätzliches chemotherapeutisches Mittel zur Verwendung bei der Behandlung oder Vorbeugung von testikulären adrenalen Resttumoren (TART) oder ovariellen adrenalen Resttumoren (OART) bei einem Subjekt, das dessen bedarf, wobei das zusätzliche chemotherapeutische Mittel ein Glucocorticoid, ein Mineralocorticoid, ein ACAT 1-Inhibitor oder ein Antiandrogen ist.

14. CRF_1-Antagonist und zusätzliches chemotherapeutisches Mittel zur Verwendung nach Anspruch 13, wobei das Glucocorticoid Beclomethason, Betamethason, Budesonid, Cortison, Dexamethason, Hydrocortison, Methylprednisolon, Prednisolon, Prednison oder Triamcinolon ist.

15. CRF_1-Antagonist zur Verwendung nach Anspruch 4, wobei R^3 Cl, Br, Methyl oder Trifluormethyl ist.

Revendications

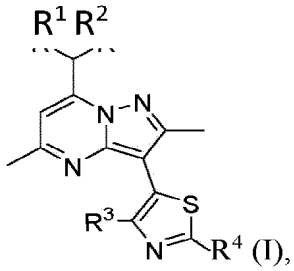
1. Un antagoniste du facteur de libération de corticotropine de type 1 (CRF_1) ou un sel pharmaceutiquement acceptable de celui-ci, destiné à être utilisé dans le traitement ou la prévention des tumeurs surrénaliennes testiculaires au repos (TART) ou des tumeurs surrénaliennes ovariennes au repos (OART) chez un sujet qui le nécessite

2. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 1, dans lequel le sujet présente une hyperplasie

congénitale des surrénales (CAH).

3. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 1, dans lequel le traitement consiste en une réduction de la taille et/ou du nombre des tumeurs.

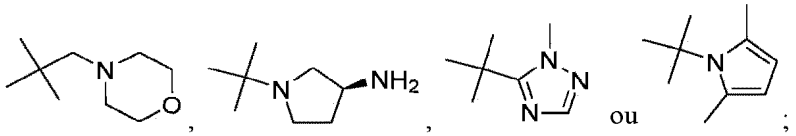
4. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 1, **caractérisé en ce que** l'antagoniste du CRF_1 comprend un composé 10 répondant à la formule structurale (I) :



(I),

ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel :

R^1 et R^2 représentent indépendamment un éthyle ou un n-propyle ;
R^3 représente un hydrogène, Cl, Br, méthyle, trifluorométhyle ou méthoxy ; et
R^4 représente un hydrogène, Br, R^aR^bN-, méthoxyméthyle, n-butyle, acétamido, pyridine-4-yle, morpholine-4-yle,

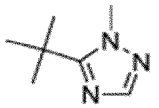


ou ;

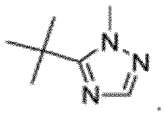
R^a et R^b représentent indépendamment un hydrogène, un alkyle en C_1-C_3, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, ou $CH_3CH_2CH_2NHCH_2CH_2$-.

5. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 4, dans lequel R^3 représente un Cl, Br ou méthyle.

6. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 4, dans lequel R^4 représente un Br, R^aR^bN-, pyridine-4-yle, morpholine-4-yle, ou

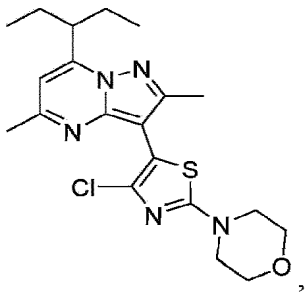


7. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 4, dans lequel R^4 est un morpholine-4-yle ou



8. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 4, dans lequel R^4 représente un hydrogène, Br, R^aR^bN- et R^a ainsi que R^b sont indépendamment un alkyle en C_1-C_3.

9. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 4, dans lequel le composé est



ou un sel pharmaceutiquement acceptable de celui-ci.

10. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 1, dans lequel un schéma posologique de l'antagoniste du CRF_1, ou d'un sel pharmaceutiquement acceptable de celui-ci, est d'environ 5 à 400 mg/jour pour le sujet.

11. L'antagoniste du CRF_1 ou un sel pharmaceutiquement acceptable de celui-ci destiné à être utilisé selon la revendication 1, pour une utilisation en administration orale

12. L'antagoniste du CRF_1 destiné à être utilisé selon la revendication 1, dans lequel l'antagoniste du CRF_1, ou un sel pharmaceutiquement acceptable de celui-ci, est formulé sous forme de capsule ou de comprimé.

13. L'antagoniste du CRF_1 de la revendication 1 et un agent chimiothérapeutique supplémentaire, destinés à être utilisés dans le traitement ou la prévention des tumeurs surrénaliennes testiculaires au repos (TART) ou des tumeurs surrénaliennes ovariennes au repos (OART) chez un sujet le nécessitant, l'agent chimiothérapeutique supplémentaire étant un glucocorticoïde, un minéralocorticoïde, un inhibiteur de l'ACAT1 ou un antiandrogène.

14. L'antagoniste du CRF_1 et l'agent chimiothérapeutique supplémentaire destinés à être utilisés selon la revendication 13, dans lesquels le glucocorticoïde est la béclométhasone, la bétaméthasone, le budésonide, la cortisone, la dexaméthasone, l'hydrocortisone, la méthylprednisolone, la prednisone ou la triamcinolone

15. L'antagoniste du CRF1 destiné à être utilisé selon la revendication 4, dans lequel R^3 représente un Cl, Br, méthyle ou trifluorométhyle.

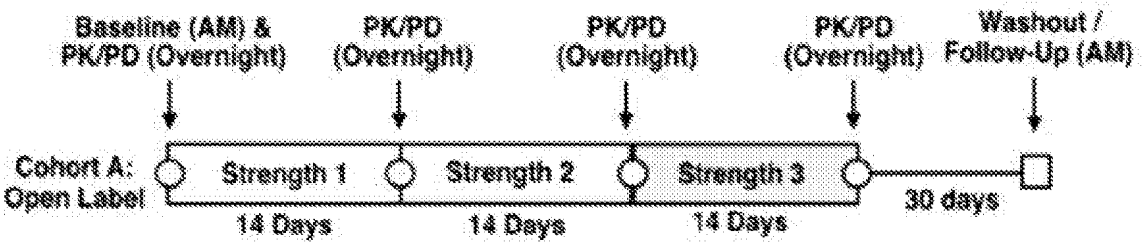

Baseline (AM) & PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
Washout / Follow-Up (AM)
Cohort A: Open Label
Strength 1
Strength 2
Strength 3
30 days
14 Days
14 Days
14 Days

FIG. 1A

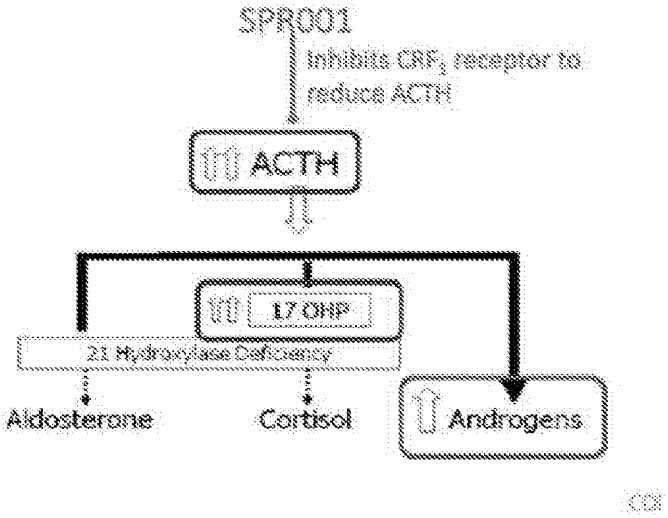

SPR001
Inhibits CRF1 receptor to reduce ACTH
ACTH
17 OHP
21 Hydroxylase Deficiency
Aldosterone
Cortisol
Androgens

FIG. 1B

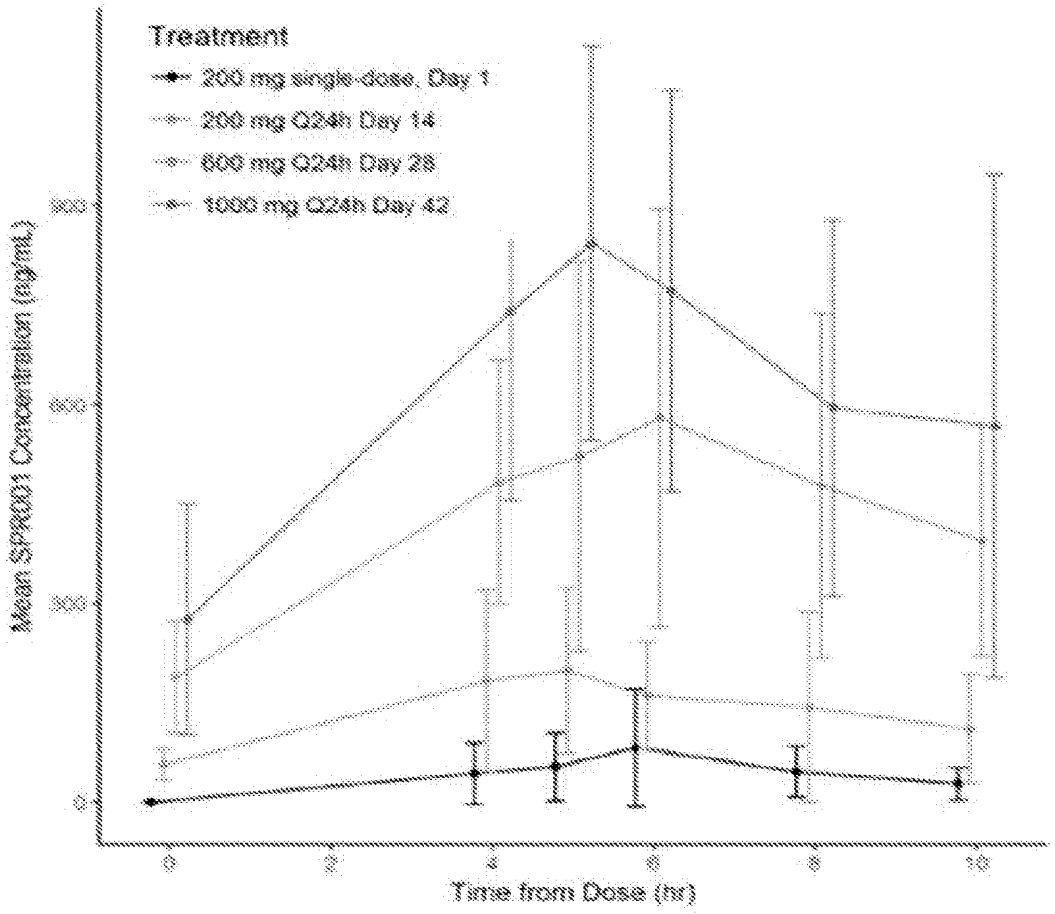

Treatment
200 mg single-dose, Day 1
200 mg Q24h Day 14
600 mg Q24h Day 28
1000 mg Q24h Day 42
Mean SPR001 Concentration (ng/mL)
900
600
300
0
0
2
4
6
8
10
Time from Dose (hr)

FIG. 2

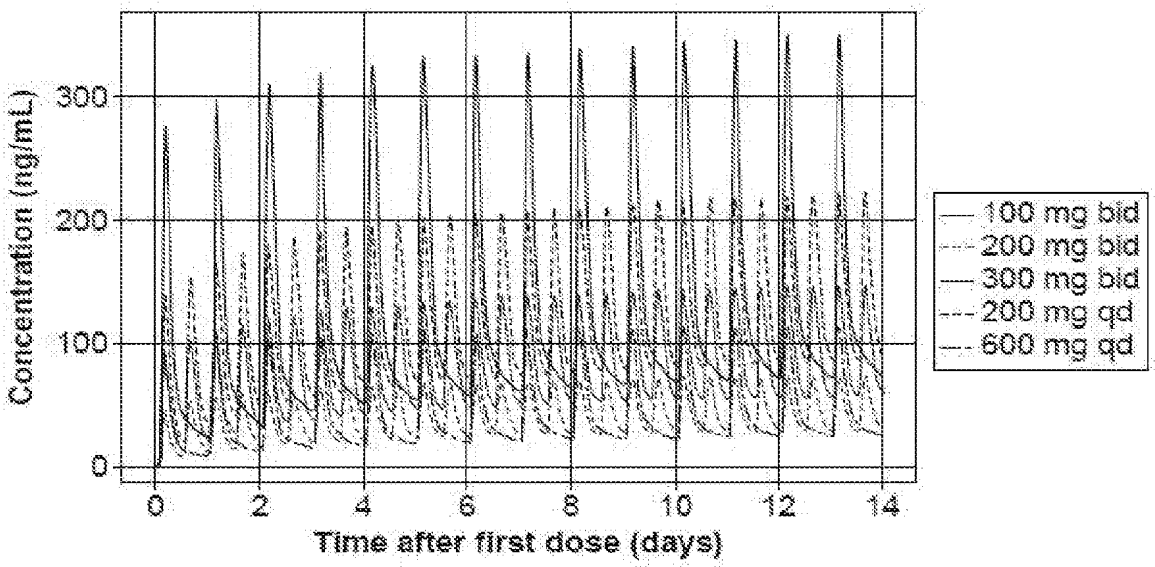

Concentration (ng/mL)
300
200
100
0
0
2
4
6
8
10
12
14
Time after first dose (days)
100 mg bid
200 mg bid
300 mg bid
200 mg qd
600 mg qd

FIG. 3

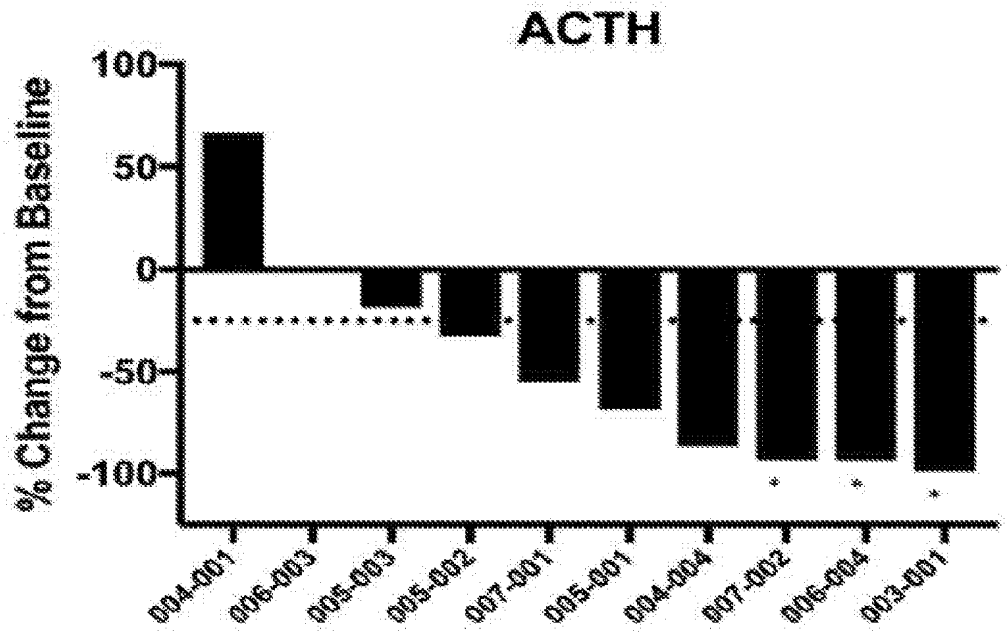

ACTH
% Change from Baseline
100
50
0
-50
-100
004-001
006-003
005-003
005-002
007-001
005-001
004-004
007-002
006-004
003-001

FIG. 4

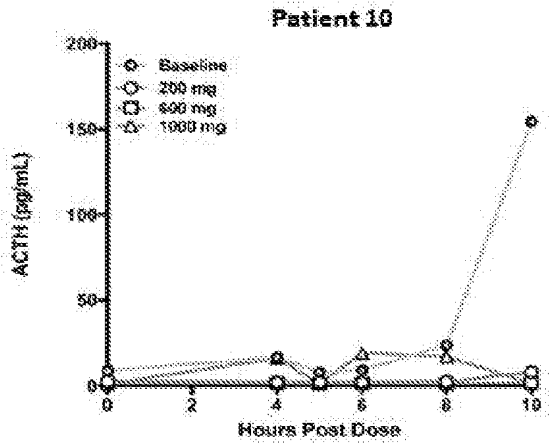


FIG. 5A

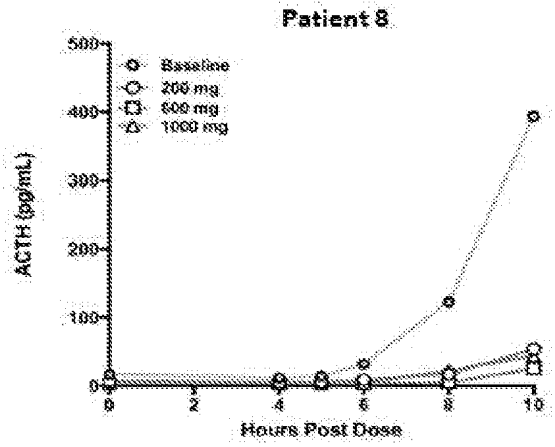


FIG. 5B

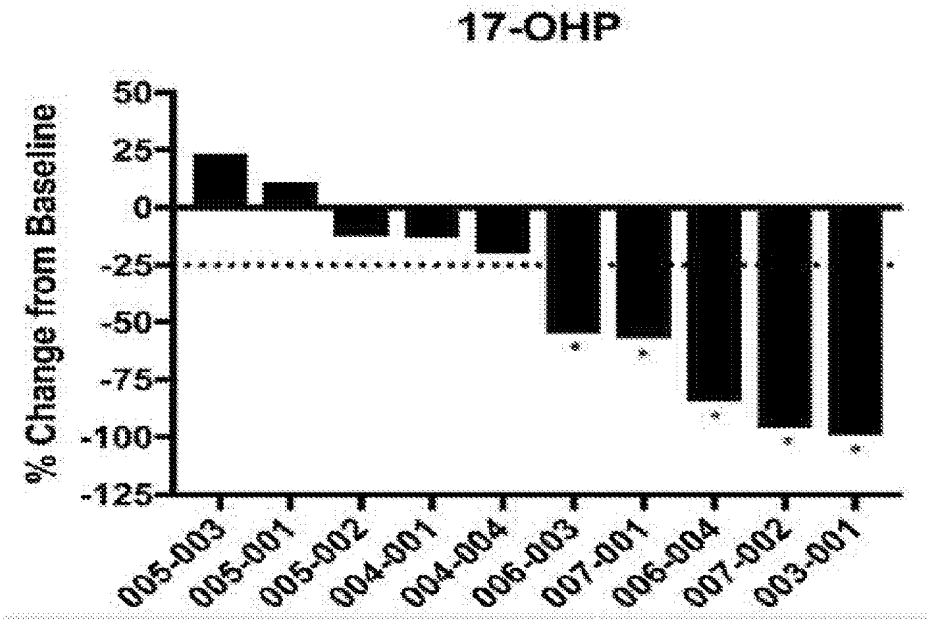


FIG. 6

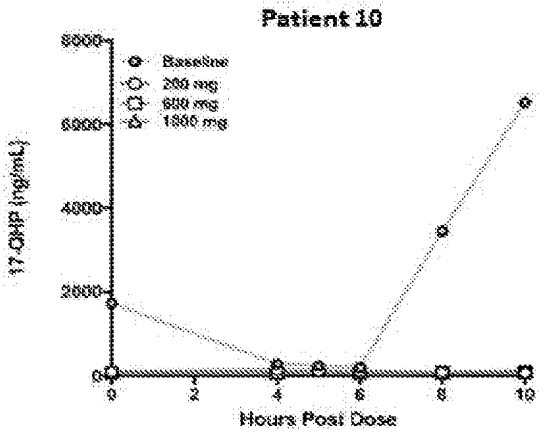


FIG. 7A

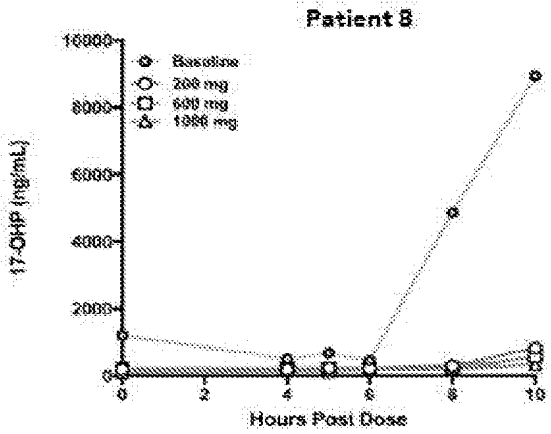


FIG. 7B

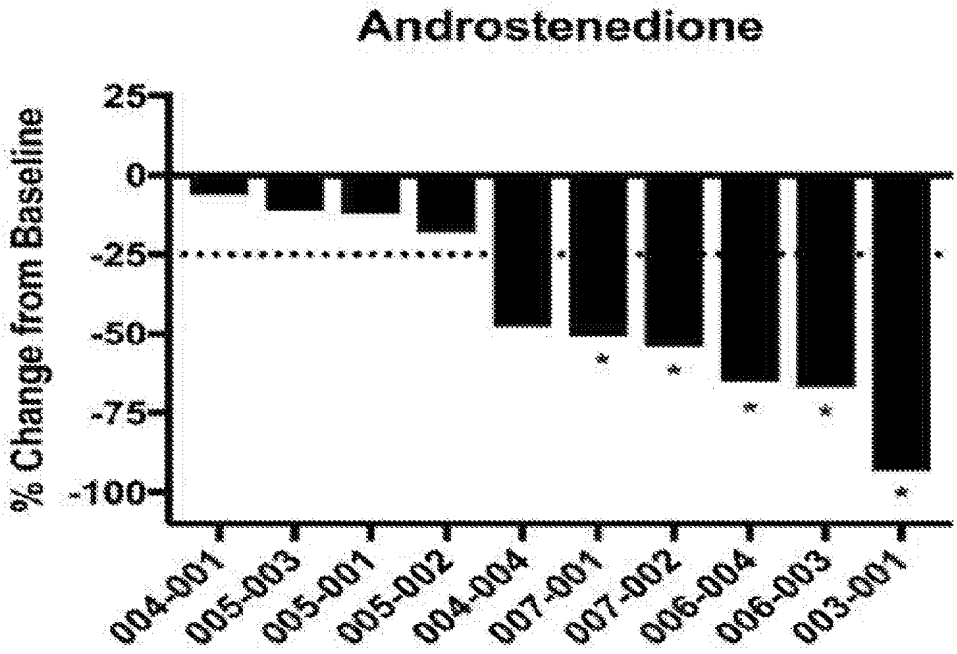


FIG. 8

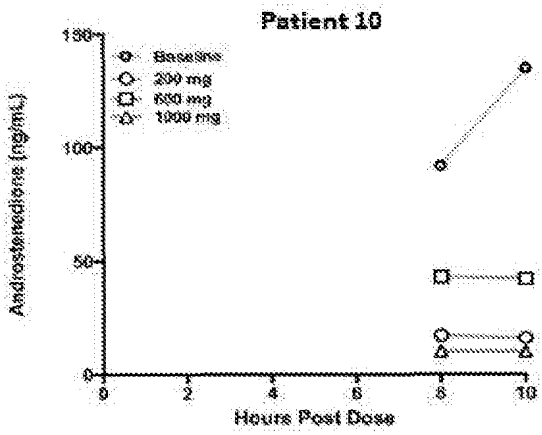


FIG. 9A

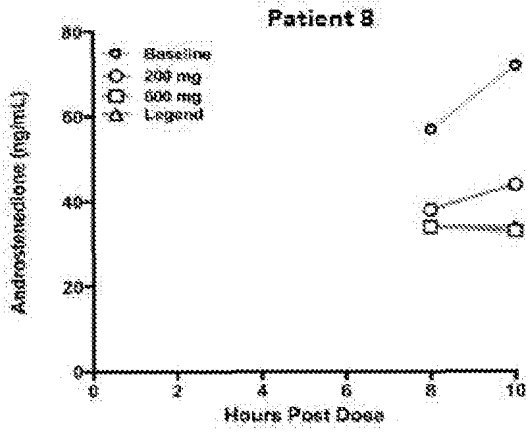


FIG. 9B

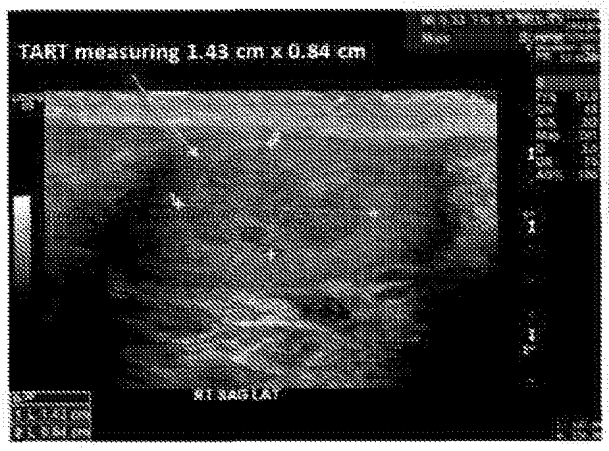


FIG. 10A

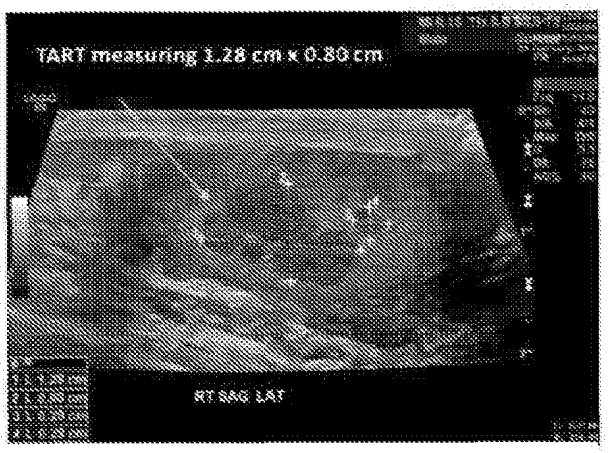


FIG. 10B

In Vitro Binding Assay

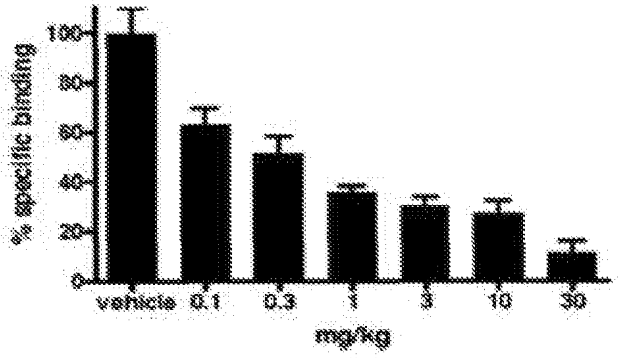


FIG. 11A

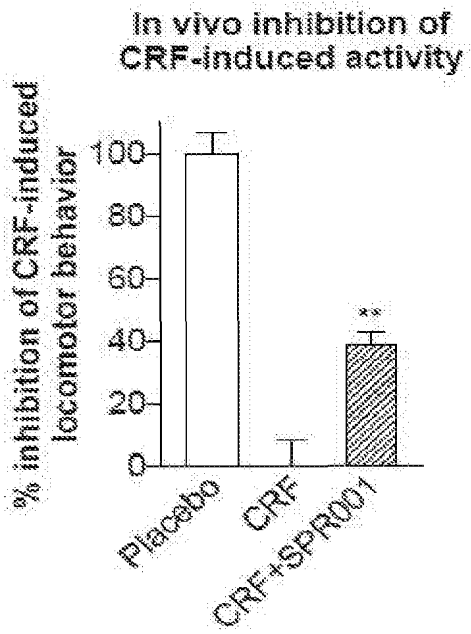


FIG. 11B

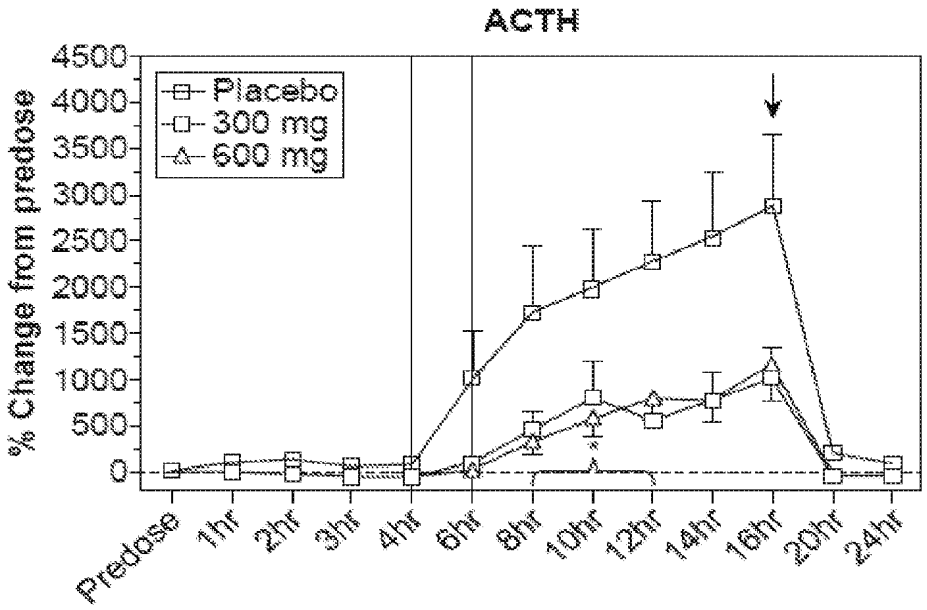


FIG. 12A

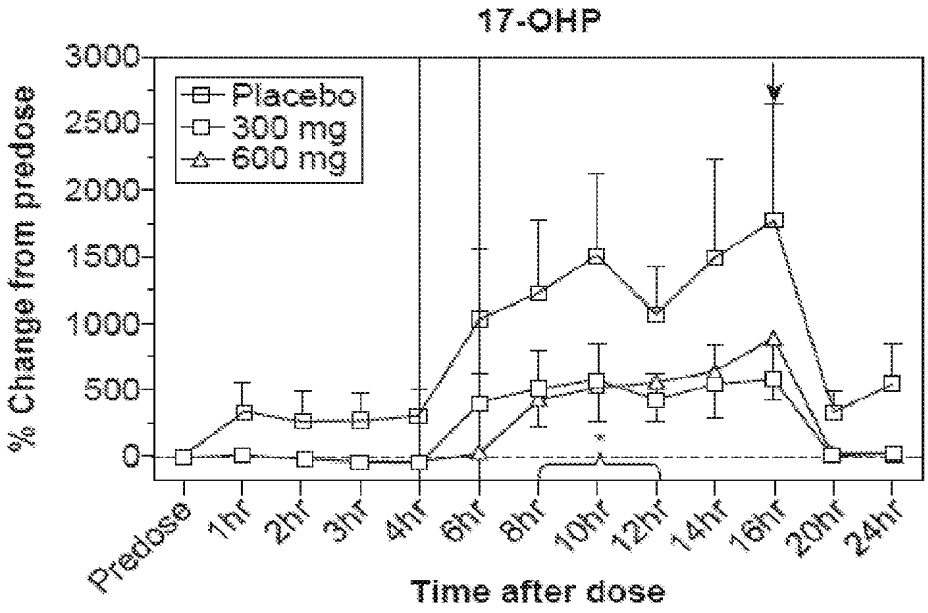


FIG. 12B

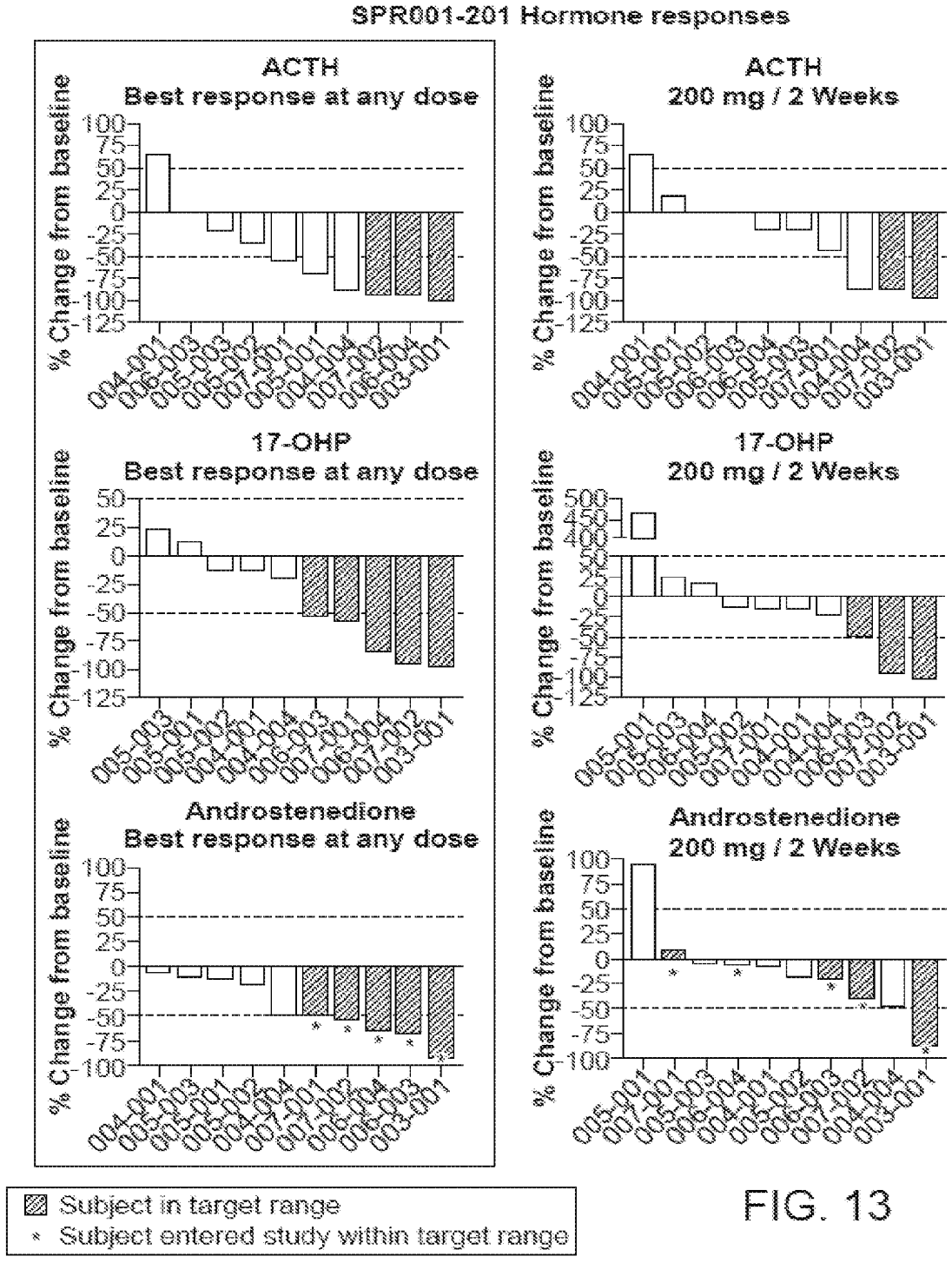


FIG. 13

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

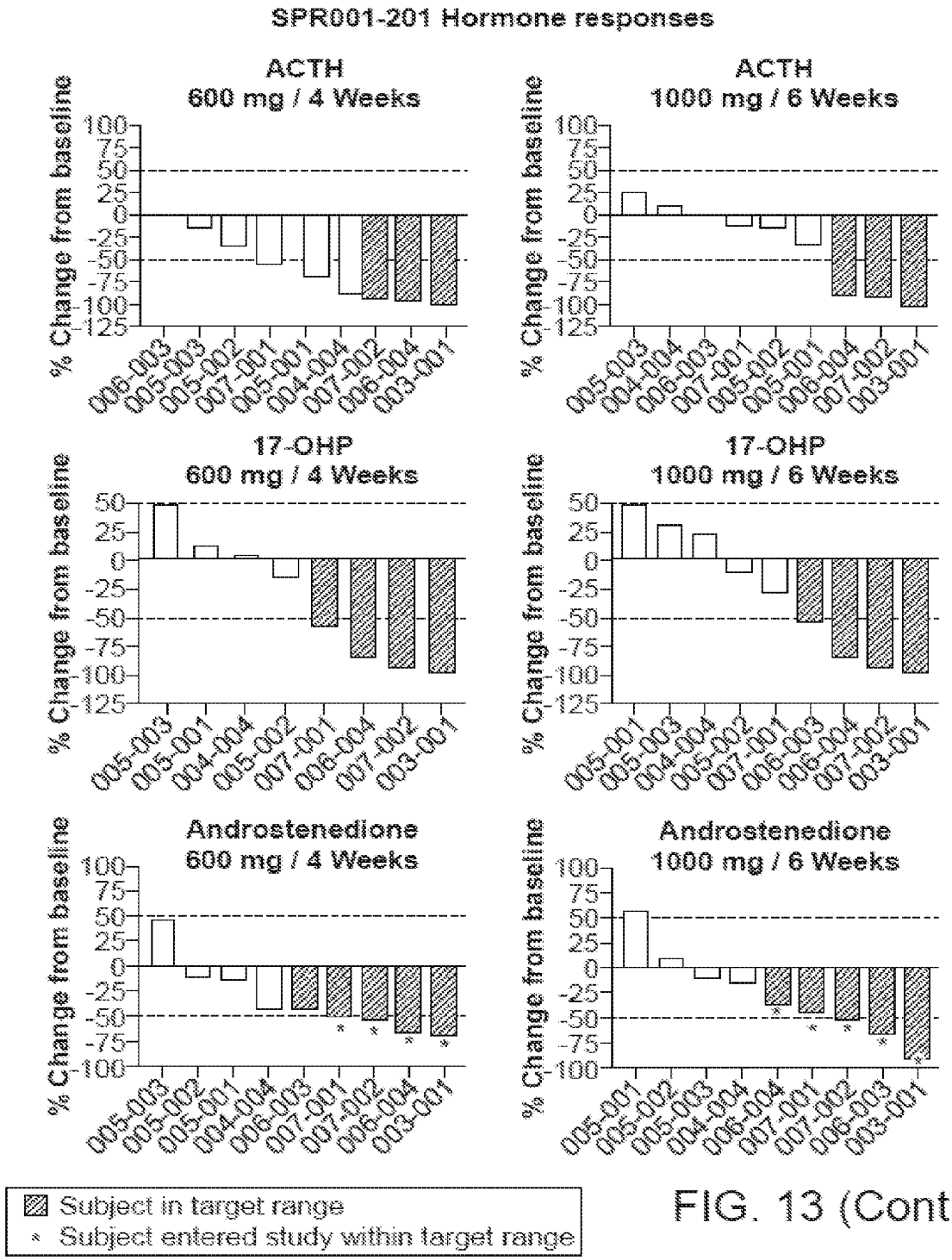


FIG. 13 (Cont.)

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

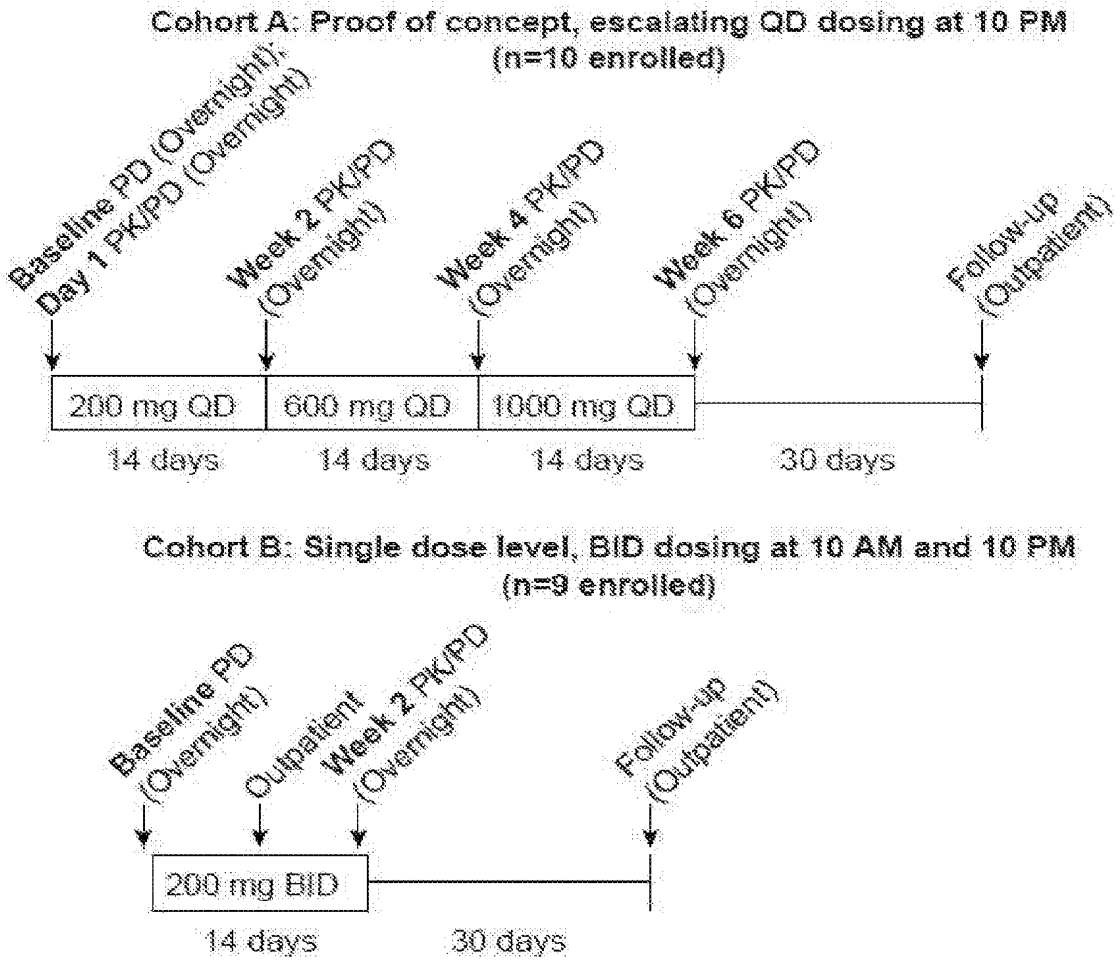

Cohort A: Proof of concept, escalating QD dosing at 10 PM
(n=10 enrolled)
Baseline PD (Overnight); Day 1 PK/PD (Overnight)
Week 2 PK/PD (Overnight)
Week 4 PK/PD (Overnight)
Week 6 PK/PD (Overnight)
Follow-up (Outpatient)
200 mg QD
600 mg QD
1000 mg QD
14 days
14 days
14 days
30 days
Cohort B: Single dose level, BID dosing at 10 AM and 10 PM
(n=9 enrolled)
Baseline PD (Overnight)
Outpatient
Week 2 PK/PD (Overnight)
Follow-up (Outpatient)
200 mg BID
14 days
30 days

FIG. 14

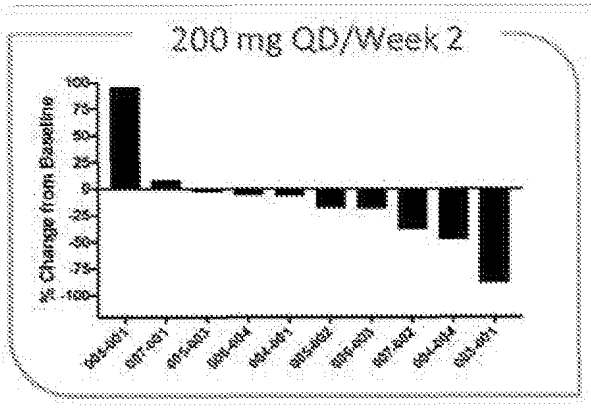


FIG. 15A

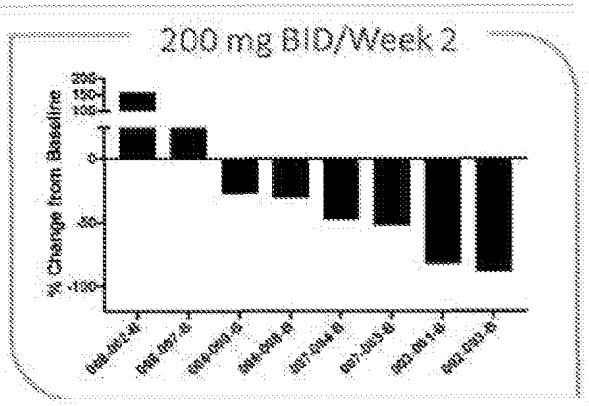


FIG. 15B

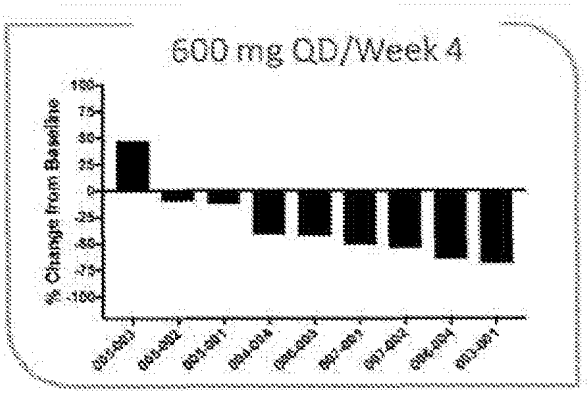


FIG. 15C

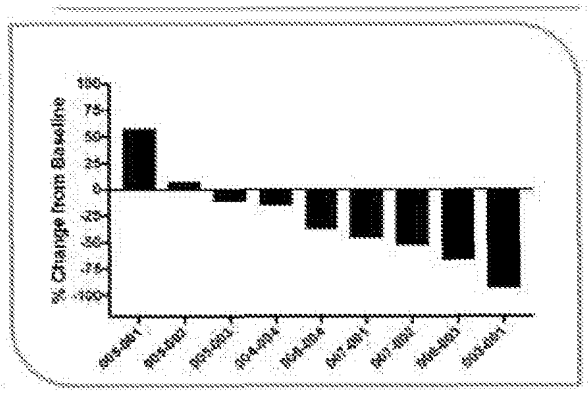


FIG. 15D

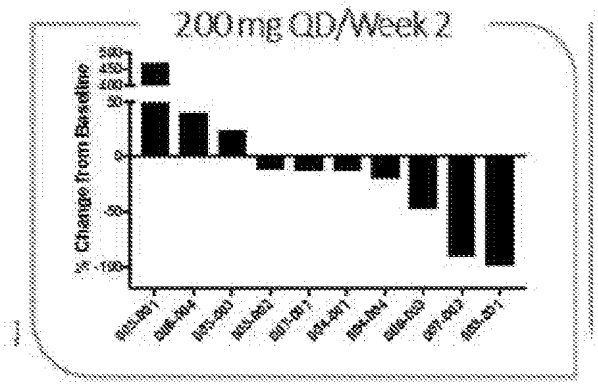


FIG. 16A

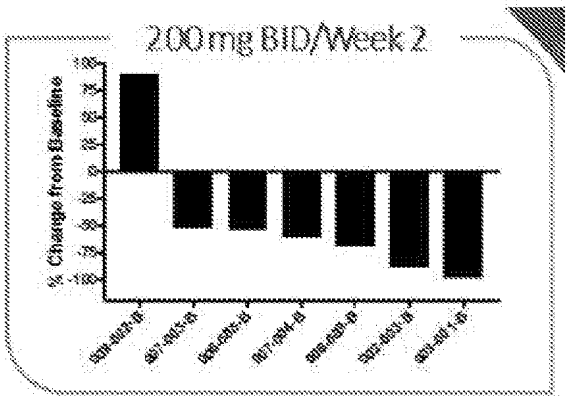


FIG. 16B

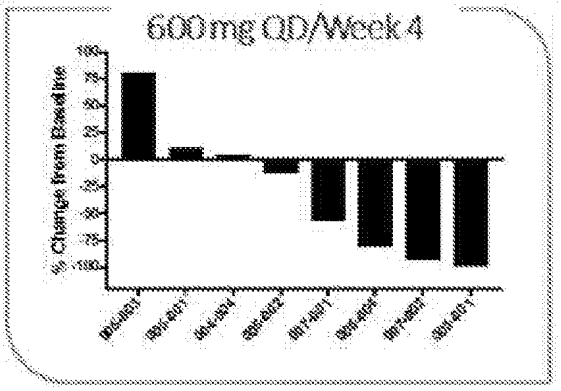


FIG. 16C

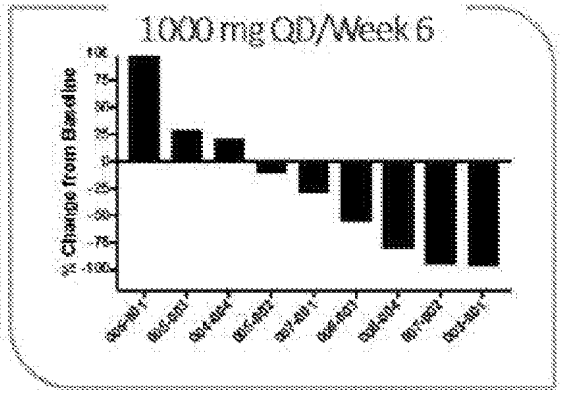


FIG. 16D

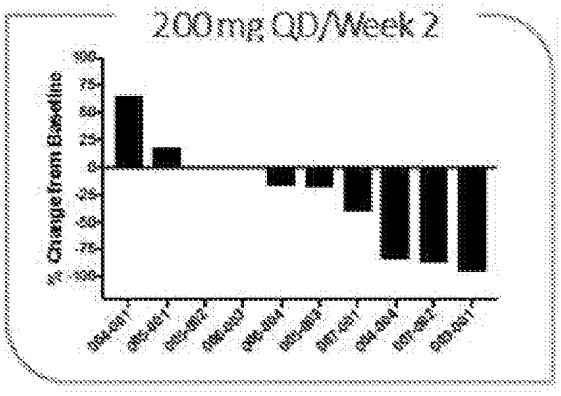


FIG. 17A

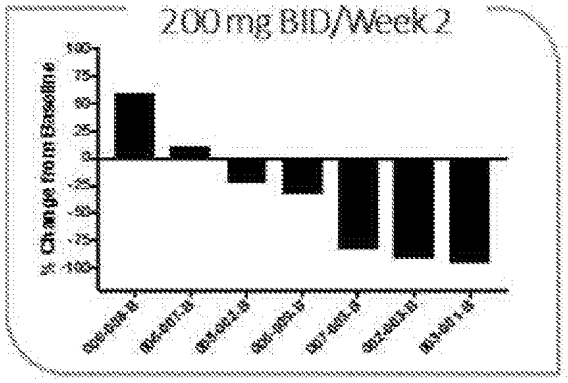


FIG. 17B

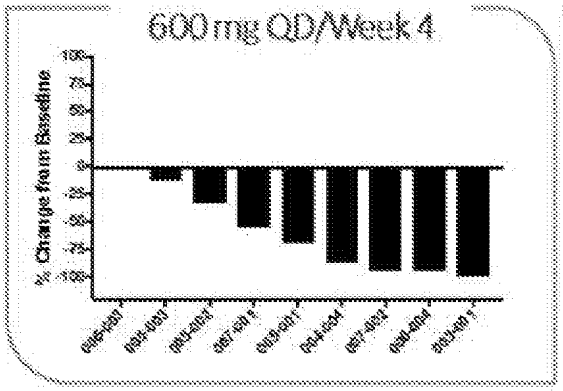


FIG. 17C

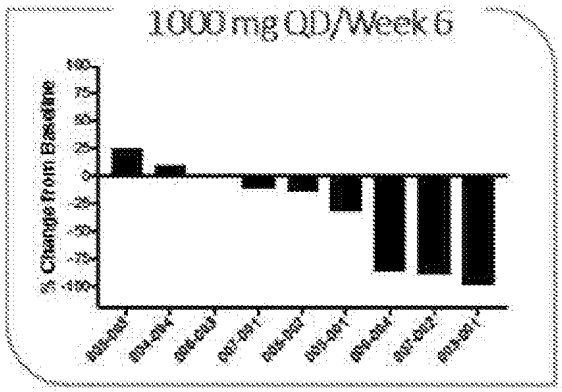


FIG. 17D

REFERENCES CITED IN THE DESCRIPTION

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**08/13/2025 05:50:29 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Jennifer Vail
PATENT CENTER #	71844123	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

TOTAL DOCUMENTS: 42

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710_306_IDS.pdf		13	-	351 KB
Spruce 50535-710_306_IDS-TRAN.LET.pdf	(1-4)	4	Transmittal Letter	155 KB
Spruce 50535-710_306_IDS-IDS.pdf	(5-13)	9	Information Disclosure Statement (IDS) Form (SB08)	250 KB
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NPL_AYCAN_Prevalence_long_667_672_2013.pdf		6	Non Patent Literature	619 KB
NPL_CLAAHSEN_VAN_DER_GRINTEN_Prevalence_te		6	Non Patent Literature	851 KB

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NPL_AUCHUS_Management_Considerations_190_197_2015.pdf	8	Non Patent Literature	1600 KB
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NPL_NEUROCRIN_V_SPRU	3	Non Patent Literature	48 KB

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NPL_NEUROCRIN_V_SPRUCE_PatentOwnersResponse_08JUL2025.pdf	6	Non Patent Literature	142 KB
NPL_Spruce_Biosciences_announces_1_4_2024.pdf	4	Non Patent Literature	787 KB
NPL_REISCH_High_prevalence_1665_1670_2009.pdf	6	Non Patent Literature	730 KB
NPL_NISSEN_clinical_case_1_7_2014.pdf	7	Non Patent Literature	1004 KB
NPL_FLECK_Binding_Kinetics_518_531_2012.pdf	14	Non Patent Literature	4234 KB
NPL_Spruce_Biosciences_announces_1_7_2024.pdf	7	Non Patent Literature	1493 KB
NPL_TURCU_Supplemental_Single_1174_1180_2016.pdf	9	Non Patent Literature	1210 KB
NPL_TURCU_Novel_treatment_225_232_2016.pdf	14	Non Patent Literature	1339 KB
NPL_World_Drug_Information_369_370_2018.pdf	2	Non Patent Literature	76 KB
NPL_STIKKELBROECK_High_prevalence_5721_5728_2001.pdf	8	Non Patent Literature	2403 KB
NPL_US62822815_Provisional_2019_03_23.pdf	25	Non Patent Literature	1257 KB
NPL_WALDRON_Spruce_sa	2	Non Patent Literature	1056 KB

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NPL_YAMADA_New_class_1075_1078_2004.pdf	4	Non Patent Literature	1208 KB
NPL_YASIR_Corticosteroid_Adverse_2023.pdf	14	Non Patent Literature	1011 KB
NPL_YU_Clinical_manifestations_155_161_2015.pdf	7	Non Patent Literature	1223 KB
NPL_WANG_Diagnosis_testicular_1_6_2015.pdf	6	Non Patent Literature	2380 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**08/13/2025 05:50:29 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Jennifer Vail
PATENT CENTER #	71844123	AUTHORIZED BY	Kaia Parenti
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 232415	**E20258CH51446106**	**Jennifer Vail**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	280.00	1	280.00
1834	FILING AN INFORMATION DISCLOSURE STATEMENT THAT CAUSES THE CUMULATIVE NUMBER OF APPLICANT-PROVIDED ITEMS OF INFORMATION TO EXCEED 200	300.00	1	300.00
			TOTAL AMOUNT:	**$580.00**

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**08/18/2025 02:19:45 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Colleen Mensching
PATENT CENTER #	71902493	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710.306 - POA.pdf	2	Power of Attorney	355 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce 50535-710.306 - POA.pdf	9F16E462A7B6446D1D0B2C61358BC9C6F2CE67D34CCED6BB46447B5F8D1DEA0C47F41A58CA2166F9E4C81B25830BC4D5F05101F70959BF254CBCF0EE557BF567

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New Applications Under 35 U.S.C. 111

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

PTO/AIA/82A (07-13)
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Application Number	19/043,264
Filing Date	01/31/2025
First Named Inventor	Alexis HOWERTON
Title	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS
Art Unit	1627
Examiner Name	Sarah PIHONAK
Attorney Docket Number	50535-710.306

SIGNATURE of Applicant or Patent Practitioner

Signature	/Victoria Cheng/	Date (Optional)	2025-08-18
Name	Victoria Cheng	Registration Number	79,641
Title (if Applicant is a juristic entity)	Patent Practitioner		
Applicant Name (if Applicant is a juristic entity)	Spruce Biosciences, Inc.		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of 1 forms are submitted.

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Document Description: Power of Attorney

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I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 21971

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

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Address					
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Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Spruce Biosciences, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Signed by: Samir Ghanta A8FEB31D8F9452...	Date (Optional)	11-Aug-2025
Name	Samir Ghanta		
Title	President and CFO		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

21971 7590 08/18/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER
PIHONAK, SARAH

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
08/18/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary	Application No. 19/043,264	Applicant(s) HOWERTON et al.	
	Examiner SARAH PIHONAK	Art Unit 1627	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 7/24/25.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-21 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-21 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Status of Claims

1. Claims 1-21 are pending as of the response and amendments filed on 7/25/25.

The rejections under 35 USC 112(b), 102(a)(1), and 103 are withdrawn in consideration of the amendments.

The amendments to the specification, filed on 7/24/25, which follow the certificate of correction accepted for US 11304950 are acknowledged and accepted.

The previous nonstatutory double patenting rejections over the claims of US 10849908 B2, US 11007201 B2, US 11311549 B2, US 11344557 B2, and US 11351177 B2 are withdrawn in view of the amendments.

However, the nonstatutory double patenting rejections over the claims of US 11304950 B2, 18941832, 19043275 and 19043303 are maintained. Applicants have stated in the response filed on 7/24/25 that the amendments to the claims render them patentably distinct from the claims of the above cited US patents and copending applications, but the examiner respectfully disagrees, as the above disclosed US patents and copending applications are drawn to treating a common patient population, subjects with OART, by administering the same CRF1 antagonists. These rejections will be reiterated with modification to address the amended claims.

2. Claims 1-21 were examined and are rejected.

Claim Rejections-Nonstatutory Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

Claims 1-5, 8-14, and 17-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 and 19 of U.S. Patent No. 11304950 B2 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003; and Grigoriadis, WO 2015112642 A1, publ. 7/30/2015. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1 antagonist to a subject having ovarian adrenal rest rumors and CAH (see patented claims 1-2 and instant claims 1 and 5). The instant and patented claims differ from each other as the patented claims don't explicitly recite treating menstrual

irregularities or infertility, as recited in instant claim 4. However, Stikkelbroeck teaches females with CAH can have irregular menstrual cycles due to adrenal androgen excess (p. 1030, 1st para). Stikkelbroeck further teaches females with CAH can develop adrenal rest tumors in the ovaries which replace normal ovarian tissue, causing impaired menstrual cycling (p. 1034, right col., last para-p. 1035, left col., top para). Therefore, it would have been prima facie obvious to have applied the instantly claimed method to treat menstrual irregularities in a subject with CAH and ovarian adrenal rest tumors, and have had a reasonable expectation of success. Moreover, it would have been prima facie obvious that by administering the same CRF1 antagonist to treat the same patient population, infertility as recited by instant claim 4 would have also been treated.

Furthermore, Grigoriadis teaches corticotropin releasing factor-1 (CRF1) receptor antagonists for the treatment of congenital adrenal hyperplasia (CAH) (title & abstract; p. 1, lines 3-5). Grigoriadis teaches CAH as a group of autosomal recessive genetic disorders that cause little to no cortisol biosynthesis and often 21-hydroxylase deficiency; ACTH production is excessive (p. 1, line 6-p. 2, line 3). CAH affects both males and females (p. 7, lines 22-28). Grigoriadis teaches treatment of CAH typically involves glucocorticoids to establish sufficient cortisol production and for reducing elevated ACTH levels, and suppression of ACTH prevents menstrual disturbances in women (p. 7, line 29-p. 8, line 11). An issue with glucocorticoid therapy is that the doses required to achieve sufficient suppression of excess androgens are usually well above the normal physiologic dose, and over time glucocorticoid therapy can lead to increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density (p. 9, lines 1-12). Grigoriadis teaches treatment of human and non-human animals; a

therapeutically effective dose is taught to range from about 50-1000 mg. (p. 24, line 3-p. 25, line 7). Grigoriadis teaches various routes of administration, including oral (p. 25, lines 15-21). Grigoriadis teaches administration of a CRF1 receptor antagonist as described results in a clinically significant reduction of both ACTH and 17-OHP levels relative to placebo, including a reduction of at least 25% (p. 28, lines 10-19). Grigoriadis teaches pharmaceutical compositions comprising CRF1 receptor antagonists in the form of tablets or capsules (p. 28, line 20-p. 29, line 16). Grigoriadis further teaches the dose also depends on the patient's condition, stage of disease, severity of symptoms; although bedtime administration is exemplified, the timing of administration can also be adjusted depending on various factors (p. 25, line 22-p. 26, line 20). Therefore, as the patented claims recite the method provides a reduction in ACTH levels, and elevated ACTH levels are associated with menstrual irregularities as taught by Grigoriadis, it would have been prima facie obvious to have modified the patented method by treating menstrual irregularities in a subject with CAH and ovarian adrenal rest tumors, and have had a reasonable expectation of success. Additionally, the amount of CRF1 antagonist administered is the same (from 10-400 mg/day in patented claim 13 compared to 10-400 mg/day as recited by instant claim 8); wherein the CRF1 antagonist is formulated as a capsule or tablet (see instant claim 18 & patented claim 15). Both sets of claims explicitly recite the CRF1 antagonist of instant claims 1-2 (see patented claim 11). As Grigoriadis teaches the dose and timing of administration of the CRF1 receptor antagonist can be adjusted based on various factors, it would have been prima facie obvious to have administered the CRF1 receptor antagonist once per day as recited by instant claim 13, or twice per day as recited by instant claim 14. For these

reasons the instant and patented claims are obvious variants of each other and are not patentably distinct.

4. Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 72-91 of copending application 18941832 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1 antagonist to a subject having an ovarian adrenal rest tumor and CAH (see copending claims 72 and 75-76, and instant claims 1 and 5). The instant and copending claims differ from each other as the copending claims are not explicitly drawn to treating menstrual irregularities. However, Stikkelbroeck teaches females with CAH can have irregular menstrual cycles due to adrenal androgen excess (p. 1030, 1st para). Stikkelbroeck further teaches females with CAH can develop adrenal rest tumors in the ovaries which replace normal ovarian tissue, causing impaired menstrual cycling (p. 1034, right col., last para-p. 1035, left col., top para). Therefore, it would have been prima facie obvious to have applied the instantly claimed method to treat menstrual irregularities in a subject with CAH and ovarian adrenal rest tumors, and have had a reasonable expectation of success.

Additionally, the amount of CRF1 antagonist administered is overlapping (from 5-800 mg/day in copending claim 78 compared to 10-400 mg/day as recited by instant claim 8); wherein the CRF1 antagonist is formulated as a capsule or tablet (see instant claim 18 & copending claim 91); wherein the treated subject is in a fed state (copending claim 84 and instant claims 14-15); and wherein the CRF1 antagonist is administered twice per day

(copending claim 83 & instant claim 14). Both sets of claims explicitly recite the same CRF1 antagonists (see copending claim 72 & instant claim 1); and reduction of the same biomarkers selected from 17-OHP, ACTH, A4, LH, FSH, SHBG, renin, or aldosterone (see instant claim 19 & copending claim 86). As CAH affects females, including women and adolescent females (see Stikkelbroeck, p. 1030, right col., last para-p. 1031, left col., top para), it would have been prima facie obvious to have applied the copending method to treat an adolescent female as recited by instant claim 6, and a female at least 18 years or older as recited by instant claim 7. Moreover, it would have been prima facie obvious that by administering the same CRF1 antagonist to treat the same patient population, infertility as recited by instant claim 4 would have also been treated.

For these reasons the instant and copending claims are obvious variants of each other and are not patentably distinct.

5. Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5 and 9-21 of copending application 19043275 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1 antagonist to a subject having an ovarian adrenal rest tumor and CAH (see copending claims 1 & 4-5, and instant claims 1 and 5). The instant and copending claims differ from each other as the copending claims are not drawn to treating menstrual irregularities. However, Stikkelbroeck teaches females with CAH can have irregular menstrual cycles due to adrenal androgen excess (p. 1030, 1st para). Stikkelbroeck

further teaches females with CAH can develop adrenal rest tumors in the ovaries which replace normal ovarian tissue, causing impaired menstrual cycling (p. 1034, right col., last para-p. 1035, left col., top para). Therefore, it would have been prima facie obvious to have applied the instantly claimed method to treat menstrual irregularities in a subject with CAH and ovarian adrenal rest tumors, and have had a reasonable expectation of success. Moreover, it would have been prima facie obvious that by administering the same CRF1 antagonist to treat the same patient population, infertility as recited by instant claim 4 would have also been treated.

Additionally, the amount of CRF1 antagonist administered is the same (10-400 mg/day as recited by instant claim 8 and copending claim 11); wherein the CRF1 antagonist is formulated as a capsule or tablet (see instant claim 18 & copending claim 21); wherein the treated subject is in a fed state (copending claims 18-19 and instant claims 14-15); and wherein the CRF1 antagonist is administered once per day (copending claim 16 & instant claim 13); and the CRF1 antagonist is administered twice per day (copending claim 17 & instant claim 14). Both sets of claims explicitly recite the same CRF1 antagonists (see copending claim 1 & instant claim 1); treatment of an adolescent (see copending claim 9 & instant claim 6); and treatment of a subject at least 18 years of age (copending claim 10 & instant claim 7). For these reasons the instant and copending claims are obvious variants of each other and are not patentably distinct.

6. Claims 1-13 and 17-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending application 19043303 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003. Although the

claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1 antagonist to a subject having an ovarian adrenal rest tumor and CAH (see copending claims 1 & 5, and instant claims 1 and 5). The instant and copending claims differ from each other as the copending claims are not drawn to treating not menstrual irregularities. However, Stikkelbroeck teaches females with CAH can have irregular menstrual cycles due to adrenal androgen excess (p. 1030, 1st para). Stikkelbroeck further teaches females with CAH can develop adrenal rest tumors in the ovaries which replace normal ovarian tissue, causing impaired menstrual cycling (p. 1034, right col., last para-p. 1035, left col., top para). Therefore, it would have been prima facie obvious to have applied the instantly claimed method to treat menstrual irregularities in a subject with CAH and ovarian adrenal rest tumors, and have had a reasonable expectation of success. Moreover, it would have been prima facie obvious that by administering the same CRF1 antagonist to treat the same patient population, infertility as recited by instant claim 4 would have also been treated.

Additionally, the amount of CRF1 antagonist administered is the same (10-400 mg/day as recited by instant claim 8 and copending claim 8); wherein the CRF1 antagonist is formulated as a capsule or tablet (see instant claim 18 & copending claim 16); wherein the CRF1 antagonist is administered once per day (copending claim 13 & instant claim 13); and the CRF1 antagonist is administered twice per day (copending claim 14 & instant claim 14). Both sets of claims explicitly recite the same CRF1 antagonists (see copending claim 1 & instant claim 1); treatment of an adolescent (see copending claim 9 & instant claim 6); and treatment of a subject at least 18 years of age (copending claim 10 & instant claim 7). As CAH affects females, including

women and adolescent females (see Stikkelbroeck, p. 1030, right col., last para-p. 1031, left col., top para), it would have been prima facie obvious to have applied the copending method to treat an adolescent female as recited by instant claim 6, and a female at least 18 years or older as recited by instant claim 7. For these reasons the instant and copending claims are obvious variants of each other and are not patentably distinct.

Information Disclosure Statement

7. The IDS filed on 7/24/25 and 8/13/25 have been considered.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any nonprovisional extension fee (37 CFR 1.17(a)) pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

8. Claims 1-21 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached Monday-Friday 9:00-5:30 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached at 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SARAH . PIHONAK
Primary Examiner
Art Unit 1627

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

CPC - Searched*		
Symbol	Date	Examiner
a61k31/519; a61p5/06,08	04/21/2025	s.p.
a61k31/519, 5377; a61p5/06,08	08/13/2025	s.p.

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
a61k31/519; a61p5/06,08	04/21/2025	s.p.
inventor & applicant search in PE2E, patent data portal	04/21/2025	s.p.
invention & claims search in stn, PE2E	04/21/2025	s.p.
a61k31/519, 5377; a61p5/06,08	08/13/2025	s.p.
inventor & applicant search in PE2E, patent data portal	08/13/2025	s.p.
invention & claims search in PE2E	08/13/2025	s.p.

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	652	(corticotropin adj8 factor adj8 antagon*) AND (menstruation OR menstrual)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:36 PM
L2	200	((corticotropin adj8 factor adj8 antagon*) OR (CRF1 adj8 antagon*)).ab,ti,clm. AND L1	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:37 PM
L3	276	(corticotropin adj8 factor adj8 antagon*) AND (dysmenorrhea)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:42 PM
L4	42	((corticotropin adj8 factor adj8 antagon*) OR (CRF1 adj8	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY,	OR	ON	ON	2025/04/18 05:42 PM

		antagon*)).ab,ti,clm. AND L3	CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L5	192	(((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND (L2 OR L4)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:53 PM
L6	31	((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/04/18 06:11 PM
L7	21	((("HOWERTON") near3 ("Alexis"))).INV.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/04/18 06:11 PM
L8	21	((("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/04/18 06:11 PM
L9	23	(L2 OR L4) AND (L6 OR L7 OR L8)	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/04/18 06:12 PM
L10	6002	(a61k31/519 OR a61p5/06,08).cpc. AND (menstrual OR menstruation OR dysmenorrhea OR dysmennorhea OR dysmennorrhea)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 06:14 PM
L11	140	(corticotropin adj8 factor	(US-PGPUB; USPAT;	OR	ON	ON	2025/04/18

		adj8 antagon*) AND L10	USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				06:14 PM
L12	96	((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L11	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 06:15 PM
L13	19	("10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220143037" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2025/04/21 09:32 AM
L14	940	(a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 antagon*)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS,	OR	ON	ON	2025/04/21 10:26 AM

			IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L15	877	(((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L14	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 10:26 AM
L16	286	L15 AND (corticotropin adj8 releas* adj8 factor adj8 antagon*).ab,ti,clm.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 10:27 AM
L17	484	(corticotropin adj8 factor adj8 antagon*) AND (amenorrhea)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 12:48 PM

L18	489	(corticotropin adj8 factor adj8 antagon*) AND (amenorrhea OR menorrhagia)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 12:48 PM
L19	423	(((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 12:49 PM
L20	31	"1200419".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 01:07 PM
L21	1	"6586456".pn.	(USPAT)	OR	ON	ON	2025/04/21 01:08 PM
L22	272	(congenital adj6 adrenal adj6 hyperplasia) WITH (menorrhagia OR dysmenorrhea OR menstrual OR menstruation)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV,	OR	ON	ON	2025/04/21 03:18 PM

			MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L23	216	(((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L22	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 03:18 PM
L24	7	"2015112642".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 04:20 PM
L25	3	L24 AND (time OR frequency)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 04:21 PM
L26	2	L24 AND (one OR once OR twice)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP,	OR	ON	ON	2025/04/21 04:21 PM

			ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L27	1	L24 AND (day OR daily)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 04:21 PM
L28	1	"20100222339".pn.	(US-PGPUB)	OR	ON	ON	2025/04/21 04:48 PM
L29	1	L28 AND adrenal	(US-PGPUB)	OR	ON	ON	2025/04/21 04:48 PM
L30	0	L28 AND adrenal AND (tablet* OR capsule*)	(US-PGPUB)	OR	ON	ON	2025/04/21 04:48 PM
L31	1	"12098152".pn.	(USPAT)	OR	ON	ON	2025/04/21 05:46 PM
L32	54	("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/05 03:00 PM

		"20220143037" OR "20230159533" OR "20230321112" OR "20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177404" OR "20250195527" OR "8030304" OR "8563718" OR "10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn.					
L33	36	("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR "20220143037" OR "20230159533" OR "20230321112" OR	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/05 03:06 PM

		"20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177404" OR "20250195527" OR "8030304" OR "8563718").pn.					
L34	1	"20250177403".pn.	(US-PGPUB)	OR	ON	ON	2025/08/13 03:01 PM
L35	23	(a61k31/519,5377 OR a61p5/06,08).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 (inhibit* OR antagon* OR block*)) AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/08/13 03:04 PM
L36	28	(Artificial Intelligence) More like doc: US-20250177403-A1 Text: (JP-H0971528-A OR AU-2007231549-A1 OR RS-51545-B OR US-20100203048-A1 OR IL-317035-A OR BR-112020002967-A2 OR US-20210137935-A1 OR US-20250177403-A1 OR HK-40040045-A OR US-20250177404-A1 OR US-20250195527-A1 OR US-20250064812-A1 OR US-11304950-B2 OR HK-40040045-B OR EP-3784233-B1 OR AU-2023203095-A1 OR CA-3098562-A1 OR US-20210038604-A1 OR BR-112020024062-A2 OR US-20220211711-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/08/13 03:06 PM
L37	14	L36 AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY,	OR	ON	ON	2025/08/13 03:07 PM

			CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L38	35	((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/13 03:07 PM
L39	24	((("HOWERTON") near3 ("Alexis")) OR (("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2025/08/13 03:08 PM
L40	8	(L38 OR L39) AND (corticotropin adj8 releas* adj8 factor adj8 (inhibit* OR antagon* OR block*)) AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/13 03:08 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	7	(a61k31/519,5377 OR a61p5/06,08).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 (inhibit* OR antagon* OR block*)) AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/13 03:06 PM

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	9	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	EP-3784233-B1	06-05-2024	SPRUCE BIOSCIENCES INC [US]		☐

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	08/14/2025

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	AUCHUS, Richard J. et al. Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	002	AUCHUS, Richard J. et al. Supplemental Information: Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	003	AUCHUS, Richard J. Management Considerations for the Adult With Congenital Adrenal Hyperplasia. Molecular and Cellular Endocrinology 408:190-197 (2015).	☐
	004	AVILA, N. A. et al. Testicular adrenal rest tissue in congenital adrenal hyperplasia: serial sonographic and clinical findings. AJR. American journal of roentgenology 172(5):1235-1238 (1999).	☐
	005	AYCAN, Zehra et al. Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia. Clinical endocrinology 78(5):667-672 (2013).	☐
	006	CLAAHSEN-VAN DER GRINTEN, H. L. et al. Testicular adrenal rest tumours in congenital adrenal hyperplasia. International Journal of pediatric endocrinology 2009:624823, 1-8 (2009).	☐
	007	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Prevalence of testicular adrenal rest tumours in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. European journal of endocrinology 157(3):339-344 (2007).	☐
	008	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Repeated successful induction of fertility after replacing hydrocortisone with dexamethasone in a patient with congenital adrenal hyperplasia and testicular adrenal rest tumors. Fertility and Sterility 88(3):705.e5-705.e8 (2007).	☐

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	08/14/2025

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	3	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	009	ClinicalTrials.gov Identifier: NCT04457336. A Ph2b to Evaluate Clinical Efficacy and Safety of Tildacerfont in Adult CAH, Record created June 25, 2020. pp. 1-17. [retrieved on 2025-08-12] Available at URL: https://clinicaltrials.gov/study/NCT04457336.	☐
	010	DELFINO, Michele et al. Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia: prevalence and sonographic, hormonal, and seminal characteristics. Journal of ultrasound in medicine 31(3):383-388 (2012).	☐
	011	ENGELS, Manon et al. Testicular adrenal rest tumors: current insights on prevalence, characteristics, origin, and treatment. Endocrine Reviews 40(4):973-987 (2019).	☐
	012	EP19793181.9 Brief Communication - Opposition Proceedings dated August 5, 2025.	☐
	013	EP19793181.9 Reply from the opponent to submission of proprietor dated July 18, 2025.	☐
	014	EP19793181.9 Reply of the Patent Proprietor to the notice(s) of opposition dated June 18, 2025.	☐
	015	FLECK, Beth A. et al. Binding Kinetics Redefine the Antagonist Pharmacology of the Corticotropin-releasing Factor Type 1 Receptor. The Journal of Pharmacology and Experimental Therapeutics 341(2):518-531 (2012).	☐
	016	JOSEPH, Dana N., and Shannon Whirledge. Stress and the HPA axis: balancing homeostasis and fertility. International journal of molecular sciences 18(10):2224, 1-15 (2017).	☐
	017	MA, Li et al. Sonographic features of the testicular adrenal rests tumors in patients with congenital adrenal hyperplasia: a single-center experience and literature review. Orphanet Journal of Rare Diseases 14(1):242, 1-8 (2019).	☐

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				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	018	MAZZILLI, Rossella et al. The High Prevalence of Testicular Adrenal Rest Tumors in Adult Men With Congenital Adrenal Hyperplasia Is Correlated With ACTH Levels. Front Endocrinol (Lausanne) 10:335 (2019).	☐
	019	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Defence dated March 13, 2025 (Claim No. HP-2025-000005) (pp. 1-3).	☐
	020	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Grounds of Invalidity dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	021	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Particulars of Claim dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	022	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Patent Owner's Response in U.S. Patent No. 12,115,166 dated July 8, 2025 (pp 1-6) (PGR-2025-00032).	☐
	023	Neurocrine Biosciences, Inc. (Plaintiff) v. Spruce Biosciences, Inc. (Defendant). Memorandum dated June 9, 2025 (Case No. 1:25-cv-00059-JDW (pp. 1-10).	☐
	024	NISSEN, Trygve et al. The clinical case report: a review of its merits and limitations. BMC Research Notes 7:264, 1-7 (2014).	☐
	025	REISCH, Nicole et al. High prevalence of reduced fecundity in men with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 94(5):1665-1670 (2009).	☐
	026	Spruce Biosciences announces topline results from CAHMELIA-203 in adult classic CAH and CAHPTAIN-205 in pediatric classic CAH. Spruce Biosciences :1-7 (2024).	☐

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	027	Spruce Biosciences announces topline results from CAHMELIA-204 in adult CAH and CAHPTAIN-205 in adult and pediatric CAH. Spruce Biosciences :1-4 (2024).	☐
	028	STIKKELBROECK, Nike M. M. L. et al. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 86(12):5721-5728 (2001).	☐
	029	The Journal of Clinical Endocrinology and Metabolism Author Guidelines. Oxford Academic (2025); [retrieved on 2025-06-09]. Available at URL: https://academic.oup.com/jcem/pages/author_guidelines.	☐
	030	TURCU, Adina F. and Richard J. Auchus. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinology and Metabolism Clinics 44(2):275-296 (2015).	☐
	031	TURCU, Adina F., and Richard J. Auchus. Novel treatment strategies in congenital adrenal hyperplasia. Current Opinion in Endocrinology, Diabetes and Obesity 23(3):225-232 (2016).	☐
	032	TURCU, Adina F. et al. Supplemental Information: Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016).	☐
	033	U.S. Provisional Application No. 62/822,815 filed on March 23, 2019.	☐
	034	WALDRON, James. Spruce saws off only drug after 2nd hyperplasia fail, leaving biotech's direction in doubt. Fierce Biotech :1-2 (2024).	☐
	035	WANG, Zhu et al. Diagnosis of testicular adrenal rest tumors on ultrasound: a retrospective study of 15 cases report. Medicine 94(36):e1471, 1-6 (2015).	☐

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	036	World Health Organization Drug Information, 32(2):369-370 (2018).	☐
	037	YAMADA, Yasuki et al. New class of corticotropin-releasing factor (CRF) antagonists: small peptides having high binding affinity for CRF receptor. Journal of medicinal chemistry 47(5):1075-1078 (2004).	☐
	038	YASIR, Muhammad et al. Corticosteroid Adverse Effects. StatPearls, July 3, 2023; [retrieved on 2025-06-17]. Available at URL: https://www.ncbi.nlm.nih.gov/books/NBK531462/ pp. 1-14.	☐
	039	YU, Min Kyung et al. Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia. Annals of pediatric endocrinology and metabolism 20(3):155-161 (2015).	☐

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Sheet	7	of	9	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

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Signature:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-08-13
Name/Print	Kaia R. Parenti	Registration Number	81050

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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	001	US-8030304	10-04-2011	CHEN et al.	
	002	US-8563718	10-22-2013	RIZZO; John Robert et al.	
	003	US-11708372	07-25-2023	REDDY; Dasharatha et al.	
	004	US-11858932	01-02-2024	BARNES; Christopher et al.	
	005	US-12098152	09-24-2024	BARNES; Christopher et al.	
	006	US-20020013357	01-31-2002	NADKARNI; Sreekant et al.	
	007	US-20030008885	01-09-2003	HE; Liqi et al.	
	008	US-20050209250	09-22-2005	ROMANO; Steve	
	009	US-20060078623	04-13-2006	DHOOT; Nikhil et al.	
	010	US-20090076266	03-19-2009	DAUGULIS; Olafs et al.	
	011	US-20100022560	01-28-2010	CHEN; Zhaogen et al.	
	012	US-20100155595	06-24-2010	GHOSHAL; Amit [Us] et al.	
	013	US-20110136865	06-09-2011	BUNTINX; Erik	
	014	US-20110160168	06-30-2011	DHINGRA; Om	
	015	US-20110166345	07-07-2011	RIZZO; John Robert et al.	
	016	US-20130045979	02-21-2013	SANFILIPPO; Louis	
	017	US-20170333126	11-23-2017	SOBOTKA; Paul	

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	018	US-20180110554	04-26-2018	ZARINS; Denise Marie et al.	
	019	US-20190262349	08-29-2019	HOWERTON; Alexis et al.	
	020	US-20200255436	08-13-2020	HOWERTON; Alexis et al.	
	021	US-20210015827	01-21-2021	HOWERTON; Alexis et al.	
	022	US-20210038604	02-11-2021	HOWERTON; Alexis et al.	
	023	US-20210137935	05-13-2021	HOWERTON; Alexis et al.	
	024	US-20210322430	10-21-2021	HOWERTON; Alexis et al.	
	025	US-20210361664	11-25-2021	HOWERTON; Alexis et al.	
	026	US-20220133742	05-05-2022	GHOSH; Sangita et al.	
	027	US-20220133742	05-05-2022	GHOSH; Sangita et al.	
	028	US-20220143037	05-12-2022	HOWERTON; Alexis et al.	
	029	US-20230159533	05-25-2023	REDDY; Dasharatha et al.	
	030	US-20230321112	10-12-2023	HOWERTON; Alexis et al.	
	031	US-20230414627	12-28-2023	HOWERTON; Alexis et al.	
	032	US-20240043432	02-08-2024	REDDY; Dasharatha et al.	
	033	US-20240261300	08-08-2024	GHOSH; Sangita et al.	

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	034	US-20240293421	09-05-2024	REDDY; Dasharatha et al.	
	035	US-20250064812	02-27-2025	HOWERTON; Alexis et al.	
	036	US-20250177404	06-05-2025	HOWERTON; Alexis et al.	
	037	US-20250195527	06-19-2025	HOWERTON; Alexis et al.	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	CN-101516835-A	08-26-2009	OSURF OHIO STATE UNIVERSITY RE [US]	Abstract:	☒
	002	EP-2094709-B1	09-15-2010	LILLY CO ELI [US]		☐
	003	EP-3984523-A1	04-20-2022	NEUROCRINE BIOSCIENCES INC [US], et al.		☐
	004	JP-2000302693-A	10-31-2000	PFIZER PROD INC.	Abstract:	☒
	005	KR-19990067391-A	08-16-1999	JANSSEN PHARMACEUTICA NV [BE], et al.	Machine Translation:	☒

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				Application Number	19/043,264
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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	16	Attorney Docket Number	50535-710.306

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	006	WO-0059908-A2	10-12-2000	DU PONT PHARM CO [US]		☐
	007	WO-0123388-A2	04-05-2001	NEUROGEN CORP [US], et al.		☐
	008	WO-02072202-A1	09-19-2002	BRISTOL MYERS SQUIBB PHARMA CO [US]		☐
	009	WO-2005020910-A2	03-10-2005	PHARMACIA CORP [US], et al.		☐
	010	WO-2005063755-A1	07-14-2005	SB PHARMCO INC [US], et al.		☐
	011	WO-2005079868-A2	09-01-2005	SB PHARMCO INC [US], et al.		☐
	012	WO-2006102194-A1	09-28-2006	LILLY CO ELI [US], et al.		☐
	013	WO-2010039678-A1	04-08-2010	LILLY CO ELI [US], et al.		☐
	014	WO-2013160317-A2	10-31-2013	HOLSBOERMASCHMEYER NEUROCHEMIE GMBH [DE]		☐
	015	WO-2020115555-A2	06-11-2020	NEUROCRINE BIOSCIENCES INC [US], et al.		☐

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	016	WO-2021016208-A1	01-28-2021	SPRUCE BIOSCIENCES INC [US]		☐
	017	WO-2022036123-A1	02-17-2022	SPRUCE BIOSCIENCES INC [US]		☐
	018	WO-2023091684-A1	05-25-2023	SPRUCE BIOSCIENCES INC [US]		☐
	019	WO-9413676-A1	06-23-1994	PFIZER [US], et al.		☐
	020	WO-9729109-A1	08-14-1997	JANSSEN PHARMACEUTICA NV [BE], et al.		☐
	021	WO-9803510-A1	01-29-1998	DU PONT MERCK PHARMA [US]		☐
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	001	ABCAM CP 154526 Hydrochloride, Non-Peptide CRF1 Receptor Antagonist AB141429. [Internet] ABCAM. Retrieved from URL: https://www.abcam.com/products/biochemicals/cp-154526-hydrochloride-non-peptide-crf1-receptor-antagonist-ab141429.html. 2 pages.	☐
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	026	NELLA et al. A Phase 2 Study of Continuous Subcutaneous Hydrocortisone Infusion in Adults With Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 101(12):4690-4698 (2016).	☐
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	033	PCT/US2007/078605 Written Opinion dated March 20, 2009.	☐
	034	PCT/US2009/058722 International Search Report and Written opinion dated January 25, 2010.	☐
	035	PCT/US2009/058722 International Search Report dated April 8, 2010.	☐

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	036	PCT/US2009/058722 Written Opinion dated April 2, 2011.	☐
	037	PCT/US2018/046707 International Search Report and Written Opinion dated October 24, 2018.	☐
	038	PCT/US2018/046760 International Search Report and Written Opinion dated October 24, 2018.	☐
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	045	SPRUCE BIOSCIENCES, INC. Study to Evaluate the Safety and Efficacy of SPR001 in Subjects with Classic Congenital Adrenal Hyperplasia. 2018. Pages 1-7.	☐
	046	THAKRAL, Naveen K. et al. Salt Disproportionation in the Solid State: Role of Solubility and Counterion Volatility. Molecular pharmaceutics 13(12):4141-4151 (2016).	☐
	047	TRAPP et al. Congenital adrenal hyperplasia: an update in children. Curr Opin Endocrinol Diabetes Obes. 18(3):166-70 (2011).	☐
	048	TURCU, Adina F. et al. Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016).	☐
	049	U.S. Serial No. 17/586,228 Office Action dated June 10, 2022.	☐
	050	U.S. Serial No. 13/063,226 Office Action dated January 24, 2013.	☐
	051	U.S. Serial No. 16/388,620 Office Action dated July 15, 2019.	☐
	052	U.S. Serial No. 16/388,620 Office Action dated November 25, 2019.	☐
	053	U.S. Serial No. 16/639,540 Office Action dated July 11, 2022.	☐
	054	U.S. Serial No. 16/639,540 Office Action dated March 28, 2024.	☐
	055	U.S. Serial No. 16/639,540 Office Action dated May 25, 2023.	☐

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	08/14/2025

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	12	of	16	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	056	U.S. Serial No. 16/639,540 Office Action dated November 16, 2021.	☐
	057	U.S. Serial No. 16/639,540 Office Action dated September 28, 2023.	☐
	058	U.S. Serial No. 16/639,541 Office Action dated April 4, 2022.	☐
	059	U.S. Serial No. 17/063,592 Office Action dated December 7, 2021.	☐
	060	U.S. Serial No. 17/078,054 Office Action dated December 14, 2020.	☐
	061	U.S. Serial No. 17/359,411 Office Action dated January 6, 2022.	☐
	062	U.S. Serial No. 17/359,414 Office Action dated November 16, 2021.	☐
	063	U.S. Serial No. 17/586,228 Office Action dated March 30, 2022.	☐
	064	U.S. Serial No. 18/078,649 Office Action dated March 21,2024.	☐
	065	U.S. Serial No. 18/078,649 Office Action dated October 9, 2024.	☐
	066	U.S. Serial No. 18/078,649 Office Action dated September 8, 2023.	☐
	067	U.S. Serial No. 18/307,718 Office Action dated October 12, 2023.	☐
	068	U.S. Serial No. 19/043,275 Office Action dated May 30, 2025.	☐

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	08/14/2025

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	13	of	16	Attorney Docket Number	50535-710.306

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	069	VARMA. Excipients used in the Formulation of Tablets. https://www.rroij.com/openaccess/excipients-used-in-the-formulationof-tablets-.php?aid=78260 Revised date: 26/07/2016.	☐
	070	WILLIAMS, John P. Corticotropin-releasing factor 1 receptor antagonists: a patent review. Expert Opin Ther Pat 23(8):1057-68 (2013).	☐
	071	ZHANG et al. D-Level Essay in Statistics, 2009, How to Analyze Change from Baseline. Available at http://www.statistics.du.se/essays/D09 Zhang%20Ling%20&%20Han%20Kun.pdf (6/10/2009).	☐
	072	ZORRILLA, Eric P. et al., Progress in Corticotropin-Releasing Factor-1 Antagonist Development. Drug Discov Today 15(9-10):371-383 (2010).	☐
	073	ZORRILLA, Eric P. et al. The therapeutic potential of CRF1 antagonists for anxiety. Expert opinion on investigational drugs 13(7):799-828 (2004).	☐

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	08/14/2025

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				Examiner Name	PIHONAK, SARAH
Sheet	14	of	16	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☐ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☒ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2025-07-24
Name/Print	Victoria Cheng	Registration Number	79641

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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				Examiner Name	PIHONAK, SARAH
Sheet	15	of	16	Attorney Docket Number	50535-710.306

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306

CONFIRMATION NO. 6961

21971
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

POA ACCEPTANCE LETTER

OC00000009225731

Date Mailed: 08/20/2025

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/18/2025.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/qnguyen/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,264	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**6961**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: October 27, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: October 27, 2025

By: / Victoria Cheng /
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	8	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	8	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	BACON et al., Effect of Cortisol Treatment on Hormonal Relationships in Congenital Adrenal Hyperplasia. Clinical Endocrinology 6:113-126 (1977).	☐
	002	BENVENGA et al., Testicular adrenal rests: evidence for luteinizing hormone receptors and for distinct types of testicular nodules differing for their autonomization. European Journal of Endocrinology 141:231-237 (1999).	☐
	003	BRADLEY, D. Anawalt et al. Chapter 12: Testes. Greenspan's Basic & Clinical Endocrinology. 10th ed. New York: McGraw-Hill Education (pp. 413-442) (2018).	☐
	004	ÇAKIR et al., Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia. J Clin Res Pediatr Endocrinol 4(2):94-100 (2012).	☐
	005	Chemical Abstracts Service. CAS Registry: 752253-39-7. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-((1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-2-propyn-1-yl-2-thiazolamine: pp. 1-35. STN Entry Date October 11, 2005. Retrieved October 14, 2025. Retrieved from :https://pubchem.ncbi.nlm.nih.gov/compound/5282340.	☐
	006	CLAAHSEN et al., Testicular Tumors in Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency Show Functional Features of Adrenocortical Tissue. J Clin Endocrinol Metab. 92(9):3674-80 (2007).	☐
	007	EP3784233 Case Details for ACT_34386/2025 (1 pg) (2025).	☐
	008	FDA Approves New Treatment for Congenital Adrenal Hyperplasia, US Food and Drug Administration, December 13, 2024. Available at URL: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-congenital-adrenal-hyperplasia? pp.1-2.	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	3	of	8	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	009	GUPTA et al., Corticosteroid Physiology and Principles of Therapy. Indian J Pediatr 75(10):1039-1044 (2008).	☐
	010	GWATHMEY et al., Glucocorticoid-Induced Fetal Programming Alters the Functional Complement of Angiotensin Receptor Subtypes Within the Kidney. Hypertension 57(3):620-6 (2011).	☐
	011	HINDMARSH et al., Congenital Adrenal Hyperplasia A Comprehensive Guide. Elsevier, ISBN: 978-0-12-811483-4 (pp. 263-264 and 319-320) (2017).	☐
	012	MATSUBARA. Pathophysiological Role of Angiotensin II Type 2 Receptor in Cardiovascular and Renal Diseases. Circ Res. 83:1182-1191 (1998).	☐
	013	MESA et al., Immunophenotypic differences between neoplastic and non-neoplastic androgen-producing cells containing and lacking Reinke crystals. Virchows Arch. 469(6):679-686 (2016).	☐
	014	MORRIS, David. Steroid-induced Diabetes and Hyperglycaemia. Part 1: Mechanisms and Risks. Diabetes & Primary Care 20(4):151-153 (2018).	☐
	015	NAGURNEY et al., The Accuracy and completeness of Data Collected by Prospective and Retrospective Methods. ACAD EMERG MED 12(9):884-95 (September 2005).	☐
	016	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Denying Institution of Inter Partes Review in U.S. Patent No. 12,115,166 dated October 03, 2025 (pp 1-3) (PGR-2025-00032).	☐
	017	NEWFIELD, Ron S. et al. Crinecerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents with Congenital Adrenal Hyperplasia. The Journal of Clinical Endocrinology & Metabolism 108(11):2871-2878 (2023).	☐

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	018	POYRAZOGLU et al., Prevalence of testicular microlithiasis in males with congenital adrenal hyperplasia and its association with testicular adrenal rest tumors. Horm Res Paediatr. 73:443-448 (2010).	☐
	019	Regulation (EC) No 141/2000 Of the European Parliament and of the Council of 16 December 1999 on orphan medical products (pp. 1-5).	☐
	020	SOWERS et al., Effect of dexamethasone on gonadotropin responsiveness to luteinizing hormone-releasing hormone and clomiphene in women with secondary amenorrhea. Am J Obstet Gynecol. 134(3):325-8 (1979 Jun 1).	☐
	021	SPEISER, Phyllis W. et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 103(11):4043-4088 (2018).	☐
	022	SPIERLING, Samantha R, and Eric P Zorrilla. et al. Don't stress about CRF: Assessing the translational failures of CRF1 antagonists. Psychopharmacology 234(9-10):1467-1481 (2017).	☐
	023	Spruce Power Holding Corporation. Quarterly Report (Form 10-Q) for the period ended June 30, 2024. United States Securities and Exchange Commission, August 13, 2024. Available at: https://www.sec.gov/Archives/edgar/data/1772720/000162828024037238/spru-20240630.htm pp. 1-53.	☐
	024	U.S. Serial No. 17/578,149 Office Action dated October 6, 2025.	☐
	025	U.S. Serial No. 18/438,060 Office Action dated October 7, 2025.	☐
	026	U.S. Serial No. 19/043,275 Office Action dated September 12, 2025.	☐

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	027	U.S. Serial No. 19/043,303 Office Action dated September 5, 2025.	☐
	028	World Health Organization. Drug Information 33(1):122 (2019).	☐
	029	XAVIER et al., Gene Expression Control by Glucocorticoid Receptors during Innate Immune Responses. Front. Endocrinol. 7:31 (2016).	☐
	030	XUE et al. Glucocorticoid Modulates Angiotensin II Receptor Expression Patterns and Protects the Heart from Ischemia and Reperfusion Injury. PLoS One 9(9):e106827 (2014).	☐

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PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	6	of	8	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2025-10-27
Name/Print	Victoria Cheng	Registration Number	79641

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
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Sheet	7	of	8	Attorney Docket Number	50535-710.306

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,264	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**6961**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: October 27, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: October 27, 2025

By: / Victoria Cheng /
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
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Customer No. 21971

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
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				Examiner Name	PIHONAK, SARAH
Sheet	1	of	8	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

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		None			

FOREIGN PATENT DOCUMENTS

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		None				

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Sheet	2	of	8	Attorney Docket Number	50535-710.306

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	001	BACON et al., Effect of Cortisol Treatment on Hormonal Relationships in Congenital Adrenal Hyperplasia. Clinical Endocrinology 6:113-126 (1977).	☐
	002	BENVENGA et al., Testicular adrenal rests: evidence for luteinizing hormone receptors and for distinct types of testicular nodules differing for their autonomization. European Journal of Endocrinology 141:231-237 (1999).	☐
	003	BRADLEY, D. Anawalt et al. Chapter 12: Testes. Greenspan's Basic & Clinical Endocrinology. 10th ed. New York: McGraw-Hill Education (pp. 413-442) (2018).	☐
	004	ÇAKIR et al., Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia. J Clin Res Pediatr Endocrinol 4(2):94-100 (2012).	☐
	005	Chemical Abstracts Service. CAS Registry: 752253-39-7. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-((1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-2-propyn-1-yl-2-thiazolamine: pp. 1-35. STN Entry Date October 11, 2005. Retrieved October 14, 2025. Retrieved from :https://pubchem.ncbi.nlm.nih.gov/compound/5282340.	☐
	006	CLAAHSEN et al., Testicular Tumors in Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency Show Functional Features of Adrenocortical Tissue. J Clin Endocrinol Metab. 92(9):3674-80 (2007).	☐
	007	EP3784233 Case Details for ACT_34386/2025 (1 pg) (2025).	☐
	008	FDA Approves New Treatment for Congenital Adrenal Hyperplasia, US Food and Drug Administration, December 13, 2024. Available at URL: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-congenital-adrenal-hyperplasia? pp.1-2.	☐

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	3	of	8	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	009	GUPTA et al., Corticosteroid Physiology and Principles of Therapy. Indian J Pediatr 75(10):1039-1044 (2008).	☐
	010	GWATHMEY et al., Glucocorticoid-Induced Fetal Programming Alters the Functional Complement of Angiotensin Receptor Subtypes Within the Kidney. Hypertension 57(3):620-6 (2011).	☐
	011	HINDMARSH et al., Congenital Adrenal Hyperplasia A Comprehensive Guide. Elsevier, ISBN: 978-0-12-811483-4 (pp. 263-264 and 319-320) (2017).	☐
	012	MATSUBARA. Pathophysiological Role of Angiotensin II Type 2 Receptor in Cardiovascular and Renal Diseases. Circ Res. 83:1182-1191 (1998).	☐
	013	MESA et al., Immunophenotypic differences between neoplastic and non-neoplastic androgen-producing cells containing and lacking Reinke crystals. Virchows Arch. 469(6):679-686 (2016).	☐
	014	MORRIS, David. Steroid-induced Diabetes and Hyperglycaemia. Part 1: Mechanisms and Risks. Diabetes & Primary Care 20(4):151-153 (2018).	☐
	015	NAGURNEY et al., The Accuracy and completeness of Data Collected by Prospective and Retrospective Methods. ACAD EMERG MED 12(9):884-95 (September 2005).	☐
	016	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Denying Institution of Inter Partes Review in U.S. Patent No. 12,115,166 dated October 03, 2025 (pp 1-3) (PGR-2025-00032).	☐
	017	NEWFIELD, Ron S. et al. Crinecerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents with Congenital Adrenal Hyperplasia. The Journal of Clinical Endocrinology & Metabolism 108(11):2871-2878 (2023).	☐

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Sheet	4	of	8	Attorney Docket Number	50535-710.306

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	018	POYRAZOGLU et al., Prevalence of testicular microlithiasis in males with congenital adrenal hyperplasia and its association with testicular adrenal rest tumors. Horm Res Paediatr. 73:443-448 (2010).	☐
	019	Regulation (EC) No 141/2000 Of the European Parliament and of the Council of 16 December 1999 on orphan medical products (pp. 1-5).	☐
	020	SOWERS et al., Effect of dexamethasone on gonadotropin responsiveness to luteinizing hormone-releasing hormone and clomiphene in women with secondary amenorrhea. Am J Obstet Gynecol. 134(3):325-8 (1979 Jun 1).	☐
	021	SPEISER, Phyllis W. et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 103(11):4043-4088 (2018).	☐
	022	SPIERLING, Samantha R, and Eric P Zorrilla. et al. Don't stress about CRF: Assessing the translational failures of CRF1 antagonists. Psychopharmacology 234(9-10):1467-1481 (2017).	☐
	023	Spruce Power Holding Corporation. Quarterly Report (Form 10-Q) for the period ended June 30, 2024. United States Securities and Exchange Commission, August 13, 2024. Available at: https://www.sec.gov/Archives/edgar/data/1772720/000162828024037238/spru-20240630.htm pp. 1-53.	☐
	024	U.S. Serial No. 17/578,149 Office Action dated October 6, 2025.	☐
	025	U.S. Serial No. 18/438,060 Office Action dated October 7, 2025.	☐
	026	U.S. Serial No. 19/043,275 Office Action dated September 12, 2025.	☐

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Sheet	5	of	8	Attorney Docket Number	50535-710.306

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	027	U.S. Serial No. 19/043,303 Office Action dated September 5, 2025.	☐
	028	World Health Organization. Drug Information 33(1):122 (2019).	☐
	029	XAVIER et al., Gene Expression Control by Glucocorticoid Receptors during Innate Immune Responses. Front. Endocrinol. 7:31 (2016).	☐
	030	XUE et al. Glucocorticoid Modulates Angiotensin II Receptor Expression Patterns and Protects the Heart from Ischemia and Reperfusion Injury. PLoS One 9(9):e106827 (2014).	☐

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
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TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

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TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

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SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2025-10-27
Name/Print	Victoria Cheng	Registration Number	79641

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	7	of	8	Attorney Docket Number	50535-710.306

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**10/27/2025 04:42:59 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	JENNIFER VAIL
PATENT CENTER #	72922587	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 33

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710_306_IDS.pdf		12	-	316 KB
Spruce 50535-710_306_IDS-TRAN.LET.pdf	(1-4)	4	Transmittal Letter	154 KB
Spruce 50535-710_306_IDS-IDS.pdf	(5-12)	8	Information Disclosure Statement (IDS) Form (SB08)	158 KB
NPL_EP3784233_CaseDetails_2025.pdf		1	Non Patent Literature	66 KB
NPL_FDA_Congenital_Adrenal_Hyperplasia_2024.pdf		2	Non Patent Literature	760 KB
NPL_BACON_EffectofCortisolTreatment_113-126.pdf		14	Non Patent Literature	1547 KB

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NPL_CAS_752253-39-7.pdf	35	Non Patent Literature	4567 KB
NPL_CLAAHSEN_Testicular Tumorsin_3674-80.pdf	7	Non Patent Literature	5481 KB
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NPL_SPEISER_Congenital_adrenal_4043_4088_2018_Part2.pdf	20	Non Patent Literature	14931 KB
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NPL_Spruce_Quarterly_Report_2024.pdf	53	Non Patent Literature	16322 KB

Digest

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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT
Attorney Docket No. 50535-710.306

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Alexis Howerton et al. Application No.: 19/043,264 Filing Date: January 31, 2025 Title: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS	Confirmation No.: 6961 Art Unit: 1627 Examiner: Pihonak, Sarah Customer No.: 21971 Certificate of Electronic Filing I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office's electronic filing system to the USPTO on October 27, 2025. By: / Colleen Mensching / Colleen Mensching

Mail Stop AF/RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Dear Commissioner:

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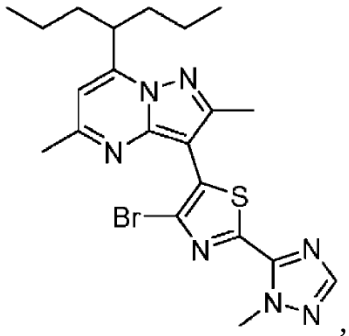
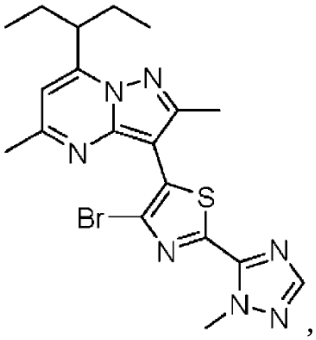
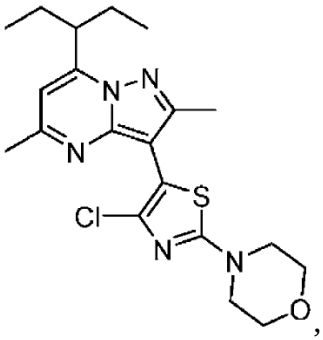
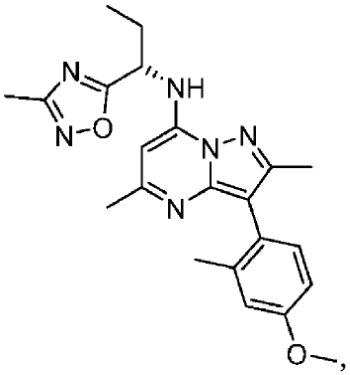
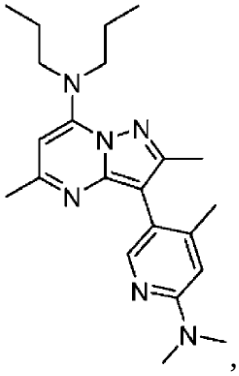
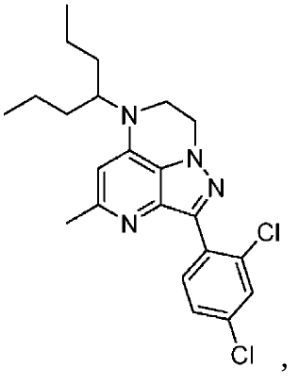
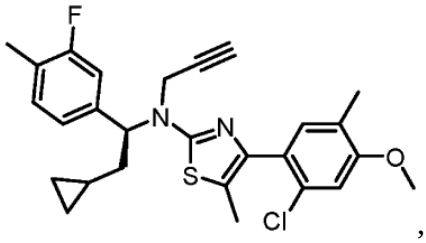
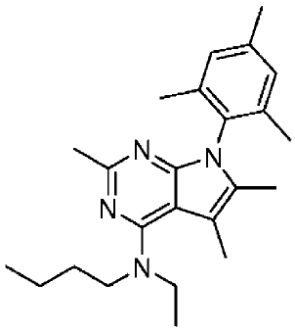
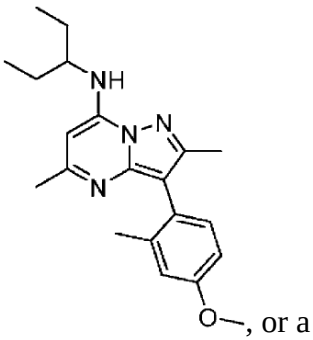
A Request for Continued Examination pursuant to 37 CFR § 1.114 is filed herewith.

Amendments to the Claims begin on page **2** of this paper.
Remarks begin on page **5** of this paper.
Conclusion begins on page **6** of this paper.

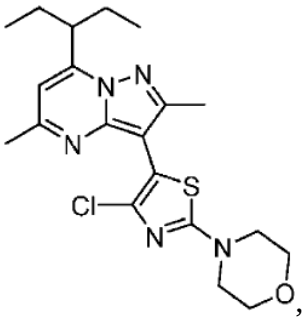
AMENDMENTS TO THE CLAIMS

Listing of the Claims

1. (Previously Presented) A method of treating ovarian adrenal rest tumors (OART) and menstrual irregularity in a subject, comprising administering to the subject a small molecule corticotropin-releasing factor type-1 (CRF_1) antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF_1 antagonist is:

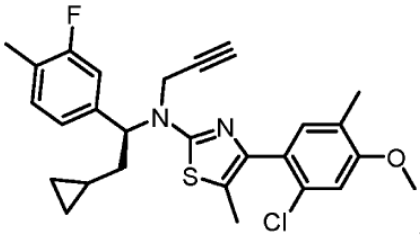
 ,  ,  ,
 ,  ,  , SSR-126374,
 ,  , or  , or a pharmaceutically acceptable salt thereof.

2. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is:



, or a pharmaceutically acceptable salt thereof.

3. (Previously Presented) The method of claim 1, wherein the small molecule CRF_1 antagonist is:



, or a pharmaceutically acceptable salt thereof.

4. (Previously Presented) The method of claim 1, further comprising treating ovulatory dysfunction or infertility.
5. (Original) The method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).
6. (Original) The method of claim 1, wherein the subject is an adolescent.
7. (Original) The method of claim 1, wherein the subject is at least 18 years or older.
8. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.
9. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 50 mg.
10. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 100 mg.
11. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 200 mg.
12. (Original) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 400 mg.

13. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered to the subject once per day.
14. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered to the subject twice per day.
15. (Original) The method of claim 13, wherein the subject is in a fed state.
16. (Original) The method of claim 14, wherein the subject is in a fed state.
17. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered orally.
18. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is formulated as a capsule or tablet.
19. (Original) The method of claim 1, wherein the administering reduces a plasma concentration of a biomarker comprising 17α-hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, androstenedione (A4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, or aldosterone, or a combination thereof.
20. (Original) The method of claim 19, wherein the biomarker is selected from the group consisting of 17-OHP, ACTH, and A4.
21. (Original) The method of claim 19, wherein the plasma concentration of the biomarker is reduced by at least 10% from baseline.

REMARKS

No claims are amended herein. Accordingly, claims 1-21 are currently pending. Allowance is respectfully requested in view of the remarks below.

Double Patenting

Claims 1-5, 8-14, and 17-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 and 19 of U.S. Patent No. 11,304,950 B2 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003; and Grigoriadis, WO 2015112642 A1, publ. 7/30/2015.

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over:

- Claims 72-91 of copending application 18941832 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003;
- Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5 and 9-21 of copending application 19043275 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003; and
- Claims 1-13 and 17-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending application 19043303 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003,

collectively the “Cited References”.

Without acquiescing to the basis of the rejection and for the purpose of compact prosecution, Applicant files herein a terminal disclaimer over U.S. Patent No. 11,304,950, and U.S. Application Nos. 18/941,832, 19/043,275, and 19/043,303. Therefore, Applicant respectfully requests withdrawal of the rejections above and allowance of the pending claims.

CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858) 350-2240.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 50535-710.306).

Respectfully submitted,

Date: October 27, 2025 By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79,641

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone: (650) 493-9300
Customer No. 21971

PATENT
Attorney Docket No. 50535-710.306

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Alexis Howerton et al. Application No.: 19/043,264 Filing Date: January 31, 2025 Title: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS	Confirmation No.: 6961 Art Unit: 1627 Examiner: Pihonak, Sarah Customer No.: 21971 Certificate of Electronic Filing I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office's electronic filing system to the USPTO on October 27, 2025. By: / Colleen Mensching / Colleen Mensching

Mail Stop AF/RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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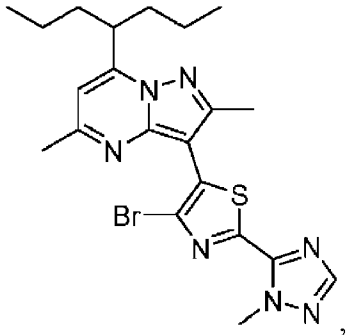
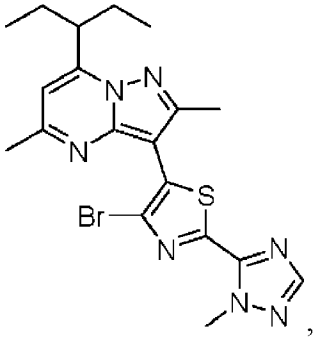
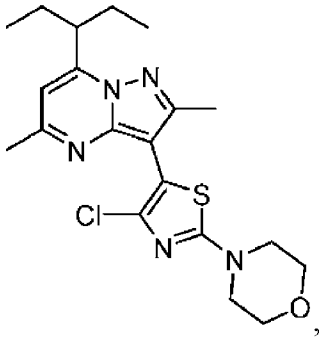
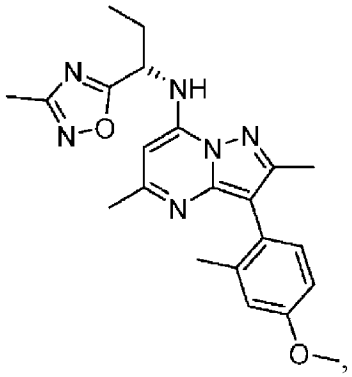
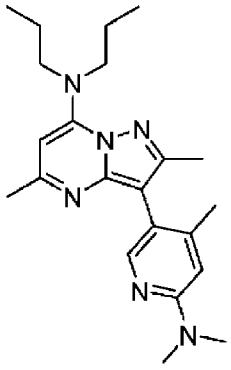
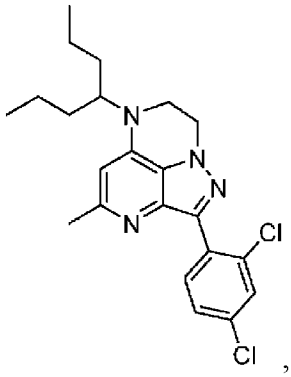
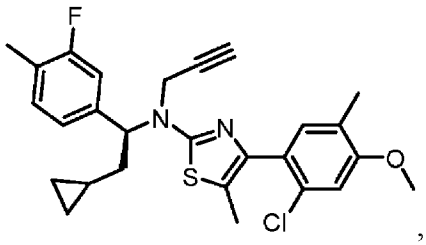
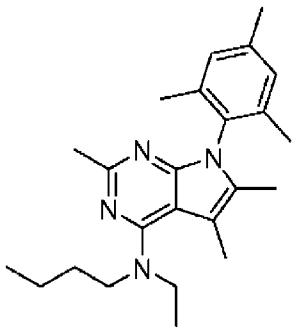
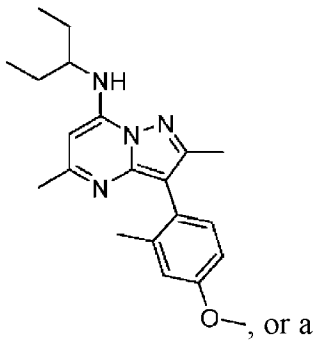
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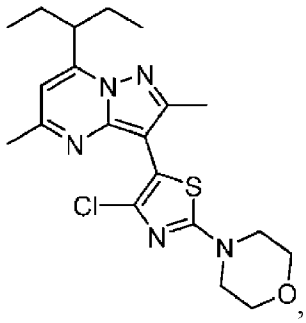
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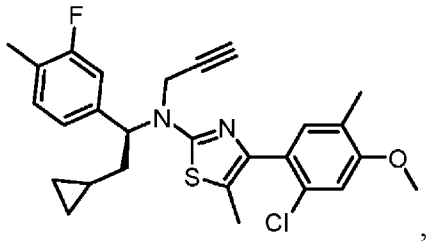

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17. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered orally.
18. (Original) The method of claim 1, wherein the small molecule CRF_1 antagonist is formulated as a capsule or tablet.
19. (Original) The method of claim 1, wherein the administering reduces a plasma concentration of a biomarker comprising 17α-hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, androstenedione (A4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, or aldosterone, or a combination thereof.
20. (Original) The method of claim 19, wherein the biomarker is selected from the group consisting of 17-OHP, ACTH, and A4.
21. (Original) The method of claim 19, wherein the plasma concentration of the biomarker is reduced by at least 10% from baseline.

REMARKS

No claims are amended herein. Accordingly, claims 1-21 are currently pending. Allowance is respectfully requested in view of the remarks below.

Double Patenting

Claims 1-5, 8-14, and 17-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 and 19 of U.S. Patent No. 11,304,950 B2 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003; and Grigoriadis, WO 2015112642 A1, publ. 7/30/2015.

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over:

- Claims 72-91 of copending application 18941832 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003;
- Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5 and 9-21 of copending application 19043275 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003; and
- Claims 1-13 and 17-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending application 19043303 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003,

collectively the "Cited References".

Without acquiescing to the basis of the rejection and for the purpose of compact prosecution, Applicant files herein a terminal disclaimer over U.S. Patent No. 11,304,950, and U.S. Application Nos. 18/941,832, 19/043,275, and 19/043,303. Therefore, Applicant respectfully requests withdrawal of the rejections above and allowance of the pending claims.

CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858) 350-2240.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 50535-710.306).

Respectfully submitted,

Date: October 27, 2025 By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79,641

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone: (650) 493-9300
Customer No. 21971

PTO/SB/30EFS (01-22)
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	19/043,264	Filing Date	2025-01-31	Docket Number (if applicable)	50535-710.306	Art Unit	1627
First Named Inventor	Spruce Biosciences, Inc.			Examiner Name	SARAH PIHONAK		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 232415

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Victoria Cheng/	Date (YYYY-MM-DD)	2025-10-27
Name	VICTORIA CHENG	Registration Number	79641

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**10/27/2025 04:02:51 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Colleen Mensching
PATENT CENTER #	72918266	AUTHORIZED BY	Victoria Cheng
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 232415	**E20250QG03539961**	**Colleen Mensching**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	1500.00	1	1500.00
			TOTAL AMOUNT:	**$1,500.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**10/27/2025 04:02:51 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

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CONFIRMATION #	6961	FILED BY	Colleen Mensching
PATENT CENTER #	72918266	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 4

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710.306 - Response Final.pdf		6	-	222 KB
Spruce 50535-710.306 - Response Final-AMSB.pdf	(1-1)	1	Amendment Submitted/Entered with Filing of Continued Prosecution Application (CPA)/Request for Continued Examination(RCE)	106 KB
Spruce 50535-710.306 - Response Final-CLM.pdf	(2-4)	3	Claims	200 KB
Spruce 50535-710.306 - Response Final-REM.pdf	(5-6)	2	Applicant Arguments/Remarks Made in an Amendment	119 KB
Spruce 50535-710.306 - RCE Final.pdf		3	Request for Continued Examination (RCE)	1631 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce 50535-710.306 - Response Final.pdf	988E9F9091ED57FE9789D3BE6B553EC195176699737B63E0A 18A4647EE671F126A62B165675E832F136C0594B48B6EB8CB0 9B408F82505698C90F067D46FFBED
Spruce 50535-710.306 - Response Final-AMSB.pdf	D5A8D498AFF759FD6453DD9BF3E5A98CB61602D0BBAE4779 BEA897D439F8F701B6C6861F5C882ABD89DB1E37284BEFCD E4246593088D2E5FF40D6A71EE2E71F7
Spruce 50535-710.306 - Response Final-CLM.pdf	9507F20848740F1E90B5337022A8F93ABB78C99B34E2110D6A 4B2E34D130A2B8FF58D104910AB4626A80ECB29103B8F4D82 953013611DE4E9F41409F7C3C4734
Spruce 50535-710.306 - Response Final-REM.pdf	E5F0AD4CA96A234C5FDF0CC403EE19BC414734156E82342C 958F965B20FDE183F759174525450CD27584FD2B936745046B 786A3D8ECF78FC470057B7CA96E2E6
Spruce 50535-710.306 - RCE Final.pdf	9AA69C8A363175AD2AAE811F6D8D383267DA9DD86E37A0B9 0C99489947399C24737C92743A462AFFB171477718BFD8568A 332E12C957EDA8F074163771F8052A

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

APPLICATION #	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET #
19043264	**01/31/2025**	**Alexis HOWERTON**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

☑ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☑ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent interest
Spruce Biosciences, Inc.	100%
Total	**100%**

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

Application #	Filing Date
18941832	11/08/2024

19043275	01/31/2025
19043303	01/31/2025

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.
In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

Patent #
11304950

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.
In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
• expires for failure to pay a maintenance fee;
• is held unenforceable;
• is found invalid by a court of competent jurisdiction;
• is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
• has all claims canceled by a reexamination certificate;
• is reissued; or
• is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal

disclaimer.

 Terminal disclaimer fee under 37 CFR 1.20(d) included with Electronic Terminal Disclaimer request.

Applicant claims the following entity status:
Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I certify, in accordance with 37 CFR 1.4(d)(4) that I am: An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Signature	Name	Registration #
/Victoria Cheng/	Victoria Cheng	79641

---

* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP 324.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**10/27/2025 02:35:03 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Victoria Cheng
PATENT CENTER #	72905171	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	3	Terminal Disclaimer-Filed (Electronic)	46 KB
grantLetter.pdf	1	Terminal Disclaimer-Electronic-Approved	18 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	1C004DD234919BC4EA7B50A38352244BA91B130A3F7BD54D BDA0492F3B3503F4B3A8933F7538278DD9F0009EBD4D7DC27 B07D74FDBF366AD92ACE42F47B05055
grantLetter.pdf	367F4AFD2AF4D825CA4BD66BD3B8C943516AF833CAE48B58

2485AA924EE39D742B0A86498232CBC5FC95126364D208F50
B734B133E3C7CFBFA51F0B45B3C36DA

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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United States Patent and Trademark Office
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APPROVAL LETTER

APPLICATION #	FILING DATE	APPLICANT/PATENT UNDER REEXAMINATION
19/043,264	**01/31/2025**	**Alexis HOWERTON**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Electronic terminal disclaimer filed on 10/27/2025

Approved

This patent is subject to a Terminal Disclaimer

Approved / Disapproved by: Electronic Terminal Disclaimer automatically approved

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**10/27/2025 02:35:03 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Victoria Cheng
PATENT CENTER #	72905171	AUTHORIZED BY	Victoria Cheng
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 232415	**E20250QE39118524**	**Victoria Cheng**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	183.00	1	183.00
			TOTAL AMOUNT:	**$183.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 19/043,264	Filing Date 01/31/2025	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)			
FOR	NUMBER FILED	NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $200 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $600 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	10/27/2025	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 21	= 0		x $200 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $600 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TONYA Q MCBRIDE/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 11/17/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 11/17/2025

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	02/17/2026

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 11/17/2025
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	02/17/2026

EXAMINER	ART UNIT	CLASS-SUBCLASS
PIHONAK, SARAH	1627	514-233200

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

21971 7590 11/17/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 11/17/2025

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice Requiring Inventor's Oath or Declaration	Application No. 19/043,264	Applicant(s) Alexis HOWERTON	
	Examiner PIHONAK, SARAH	Art Unit 1627	

This notice is an attachment to the Notice of Allowability (PTOL-37), or the Notice of Allowability For A Design Application (PTOL-37D).

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor has not yet been submitted.

An oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each inventor (for any inventor for which a compliant oath, declaration, or substitute statement has not yet been submitted) MUST be filed no later than the date on which the issue fee is paid. See 35 U.S.C. 115(f). Failure to timely comply will result in ABANDONMENT of this application.

A properly executed inventor's oath to declaration has not been received for the following inventor(s):

If applicant previously filed one or more oaths, declarations, or substitute statements, applicant may have received an informational notice regarding deficiencies therein.

The following deficiencies are noted:

INFORMAL ACTION PROBLEMS

- A properly executed inventor's oath or declaration has not been received for the following inventor(s): **Alexis HOWERTON** and **Hal GERBER**.
  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 19/043,264	Applicant(s) HOWERTON et al.	
	Examiner SARAH PIHONAK	Art Unit 1627	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 10/27/25.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-21 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/27/25 has been entered.

Status of Claims

1. Claims 1-21 are pending as of the response filed on 10/27/25.

The rejections for nonstatutory double patenting over the claims of US 11304950, 18941832, 19043275, and 19043303 are withdrawn in consideration of the acceptance of the terminal disclaimer filed on 10/27/25.

2. Claims 1-21 are allowed.

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance: Grigoriadis, WO 2015112642 A1, of record, represents the closest prior art. Grigoriadis teaches CRF1 antagonists that include those recited in the instant claims for the treatment of congenital

adrenal hyperplasia, however, treatment of a subject having an ovarian adrenal rest tumor is not taught or suggested.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Information Disclosure Statement

4. The IDS filed on 10/27/25 has been considered.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached Monday-Friday 9:00-5:30 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached at 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SARAH . PIHONAK
Primary Examiner
Art Unit 1627

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

CPC - Searched*		
Symbol	**Date**	**Examiner**
a61k31/519; a61p5/06,08	04/21/2025	s.p.
a61k31/519, 5377; a61p5/06,08	08/13/2025	s.p.
a61k31/519, 5377; a61p5/06,08	10/29/2025	s.p.

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
a61k31/519; a61p5/06,08	04/21/2025	s.p.
inventor & applicant search in PE2E, patent data portal	04/21/2025	s.p.
invention & claims search in stn, PE2E	04/21/2025	s.p.
a61k31/519, 5377; a61p5/06,08	08/13/2025	s.p.
inventor & applicant search in PE2E, patent data portal	08/13/2025	s.p.
invention & claims search in PE2E	08/13/2025	s.p.
a61k31/519, 5377; a61p5/06,08	10/29/2025	s.p.
inventor & applicant search in PE2E, patent data portal	10/29/2025	s.p.
invention & claims search in PE2E (incl. similarity), stnext	10/29/2025	s.p.

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
a61k	31/519, 5377	10/29/2025	s.p.
a61p	5/06,08	10/29/2025	s.p.

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	**Art Unit**
	SARAH PIHONAK	1627

CPC								
Symbol							**Type**	**Version**
A61K	/	31	/	519			F	2013-01-01
A61K	/	9	/	0053			A	2013-01-01
A61K	/	9	/	20			A	2013-01-01
A61K	/	9	/	48			A	2013-01-01
A61K	/	45	/	06			A	2013-01-01
A61P	/	5	/	06			A	2018-01-01
A61P	/	5	/	08			A	2018-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	21	
/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	29 October 2025	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	**Art Unit**
	SARAH PIHONAK	1627

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	31	/	519	
A61P	/	5	/	06	
A61P	/	5	/	08	

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	21	
/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	29 October 2025	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	**Art Unit**
	SARAH PIHONAK	1627

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19										
	2		11		20										
	3		12		21										
	4		13												
	5		14												
	6		15												
	7		16												
	8		17												
	9		18												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 21	
/SARAH PIHONAK/ Primary Examiner, Art Unit 1627 (Primary Examiner)	29 October 2025 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office

Part of Paper No.: 20251029-a

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	652	(corticotropin adj8 factor adj8 antagon*) AND (menstruation OR menstrual)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:36 PM
L2	200	((corticotropin adj8 factor adj8 antagon*) OR (CRF1 adj8 antagon*)).ab,ti,clm. AND L1	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:37 PM
L3	276	(corticotropin adj8 factor adj8 antagon*) AND (dysmenorrhea)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:42 PM
L4	42	((corticotropin adj8 factor adj8 antagon*) OR (CRF1 adj8	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY,	OR	ON	ON	2025/04/18 05:42 PM

		antagon*)).ab,ti,clm. AND L3	CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L5	192	(((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND (L2 OR L4)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:53 PM
L6	31	((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/04/18 06:11 PM
L7	21	((("HOWERTON") near3 ("Alexis"))).INV.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/04/18 06:11 PM
L8	21	((("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/04/18 06:11 PM
L9	23	(L2 OR L4) AND (L6 OR L7 OR L8)	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/04/18 06:12 PM
L10	6002	(a61k31/519 OR a61p5/06,08).cpc. AND (menstrual OR menstruation OR dysmenorrhea OR dysmennorhea OR dysmennorrhea)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 06:14 PM
L11	140	(corticotropin adj8 factor	(US-PGPUB; USPAT;	OR	ON	ON	2025/04/18

		adj8 antagon*) AND L10	USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				06:14 PM
L12	96	((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L11	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 06:15 PM
L13	19	("10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220143037" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2025/04/21 09:32 AM
L14	940	(a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 antagon*)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS,	OR	ON	ON	2025/04/21 10:26 AM

			IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L15	877	(((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L14	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 10:26 AM
L16	286	L15 AND (corticotropin adj8 releas* adj8 factor adj8 antagon*).ab,ti,clm.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 10:27 AM
L17	484	(corticotropin adj8 factor adj8 antagon*) AND (amenorrhea)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 12:48 PM

L18	489	(corticotropin adj8 factor adj8 antagon*) AND (amenorrhea OR menorrhagia)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 12:48 PM
L19	423	((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 12:49 PM
L20	31	"1200419".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 01:07 PM
L21	1	"6586456".pn.	(USPAT)	OR	ON	ON	2025/04/21 01:08 PM
L22	272	(congenital adj6 adrenal adj6 hyperplasia) WITH (menorrhagia OR dysmenorrhea OR menstrual OR menstruation)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV,	OR	ON	ON	2025/04/21 03:18 PM

			MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L23	216	((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L22	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 03:18 PM
L24	7	"2015112642".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 04:20 PM
L25	3	L24 AND (time OR frequency)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 04:21 PM
L26	2	L24 AND (one OR once OR twice)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP,	OR	ON	ON	2025/04/21 04:21 PM

			ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L27	1	L24 AND (day OR daily)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 04:21 PM
L28	1	"20100222339".pn.	(US-PGPUB)	OR	ON	ON	2025/04/21 04:48 PM
L29	1	L28 AND adrenal	(US-PGPUB)	OR	ON	ON	2025/04/21 04:48 PM
L30	0	L28 AND adrenal AND (tablet* OR capsule*)	(US-PGPUB)	OR	ON	ON	2025/04/21 04:48 PM
L31	1	"12098152".pn.	(USPAT)	OR	ON	ON	2025/04/21 05:46 PM
L32	54	("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/05 03:00 PM

		"20220143037" OR "20230159533" OR "20230321112" OR "20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177404" OR "20250195527" OR "8030304" OR "8563718" OR "10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn.					
L33	36	("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR "20220143037" OR "20230159533" OR "20230321112" OR	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/05 03:06 PM

		"20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177404" OR "20250195527" OR "8030304" OR "8563718").pn.					
L34	1	"20250177403".pn.	(US-PGPUB)	OR	ON	ON	2025/08/13 03:01 PM
L35	23	(a61k31/519,5377 OR a61p5/06,08).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 (inhibit* OR antagon* OR block*)) AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/08/13 03:04 PM
L36	28	(Artificial Intelligence) More like doc: US-20250177403-A1 Text: (JP-H0971528-A OR AU-2007231549-A1 OR RS-51545-B OR US-20100203048-A1 OR IL-317035-A OR BR-112020002967-A2 OR US-20210137935-A1 OR US-20250177403-A1 OR HK-40040045-A OR US-20250177404-A1 OR US-20250195527-A1 OR US-20250064812-A1 OR US-11304950-B2 OR HK-40040045-B OR EP-3784233-B1 OR AU-2023203095-A1 OR CA-3098562-A1 OR US-20210038604-A1 OR BR-112020024062-A2 OR US-20220211711-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/08/13 03:06 PM
L37	14	L36 AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY,	OR	ON	ON	2025/08/13 03:07 PM

			CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L38	35	((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/13 03:07 PM
L39	24	((("HOWERTON") near3 ("Alexis")) OR (("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2025/08/13 03:08 PM
L40	8	(L38 OR L39) AND (corticotropin adj8 releas* adj8 factor adj8 (inhibit* OR antagon* OR block*)) AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/13 03:08 PM
L41	1	"20250177403".pn.	(US-PGPUB)	OR	ON	ON	2025/10/29 11:18 AM
L42	29	(Artificial Intelligence) More like doc: US-20250177403-A1 Text: (JP-H0971528-A OR EP-2004205-A4 OR CN-101516887-B OR US-20100203048-A1 OR CN-106102740-A OR KR-20200040761-A OR WO-2019036472-A1 OR EP-3784233-B1 OR US-20250177404-A1 OR US-20250177403-A1 OR HK-40040045-A OR US-20250195527-A1 OR HK-40040045-B OR CA-3098562-A1 OR US-20210038604-A1 OR US-11304950-B2 OR US-20220211711-A1 OR US-20250064812-A1 OR EP-4438124-A2 OR AU-2023203095-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/10/29 11:18 AM

L43	21	(a61k31/519,5377 OR a61p35/00 OR a61p5/06,08).cpc. AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/10/29 11:24 AM
L44	8	(L38 OR L39) AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/10/29 11:26 AM
L45	8	"2010039678".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:51 PM
L46	0	L45 AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:51 PM
L47	7	"2016065177".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP,	OR	ON	ON	2025/10/29 12:51 PM

			ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L48	0	L47 AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:51 PM
L49	7	"2019036472".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:52 PM
L50	0	L49 AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:52 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default	Plurals	British	Time Stamp

				Operator		Equivalents	
N1	7	(a61k31/519,5377 OR a61p5/06,08).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 (inhibit* OR antagon* OR block*)) AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/13 03:06 PM
N2	7	(a61k31/519,5377 OR a61p35/00 OR a61p5/06,08).cpc. AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(US-PGPUB; USPAT)	OR	ON	ON	2025/10/29 11:25 AM

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Doc description: Information Disclosure Statement (IDS) Filed

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	8	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	10/29/2025

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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NON-PATENT LITERATURE DOCUMENTS

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	001	BACON et al., Effect of Cortisol Treatment on Hormonal Relationships in Congenital Adrenal Hyperplasia. Clinical Endocrinology 6:113-126 (1977).	☐
	002	BENVENGA et al., Testicular adrenal rests: evidence for luteinizing hormone receptors and for distinct types of testicular nodules differing for their autonomization. European Journal of Endocrinology 141:231-237 (1999).	☐
	003	BRADLEY, D. Anawalt et al. Chapter 12: Testes. Greenspan's Basic & Clinical Endocrinology. 10th ed. New York: McGraw-Hill Education (pp. 413-442) (2018).	☐
	004	ÇAKIR et al., Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia. J Clin Res Pediatr Endocrinol 4(2):94-100 (2012).	☐
	005	Chemical Abstracts Service. CAS Registry: 752253-39-7. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-((1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-2-propyn-1-yl-2-thiazolamine: pp. 1-35. STN Entry Date October 11, 2005. Retrieved October 14, 2025. Retrieved from :https://pubchem.ncbi.nlm.nih.gov/compound/5282340.	☐
	006	CLAAHSEN et al., Testicular Tumors in Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency Show Functional Features of Adrenocortical Tissue. J Clin Endocrinol Metab. 92(9):3674-80 (2007).	☐
	007	EP3784233 Case Details for ACT_34386/2025 (1 pg) (2025).	☐
	008	FDA Approves New Treatment for Congenital Adrenal Hyperplasia, US Food and Drug Administration, December 13, 2024. Available at URL: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-congenital-adrenal-hyperplasia? pp.1-2.	☐

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Examiner Signature		Date Considered	

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				Examiner Name	PIHONAK, SARAH
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	009	GUPTA et al., Corticosteroid Physiology and Principles of Therapy. Indian J Pediatr 75(10):1039-1044 (2008).	☐
	010	GWATHMEY et al., Glucocorticoid-Induced Fetal Programming Alters the Functional Complement of Angiotensin Receptor Subtypes Within the Kidney. Hypertension 57(3):620-6 (2011).	☐
	011	HINDMARSH et al., Congenital Adrenal Hyperplasia A Comprehensive Guide. Elsevier, ISBN: 978-0-12-811483-4 (pp. 263-264 and 319-320) (2017).	☐
	012	MATSUBARA. Pathophysiological Role of Angiotensin II Type 2 Receptor in Cardiovascular and Renal Diseases. Circ Res. 83:1182-1191 (1998).	☐
	013	MESA et al., Immunophenotypic differences between neoplastic and non-neoplastic androgen-producing cells containing and lacking Reinke crystals. Virchows Arch. 469(6):679-686 (2016).	☐
	014	MORRIS, David. Steroid-induced Diabetes and Hyperglycaemia. Part 1: Mechanisms and Risks. Diabetes & Primary Care 20(4):151-153 (2018).	☐
	015	NAGURNEY et al., The Accuracy and completeness of Data Collected by Prospective and Retrospective Methods. ACAD EMERG MED 12(9):884-95 (September 2005).	☐
	016	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Denying Institution of Inter Partes Review in U.S. Patent No. 12,115,166 dated October 03, 2025 (pp 1-3) (PGR-2025-00032).	☐
	017	NEWFIELD, Ron S. et al. Crinecerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents with Congenital Adrenal Hyperplasia. The Journal of Clinical Endocrinology & Metabolism 108(11):2871-2878 (2023).	☐

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Examiner Signature		Date Considered	

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	8	Attorney Docket Number	50535-710.306

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	018	POYRAZOGLU et al., Prevalence of testicular microlithiasis in males with congenital adrenal hyperplasia and its association with testicular adrenal rest tumors. Horm Res Paediatr. 73:443-448 (2010).	☐
	019	Regulation (EC) No 141/2000 Of the European Parliament and of the Council of 16 December 1999 on orphan medical products (pp. 1-5).	☐
	020	SOWERS et al., Effect of dexamethasone on gonadotropin responsiveness to luteinizing hormone-releasing hormone and clomiphene in women with secondary amenorrhea. Am J Obstet Gynecol. 134(3):325-8 (1979 Jun 1).	☐
	021	SPEISER, Phyllis W. et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 103(11):4043-4088 (2018).	☐
	022	SPIERLING, Samantha R, and Eric P Zorrilla. et al. Don't stress about CRF: Assessing the translational failures of CRF1 antagonists. Psychopharmacology 234(9-10):1467-1481 (2017).	☐
	023	Spruce Power Holding Corporation. Quarterly Report (Form 10-Q) for the period ended June 30, 2024. United States Securities and Exchange Commission, August 13, 2024. Available at: https://www.sec.gov/Archives/edgar/data/1772720/000162828024037238/spru-20240630.htm pp. 1-53.	☐
	024	U.S. Serial No. 17/578,149 Office Action dated October 6, 2025.	☐
	025	U.S. Serial No. 18/438,060 Office Action dated October 7, 2025.	☐
	026	U.S. Serial No. 19/043,275 Office Action dated September 12, 2025.	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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				Application Number	19/043,264
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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	5	of	8	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
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	027	U.S. Serial No. 19/043,303 Office Action dated September 5, 2025.	☐
	028	World Health Organization. Drug Information 33(1):122 (2019).	☐
	029	XAVIER et al., Gene Expression Control by Glucocorticoid Receptors during Innate Immune Responses. Front. Endocrinol. 7:31 (2016).	☐
	030	XUE et al. Glucocorticoid Modulates Angiotensin II Receptor Expression Patterns and Protects the Heart from Ischemia and Reperfusion Injury. PLoS One 9(9):e106827 (2014).	☐

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	6	of	8	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2025-10-27
Name/Print	Victoria Cheng	Registration Number	79641

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				Examiner Name	PIHONAK, SARAH
Sheet	7	of	8	Attorney Docket Number	50535-710.306

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

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 US 20250195527 A1   US 2025-19043303      Register|Global Dossier
 WO 2019210266 A1    WO 2019-US29486       Register|Global Dossier

=>  d his


     (FILE 'HOME' ENTERED AT 11:31:02 ON 29 OCT 2025)

     FILE 'REGISTRY' ENTERED AT 11:31:22 ON 29 OCT 2025
L1             STRUCTURE UPLOADED
L2           2 S L1 SSS SAM
L3          17 S L1 SSS FULL


     FILE 'CAPLUS' ENTERED AT 11:34:33 ON 29 OCT 2025
L4          15 S L3
L5           9 S L4 AND (AY<=2019 OR PRY<=2019 OR PY<=2019)


     FILE 'REGISTRY' ENTERED AT 11:35:57 ON 29 OCT 2025
L6             STRUCTURE UPLOADED
L7          50 S L6 SSS SAM
L8        2567 S L6 SSS FULL


     FILE 'CAPLUS' ENTERED AT 11:40:30 ON 29 OCT 2025
L9         197 S L8
               E "ADRENAL REST TUMORS"/CT
               SET EXPAND CONTINUOUS
               E E3+ALL/CT
L10          8 S E14
L11         32 S "ADRENAL REST TUMORS"/IT
L12          1 S OVARIAN ADRENAL REST TUMORS/IT
               E OVARIAN ADRENAL REST TUMORS/CT
               E E20+ALL/CT
L13         36 S E119-E124
L14          1 S L9 AND (L10 OR L11 OR L12 OR L13)


     FILE 'REGISTRY' ENTERED AT 11:43:45 ON 29 OCT 2025
L15            STRUCTURE UPLOADED
L16          1 S L15 SSS SAM
L17          8 S L15 SSS FULL


     FILE 'CAPLUS' ENTERED AT 11:45:30 ON 29 OCT 2025
L18         62 S L17
L19          2 S L18 AND (L10 OR L11 OR L12 OR L13)


     FILE 'REGISTRY' ENTERED AT 11:46:21 ON 29 OCT 2025
L20            STRUCTURE UPLOADED
L21          1 S L20 SSS SAM
L22         79 S L20 SSS FULL


     FILE 'CAPLUS' ENTERED AT 11:50:33 ON 29 OCT 2025
L23          1 S L22 AND (L10 OR L11 OR L12 OR L13)


     FILE 'REGISTRY' ENTERED AT 11:51:09 ON 29 OCT 2025
               E SSR-126374/CN
               E SSR126374/CN
               E SSR 126374/CN
L24          1 S E163


     FILE 'CAPLUS' ENTERED AT 11:51:53 ON 29 OCT 2025
L25          1 S L24 AND (L10 OR L11 OR L12 OR L13)

=>
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Docusign Envelope ID: 723AA138-C5E9-46D8-A111-5884F6F73A67

PTO/AIA/01 (06-12)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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

Title of Invention	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 18/941,832 filed on November 8, 2024.

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

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

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

WARNING:

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

LEGAL NAME OF INVENTOR

Inventor: Hal GERBER Date (Optional) :

Signature: Signed by: 5EBA0FD256B7...

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

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0032. Public burden for this form is estimated to average 1 minute per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.** If filing this completed form by mail, send to: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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Privacy Act Statement

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Routine uses of the information in this record may include disclosure to: 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law; 2) a Federal, state, local, or international agency, in response to its request; 3) a contractor of the USPTO having need for the information in order to perform a contract; 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record; 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record; 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations; 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals; 8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)); 9) the Office of Personnel Management (OPM) for personnel research purposes; and 9) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Additional Uses

Additional USPTO uses of the information in this record may include disclosure to: 1) the International Bureau of the World Intellectual Property Organization, if the record is related to an international application filed under the Patent Cooperation Treaty; 2) the public i) after publication of the application pursuant to 35 U.S.C. 122(b), ii) after issuance of a patent pursuant to 35 U.S.C. 151, iii) if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections, or an issued patent, or iv) without publication of the application or patent under the specific circumstances provided for by 37 CFR 1.14(a)(1)(v)-(vii); and/or 3) the National Archives and Records Administration, for inspection of records.

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PTO/AIA/01 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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☒ United States application or PCT international application number 18/941,832 filed on November 8, 2024.

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

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LEGAL NAME OF INVENTOR

Inventor: Alexis HOWERTON Signed by: Date (Optional) :

Signature: Alexis Howerton 1CA87741213A149B...

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

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0032. Public burden for this form is estimated to average 1 minute per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.** If filing this completed form by mail, send to: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**11/20/2025 03:39:29 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	Colleen Mensching
PATENT CENTER #	73268978	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Declaration_Alexis_HOWERTON_Spruce_50535-710.303.pdf	2	Oath or Declaration filed	361 KB

Warning: The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

Declaration_Hal_GERBER_Spruce_50535-710.303.pdf	2	Oath or Declaration filed	358 KB

Warning: The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Declaration_Alexis_HOWERTON_Spruce_50535-710.303.pdf	8DDDAB7F3B3A3047C5D60B6381668D9F62098E25156F8890771EA228925246DFCABDCD1255E601BB339381B41FFC88F861DFF46BCCE9395540E7E1774B72303A
Declaration_Hal_GERBER_Spruce_50535-710.303.pdf	EFB3648A1FEB23BC8C055AFC2FC3DA23CD9D7CB16F3BA7AE9889034B3F5E35E40A0205C4D3F16B79818A924337CEE9E603E6495E65F30882AFF284338438D659

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,264	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**6961**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: December 10, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: December 10, 2025

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
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Customer No. 21971

PTO/SB/08 (01-25)
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	6	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-6586456	07-01-2003	FONTAINE; Evelyne et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

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NON-PATENT LITERATURE DOCUMENTS			
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	001	ANAWALT, Bradley D. et al. Chapter 12: Testes. Extract from Textbook: Gardner & Shoback, Greenspan's Basic & Clinical Endocrinology, 10th ed. (McGraw-Hill Education), pps. 413, 440-441 (2018).	☐
	002	BHATT, Deepak L. et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. N Engl J Med 370(15):1393-401 (2014).	☐
	003	BROWN, Marie T. et al. Medication Adherence: WHO Cares? Mayo Clin Proc 86(4):304-314 (2011).	☐
	004	Clinical Study Protocol SPR001-201. A Phase 2, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Efficacy of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia (CAH). (8/23/2018).	☐
	005	Declaration of Associate Professor Dr Henrik Falhammar dated November 14, 2025.	☐
	006	Declaration of Professor Peter Hindmarsh dated October 23, 2025.	☐
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	010	MEENA, H. et al., Growth Pattern and Clinical Profile of Indian Children with Classical 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia on Treatment. Indian J Pediatr. 86(6):496-502 (2019).	☐
	011	U.S. Serial No. 18/078,649 Office Action dated November 18, 2025.	☐
	012	Vivian H. Lin, Curriculum Vitae (No date available).	☐

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Sheet	4	of	6	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2025-12-10
Name/Print	Victoria Cheng	Registration Number	79641

PTO/SB/08 (01-25)
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Sheet	5	of	6	Attorney Docket Number	50535-710.306

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,264	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**6961**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: December 10, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: December 10, 2025

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
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	001	ANAWALT, Bradley D. et al. Chapter 12: Testes. Extract from Textbook: Gardner & Shoback, Greenspan's Basic & Clinical Endocrinology, 10th ed. (McGraw-Hill Education), pps. 413, 440-441 (2018).	☐
	002	BHATT, Deepak L. et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. N Engl J Med 370(15):1393-401 (2014).	☐
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	6	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2025-12-10
Name/Print	Victoria Cheng	Registration Number	79641

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	5	of	6	Attorney Docket Number	50535-710.306

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	19/043,264	Filing Date	2025-01-31	Docket Number (if applicable)	50535-710.306	Art Unit	1627
First Named Inventor	Alexis HOWERTON			Examiner Name	SARAH PIHONAK		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☐ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No _____

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Victoria Cheng/	Date (YYYY-MM-DD)	2025-12-10
Name	Victoria Cheng	Registration Number	79641

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**12/10/2025 03:02:18 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	JENNIFER VAIL
PATENT CENTER #	73536454	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 15

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710.306 - 2nd RCE.pdf		3	Request for Continued Examination (RCE)	1738 KB
Spruce 50535-710_306_IDS.pdf		10	-	286 KB
Spruce 50535-710_306_IDS-TRAN.LET.pdf	(1-4)	4	Transmittal Letter	144 KB
Spruce 50535-710_306_IDS-IDS.pdf	(5-10)	6	Information Disclosure Statement (IDS) Form (SB08)	138 KB
NPL_001_Anawalt_Chapter_12_pps_413_440-441.pdf		1	Non Patent Literature	114 KB
NPL_009_Henrik_Falhammar_Curriculum_Vitae.pdf		2	Non Patent Literature	138 KB

NPL_007_Declaration_Vivian_H_Lin_14Nov2025.pdf	7	Non Patent Literature	651 KB
NPL_006_Declaration_Peter_Hindmarsh_23Oct2025.pdf	5	Non Patent Literature	912 KB
NPL_005_DeclarationOf_Henrik_Falhammar_14Nov2025.pdf	9	Non Patent Literature	1042 KB
NPL_010_MEENA_GrowthPatternand_496-502.pdf	7	Non Patent Literature	1255 KB
NPL_002_BHATT_AControlledTrial_1393-401.pdf	9	Non Patent Literature	4912 KB
NPL_004_Clinical_Study_Protocol_SPR001-201.pdf	80	Non Patent Literature	5864 KB
NPL_008_FEDOROVA_Whatistheneed_1693063.pdf	10	Non Patent Literature	7626 KB
NPL_003_BROWN_MedicationAdherence_304-314.pdf	11	Non Patent Literature	8240 KB
NPL_011_US18078649_OA_2025_11_18.pdf	9	Non Patent Literature	328 KB
NPL_012_Vivian_H_Lin_Curriculum_Vitae.pdf	2	Non Patent Literature	192 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce 50535-710.306 - 2nd RCE.pdf	FBB216B6C6463F2D3CDB3842DD0C4BB516F7C66A62062AC3A4EE387D576C4EF9740489AF954C466AD65C928F62201CCF02D26310106F6BE591FE13ECAF7C17C4
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NPL_001_Anawalt_Chapter_12	EB3BD928E90A28126242AA0B49E90F5C5DBFE6E36739767C5

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NPL_007_Declaration_Vivian_H_Lin_14Nov2025.pdf	FA4CCC21DBBE55A6678ACB803FB3EB732BBCC17419921E786CD7C217EF2CD6235F84E3F8EF8B83D39A71F2895A0BE7E13B67E5676B6BC5EFA28418A5500D4807
NPL_006_Declaration_Peter_Hindmarsh_23Oct2025.pdf	6583AD55EFEBE75C3FD6013404D5C30006E251383E1123F7C7B5454E0E3E038E01DB03BFE6946EB0240A4035333538E87E732394BE1D75B0C508B52CCDF8E7C2
NPL_005_DeclarationOf_Henrik_Falhammar_14Nov2025.pdf	3464714FD67F497A24E548367535E3CF39BA6F8F5A9E4C4F4DD7CEB01E3A75E5C00148DA85DFCD4DDC71A65D710397F4118368D0BFAA6030A7C635630796A133
NPL_010_MEENA_GrowthPatternand_496-502.pdf	DFDBB06B1EE082E264390CFB15533226B5DB8183C77DB0FB673415037E9EEE1D5908FB925606D202BB8416F87FFA0E19909C6BA1F8F7861C49B5E1BFD7470470
NPL_002_BHATT_AControlledTrial_1393-401.pdf	8A2D6173E27A39FD4A318B23B544D739F53E10012E65739AD444E9B0F2D52771CCDB179C1C833E086DB59FACB7838C5C2F4AE960370FAAA87D2D33B2877C300E
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NPL_008_FEDOROVA_Whatistheneed_1693063.pdf	2F0B6CAFEB9706566F0085F27CFFC1B40E66A8D05A9AF4D731FD2A0B1E73D6D61DD62FED04FA891D3C5E83F2FD11FCDC7017351048EB2C9EC162EF9A2CF1BEF9
NPL_003_BROWN_MedicationAdherence_304-314.pdf	7389C5EED923E2F8D550722A0F84C04A9F2DF2866E54BBF6C3557D7C7E63095475CEE0D3FCE9B13E68E371E77EB0B5A7732A49D08052B8A8579A4D310D6F5EBB
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NPL_012_Vivian_H_Lin_Curriculum_Vitae.pdf	928851BFF7613A032200794205C5294B650EE9EB92301389764F4E25FDD04819BF1C5B5E384C4ECEA89560AE00AD1A8D83F08B84177397DEF84024FC3160844B

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement

Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**12/10/2025 03:02:18 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	JENNIFER VAIL
PATENT CENTER #	73536454	AUTHORIZED BY	Victoria Cheng
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 232415	**E2025B0F03049020**	**JENNIFER VAIL**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	2860.00	1	2860.00
			TOTAL AMOUNT:	**$2,860.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 01/06/2026

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 01/06/2026

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	04/06/2026

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 01/06/2026

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	04/06/2026

EXAMINER	ART UNIT	CLASS-SUBCLASS
PIHONAK, SARAH	1627	514-233200

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

21971 7590 01/06/2026

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 01/06/2026

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 19/043,264	Applicant(s) HOWERTON et al.	
	Examiner SARAH PIHONAK	Art Unit 1627	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 12/10/25.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-21 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/10/25 has been entered.

Status of Claims

1. Claims 1-21 were allowed for reasons noted in the notice of allowance mailed on 11/17/25.

Information Disclosure Statement

2. The IDS filed on 12/10/25 has been considered.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached Monday-Friday 9:00-5:30 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached at 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SARAH . PIHONAK
Primary Examiner
Art Unit 1627

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

CPC - Searched*		
Symbol	Date	Examiner
a61k31/519; a61p5/06,08	04/21/2025	s.p.
a61k31/519, 5377; a61p5/06,08	08/13/2025	s.p.
a61k31/519, 5377; a61p5/06,08	10/29/2025	s.p.
a61k31/519, 5377; a61p5/06,08	12/17/2025	s.p.

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

Search Notes		
Search Notes	**Date**	**Examiner**
a61k31/519; a61p5/06,08	04/21/2025	s.p.
inventor & applicant search in PE2E, patent data portal	04/21/2025	s.p.
invention & claims search in stn, PE2E	04/21/2025	s.p.
a61k31/519, 5377; a61p5/06,08	08/13/2025	s.p.
inventor & applicant search in PE2E, patent data portal	08/13/2025	s.p.
invention & claims search in PE2E	08/13/2025	s.p.
a61k31/519, 5377; a61p5/06,08	10/29/2025	s.p.
inventor & applicant search in PE2E, patent data portal	10/29/2025	s.p.
invention & claims search in PE2E (incl. similarity), stnext	10/29/2025	s.p.
a61k31/519, 5377; a61p5/06,08	12/17/2025	s.p.
inventor & applicant search in PE2E, patent data portal	12/17/2025	s.p.
invention & claims search in PE2E (incl. similarity)	12/17/2025	s.p.

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
a61k	31/519, 5377	10/29/2025	s.p.
a61p	5/06,08	10/29/2025	s.p.
a61k	31/519, 5377	12/17/2025	s.p.
a61p	5/06,08	12/17/2025	s.p.

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	**Art Unit**
	SARAH PIHONAK	1627

CPC								
Symbol							**Type**	**Version**
A61K	/	31	/	519			F	2013-01-01
A61K	/	9	/	0053			A	2013-01-01
A61K	/	9	/	20			A	2013-01-01
A61K	/	9	/	48			A	2013-01-01
A61K	/	45	/	06			A	2013-01-01
A61P	/	5	/	06			A	2018-01-01
A61P	/	5	/	08			A	2018-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	21	
/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	17 December 2025	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20251217

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	**Art Unit**
	SARAH PIHONAK	1627

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	519
A61P	/	5	/	06
A61P	/	5	/	08

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 21	
/SARAH PIHONAK/ Primary Examiner, Art Unit 1627 (Primary Examiner)	17 December 2025 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,264	HOWERTON et al.
	Examiner	**Art Unit**
	SARAH PIHONAK	1627

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19										
	2		11		20										
	3		12		21										
	4		13												
	5		14												
	6		15												
	7		16												
	8		17												
	9		18												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 21	
/SARAH PIHONAK/ Primary Examiner, Art Unit 1627 (Primary Examiner)	17 December 2025 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office

Part of Paper No.: 20251217

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	652	(corticotropin adj8 factor adj8 antagon*) AND (menstruation OR menstrual)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:36 PM
L2	200	((corticotropin adj8 factor adj8 antagon*) OR (CRF1 adj8 antagon*)).ab,ti,clm. AND L1	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:37 PM
L3	276	(corticotropin adj8 factor adj8 antagon*) AND (dysmenorrhea)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:42 PM
L4	42	((corticotropin adj8 factor adj8 antagon*) OR (CRF1 adj8	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY,	OR	ON	ON	2025/04/18 05:42 PM

		antagon*)).ab,ti,clm. AND L3	CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L5	192	(((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND (L2 OR L4)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 05:53 PM
L6	31	((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/04/18 06:11 PM
L7	21	((("HOWERTON") near3 ("Alexis"))).INV.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/04/18 06:11 PM
L8	21	((("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/04/18 06:11 PM
L9	23	(L2 OR L4) AND (L6 OR L7 OR L8)	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/04/18 06:12 PM
L10	6002	(a61k31/519 OR a61p5/06,08).cpc. AND (menstrual OR menstruation OR dysmenorrhea OR dysmennorhea OR dysmennorrhea)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 06:14 PM
L11	140	(corticotropin adj8 factor	(US-PGPUB; USPAT;	OR	ON	ON	2025/04/18

		adj8 antagon*) AND L10	USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				06:14 PM
L12	96	((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L11	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/18 06:15 PM
L13	19	("10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220143037" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2025/04/21 09:32 AM
L14	940	(a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 antagon*)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS,	OR	ON	ON	2025/04/21 10:26 AM

			IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L15	877	(((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L14	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 10:26 AM
L16	286	L15 AND (corticotropin adj8 releas* adj8 factor adj8 antagon*).ab,ti,clm.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 10:27 AM
L17	484	(corticotropin adj8 factor adj8 antagon*) AND (amenorrhea)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 12:48 PM

L18	489	(corticotropin adj8 factor adj8 antagon*) AND (amenorrhea OR menorrhagia)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 12:48 PM
L19	423	((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L18	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 12:49 PM
L20	31	"1200419".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 01:07 PM
L21	1	"6586456".pn.	(USPAT)	OR	ON	ON	2025/04/21 01:08 PM
L22	272	(congenital adj6 adrenal adj6 hyperplasia) WITH (menorrhagia OR dysmenorrhea OR menstrual OR menstruation)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV,	OR	ON	ON	2025/04/21 03:18 PM

			MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L23	216	(((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20190426")) AND L22	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/04/21 03:18 PM
L24	7	"2015112642".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 04:20 PM
L25	3	L24 AND (time OR frequency)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 04:21 PM
L26	2	L24 AND (one OR once OR twice)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP,	OR	ON	ON	2025/04/21 04:21 PM

			ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L27	1	L24 AND (day OR daily)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/04/21 04:21 PM
L28	1	"20100222339".pn.	(US-PGPUB)	OR	ON	ON	2025/04/21 04:48 PM
L29	1	L28 AND adrenal	(US-PGPUB)	OR	ON	ON	2025/04/21 04:48 PM
L30	0	L28 AND adrenal AND (tablet* OR capsule*)	(US-PGPUB)	OR	ON	ON	2025/04/21 04:48 PM
L31	1	"12098152".pn.	(USPAT)	OR	ON	ON	2025/04/21 05:46 PM
L32	54	("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/05 03:00 PM

		"20220143037" OR "20230159533" OR "20230321112" OR "20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177404" OR "20250195527" OR "8030304" OR "8563718" OR "10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn.					
L33	36	("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR "20220143037" OR "20230159533" OR "20230321112" OR	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/05 03:06 PM

		"20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177404" OR "20250195527" OR "8030304" OR "8563718").pn.					
L34	1	"20250177403".pn.	(US-PGPUB)	OR	ON	ON	2025/08/13 03:01 PM
L35	23	(a61k31/519,5377 OR a61p5/06,08).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 (inhibit* OR antagon* OR block*)) AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/08/13 03:04 PM
L36	28	(Artificial Intelligence) More like doc: US-20250177403-A1 Text: (JP-H0971528-A OR AU-2007231549-A1 OR RS-51545-B OR US-20100203048-A1 OR IL-317035-A OR BR-112020002967-A2 OR US-20210137935-A1 OR US-20250177403-A1 OR HK-40040045-A OR US-20250177404-A1 OR US-20250195527-A1 OR US-20250064812-A1 OR US-11304950-B2 OR HK-40040045-B OR EP-3784233-B1 OR AU-2023203095-A1 OR CA-3098562-A1 OR US-20210038604-A1 OR BR-112020024062-A2 OR US-20220211711-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/08/13 03:06 PM
L37	14	L36 AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY,	OR	ON	ON	2025/08/13 03:07 PM

			CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L38	35	((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/13 03:07 PM
L39	24	((("HOWERTON") near3 ("Alexis")) OR (("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2025/08/13 03:08 PM
L40	8	(L38 OR L39) AND (corticotropin adj8 releas* adj8 factor adj8 (inhibit* OR antagon* OR block*)) AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/13 03:08 PM
L41	1	"20250177403".pn.	(US-PGPUB)	OR	ON	ON	2025/10/29 11:18 AM
L42	29	(Artificial Intelligence) More like doc: US-20250177403-A1 Text: (JP-H0971528-A OR EP-2004205-A4 OR CN-101516887-B OR US-20100203048-A1 OR CN-106102740-A OR KR-20200040761-A OR WO-2019036472-A1 OR EP-3784233-B1 OR US-20250177404-A1 OR US-20250177403-A1 OR HK-40040045-A OR US-20250195527-A1 OR HK-40040045-B OR CA-3098562-A1 OR US-20210038604-A1 OR US-11304950-B2 OR US-20220211711-A1 OR US-20250064812-A1 OR EP-4438124-A2 OR AU-2023203095-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/10/29 11:18 AM

L43	21	(a61k31/519,5377 OR a61p35/00 OR a61p5/06,08).cpc. AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/10/29 11:24 AM
L44	8	(L38 OR L39) AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/10/29 11:26 AM
L45	8	"2010039678".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:51 PM
L46	0	L45 AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:51 PM
L47	7	"2016065177".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP,	OR	ON	ON	2025/10/29 12:51 PM

			ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L48	0	L47 AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:51 PM
L49	7	"2019036472".pn.	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:52 PM
L50	0	L49 AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/10/29 12:52 PM
L51	1	"6586456".pn.	(USPAT)	OR	ON	ON	2025/12/17 09:33 AM
L52	1	"20250177403".pn.	(US-PGPUB)	OR	ON	ON	2025/12/17 09:51 AM

L53	25	(Artificial Intelligence) More like doc: US-20250177403-A1 Text: (JP-H0971528-A OR EP-2004205-A4 OR AT-E481405-T1 OR US-20100203048-A1 OR EP-3096756-B1 OR CN-110997667-A OR KR-20250022913-A OR US-20250195527-A1 OR EP-3784233-B1 OR HK-40040045-A OR US-20250177403-A1 OR US-20250177404-A1 OR HK-40040045-B OR AU-2023203095-A1 OR US-11304950-B2 OR AU-2019260793-B2 OR US-20250064812-A1 OR US-20240285593-A1 OR JP-7427655-B2 OR CA-3098562-A1).did.	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/12/17 09:51 AM
L54	12	L53 AND (adrenal adj8 rest adj8 (tumor* OR neoplasm* OR proliferat* OR growth*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/12/17 09:52 AM
L55	34	(a61k31/519,5377 OR a61k9/0053,20,2004,48,4841 OR a61p5/06,08 OR a61p35/00).cpc. AND ((ovary OR ovarian) adj10 adrenal adj10 (tumor* OR neoplasm* OR proliferat* OR growth*)) AND (corticotropin adj10 releas* adj10 (antagon* OR block* OR suppress* OR reduc* OR decreas*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/12/17 09:58 AM

L56	35	((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/12/17 10:01 AM
L57	24	((("HOWERTON") near3 ("Alexis")) OR (("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/17 10:01 AM
L58	9	(L56 OR L57) AND ((ovary OR ovarian) adj10 adrenal adj10 (tumor* OR neoplasm* OR proliferat* OR growth*)) AND (corticotropin adj10 releas* adj10 (antagon* OR block* OR suppress* OR reduc* OR decreas*))	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/12/17 10:02 AM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	7	(a61k31/519,5377 OR a61p5/06,08).cpc. AND (corticotropin adj8 releas* adj8 factor adj8 (inhibit* OR antagon* OR block*)) AND (ovar* adj8 adrenal adj8 (tumor* OR neoplasm*))	(US-PGPUB; USPAT)	OR	ON	ON	2025/08/13 03:06 PM
N2	7	(a61k31/519,5377 OR a61p35/00 OR a61p5/06,08).cpc. AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR block*)) AND (ovar* adj8 adrenal adj8 rest adj8 tumor*)	(US-PGPUB; USPAT)	OR	ON	ON	2025/10/29 11:25 AM
N3	8	(a61k31/519,5377 OR a61k9/0053,20,2004,48,4841 OR a61p5/06,08 OR a61p35/00).cpc. AND ((ovary OR ovarian) adj10 adrenal adj10 (tumor* OR neoplasm* OR proliferat* OR growth*)) AND (corticotropin adj10 releas* adj10 (antagon* OR block* OR suppress* OR reduc* OR decreas*))	(US-PGPUB; USPAT)	OR	ON	ON	2025/12/17 10:03 AM

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	6	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-6586456	07-01-2003	FONTAINE; Evelyne et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	6	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	ANAWALT, Bradley D. et al. Chapter 12: Testes. Extract from Textbook: Gardner & Shoback, Greenspan's Basic & Clinical Endocrinology, 10th ed. (McGraw-Hill Education), pps. 413, 440-441 (2018).	☐
	002	BHATT, Deepak L. et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. N Engl J Med 370(15):1393-401 (2014).	☐
	003	BROWN, Marie T. et al. Medication Adherence: WHO Cares? Mayo Clin Proc 86(4):304-314 (2011).	☐
	004	Clinical Study Protocol SPR001-201. A Phase 2, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Efficacy of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia (CAH). (8/23/2018).	☐
	005	Declaration of Associate Professor Dr Henrik Falhammar dated November 14, 2025.	☐
	006	Declaration of Professor Peter Hindmarsh dated October 23, 2025.	☐
	007	Declaration of Vivian H. Lin, M.D. dated November 14, 2025.	☐
	008	FEDOROVA, Olga et al. What is the need for adrenalectomy in patients with congenital adrenal hyperplasia in the era of CRF1/ACT inhibitors? Frontiers in Endocrinology (Lausanne) 16:1693063, 1-10 (2025).	☐
	009	Henrik Falhammar, M.D., Ph.D., FRACP, Curriculum Vitae (No date available).	☐

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	12/17/2025

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	3	of	6	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	010	MEENA, H. et al., Growth Pattern and Clinical Profile of Indian Children with Classical 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia on Treatment. Indian J Pediatr. 86(6):496-502 (2019).	☐
	011	U.S. Serial No. 18/078,649 Office Action dated November 18, 2025.	☐
	012	Vivian H. Lin, Curriculum Vitae (No date available).	☐

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	12/17/2025

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	6	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2025-12-10
Name/Print	Victoria Cheng	Registration Number	79641

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

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				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	5	of	6	Attorney Docket Number	50535-710.306

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,264	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**6961**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: January 12, 2026

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☒ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☒ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: January 12, 2026

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

PTO/SB/08 (01-25)
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	5	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Sheet	2	of	5	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	DEAK, T. et al. The impact of the nonpeptide corticotropin-releasing hormone antagonist antalarmin on behavioral and endocrine responses to stress. Endocrinology 140(1):79-86 (1999).	☐

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Sheet	3	of	5	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☐ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2026-01-12
Name/Print	Victoria Cheng	Registration Number	79641

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,264	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**6961**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: January 12, 2026

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☒ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☒ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: January 12, 2026

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

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Sheet	1	of	5	Attorney Docket Number	50535-710.306

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Sheet	2	of	5	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	DEAK, T. et al. The impact of the nonpeptide corticotropin-releasing hormone antagonist antalarmin on behavioral and endocrine responses to stress. Endocrinology 140(1):79-86 (1999).	☐

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☐ See attached timing statement under 37 CFR 1.97(e).

☐ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

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SIGNATURE

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Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2026-01-12
Name/Print	Victoria Cheng	Registration Number	79641

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**01/12/2026 04:35:45 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	JENNIFER VAIL
PATENT CENTER #	73941221	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710_306_IDS.pdf		9	-	271 KB
Spruce 50535-710_306_IDS-TRAN.LET.pdf	(1-4)	4	Transmittal Letter	138 KB
Spruce 50535-710_306_IDS-IDS.pdf	(5-9)	5	Information Disclosure Statement (IDS) Form (SB08)	128 KB
NPL_001_DEAK_Theimpact ofthenonpeptide_79-86.pdf		8	Non Patent Literature	237 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce 50535-710_306_IDS.pdf	B52A35184482C310A30CC18D7ED9EDAB4CB7E7D089A05CEB67B11774525268F6F655A8FDF9307BD71E03BE02BB4328E0D09014BCBB4A585504CB5A9479899E4C
Spruce 50535-710_306_IDS-TRAN.LET.pdf	101195EC97C0F5EAA64205CE0B69E9E3B14FC5F7F3F0CA2E101E772D70B7C2084EB93A8521694F2C914881EAF666BB042658C52F3ACE8B827576DD9174A215F8
Spruce 50535-710_306_IDS-IDS.pdf	2ED719EA342944BE138390C647B937130CDC33C59C68B10F30F6E6F52FD9FF59E0A1487FDD421C6A455D45FD6D7AFEDC2263850A3D1ED36DB2BFE1BA0772BBAD
NPL_001_DEAK_Theimpactofthenonpeptide_79-86.pdf	2026260EC20A6B59E3FF10CD7EBD435088D3C600E0F8CAAC995FA37C2DB2866600D995E2F600C1F9772678C8203D020BC9785ADAC0DAEE8AC3365029EFFC1AC2

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**01/12/2026 04:35:45 PM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	JENNIFER VAIL
PATENT CENTER #	73941221	AUTHORIZED BY	Victoria Cheng
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 232415	**E20261BG36128206**	**JENNIFER VAIL**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	280.00	1	280.00
			TOTAL AMOUNT:	**$280.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

21971 7590 01/16/2026

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
PIHONAK, SARAH	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
01/16/2026	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

CORRECTED ***Notice of Allowability***	**Application No.** 19/043,264	**Applicant(s)** HOWERTON et al.	
	Examiner SARAH PIHONAK	**Art Unit** 1627	**AIA (First Inventor to File) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 1/12/26.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-21 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	5	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	01/14/2026

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	5	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	DEAK, T. et al. The impact of the nonpeptide corticotropin-releasing hormone antagonist antalarmin on behavioral and endocrine responses to stress. Endocrinology 140(1):79-86 (1999).	☐

EXAMINER SIGNATURE			
Examiner Signature	/SARAH PIHONAK/	Date Considered	01/14/2026

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	3	of	5	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☐ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Victoria Cheng/	Date (YYYY-MM-DD)	2026-01-12
Name/Print	Victoria Cheng	Registration Number	79641

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	5	Attorney Docket Number	50535-710.306

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 01/06/2026

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Jennifer Vail	(Typed or printed name)
/jvail/	(Signature)
2/6/2026	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	01/31/2025	Alexis HOWERTON	50535-710.306	6961

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1290	$0.00	$0.00	$1290	04/06/2026

EXAMINER	ART UNIT	CLASS-SUBCLASS
PIHONAK, SARAH	1627	514-233200

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 WILSON SONSINI GOODRICH & ROSATI
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: SPRUCE BIOSCIENCES, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): South San Francisco, California

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☐ Applicant asserting small entity status. See 37 CFR 1.27

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Authorized Signature /Victoria Cheng/ Date February 2, 2026

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**02/02/2026 11:36:09 AM Z ET**	**50535-710.306**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6961	FILED BY	JENNIFER VAIL
PATENT CENTER #	74284602	AUTHORIZED BY	Victoria Cheng
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 232415	**E202622B36376429**	**JENNIFER VAIL**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1501	UTILITY ISSUE FEE	1290.00	1	1290.00
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,264	**02/02/2026 11:36:09 AM Z ET**	**50535-710.306**

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CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710.306 Issue Fee Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	105 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce 50535-710.306 Issue Fee Transmittal.pdf	117066CCF5E32B2EC48AA3C08230A5672BC70A3A802DA0053 6BDE2D99206299DCA374038C4920235DA9D7B06E602C0ECE 20C1717D98B87975421390114E9D614

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,264	03/10/2026	12569490	50535-710.306	6961

21971 7590 02/25/2026

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The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

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(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Alexis HOWERTON, San Francisco, CA;
Hal GERBER, San Francisco, CA;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Spruce Biosciences, Inc., South San Francisco, CA;

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Patent

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If the application for this patent was filed on or after June 8, 1995, the term of this patent begins on the date on which this patent issues and ends twenty years from the filing date of the application or, if the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121, 365(c), or 386(c), twenty years from the filing date of the earliest such application ("the twenty-year term"), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b), and any extension as provided by 35 U.S.C. 154(b) or 156 or any disclaimer under 35 U.S.C. 253.

If this application was filed prior to June 8, 1995, the term of this patent begins on the date on which this patent issues and ends on the later of seventeen years from the date of the grant of this patent or the twenty-year term set forth above for patents resulting from applications filed on or after June 8, 1995, subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b) and any extension as provided by 35 U.S.C. 156 or any disclaimer under 35 U.S.C. 253.

US012569490B2

(12) **United States Patent**
Howerton et al.

(10) **Patent No.: US 12,569,490 B2**
(45) **Date of Patent: *Mar. 10, 2026**

(54) **METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS**

(71) Applicant: **Spruce Biosciences, Inc.**, South San Francisco, CA (US)

(72) Inventors: **Alexis Howerton**, San Francisco, CA (US); **Hal Gerber**, San Francisco, CA (US)

(73) Assignee: **SPRUCE BIOSCIENCES, INC.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **19/043,264**

(22) Filed: **Jan. 31, 2025**

(65) **Prior Publication Data**

US 2025/0177403 A1 Jun. 5, 2025

Related U.S. Application Data

(63) Continuation of application No. 18/941,832, filed on Nov. 8, 2024, which is a continuation of application No. 17/667,285, filed on Feb. 8, 2022, now abandoned, which is a continuation of application No. 17/081,694, filed on Oct. 27, 2020, now Pat. No. 11,304,950, which is a continuation of application No. PCT/US2019/029486, filed on Apr. 26, 2019.

(60) Provisional application No. 62/822,815, filed on Mar. 23, 2019, provisional application No. 62/663,951, filed on Apr. 27, 2018.

(51) **Int. Cl.**

A61K 31/519	(2006.01)
A61P 5/06	(2006.01)
A61P 5/08	(2006.01)
A61K 9/00	(2006.01)
A61K 9/20	(2006.01)
A61K 9/48	(2006.01)
A61K 45/06	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/519*** (2013.01); *A61K 9/0053* (2013.01); *A61K 9/20* (2013.01); *A61K 9/48* (2013.01); *A61K 45/06* (2013.01); *A61P 5/06* (2018.01); *A61P 5/08* (2018.01)

(58) **Field of Classification Search**

CPC A61K 31/519; A61K 31/5377; A61P 5/06; A61P 5/08

See application file for complete search history.

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Primary Examiner — Sarah Pihonak

(74) *Attorney, Agent, or Firm* — WILSON SONSINI GOODRICH & ROSATI

(57) **ABSTRACT**

Provided herein are compounds and pharmaceutical compositions for the prevention and treatment of testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART).

21 Claims, 14 Drawing Sheets

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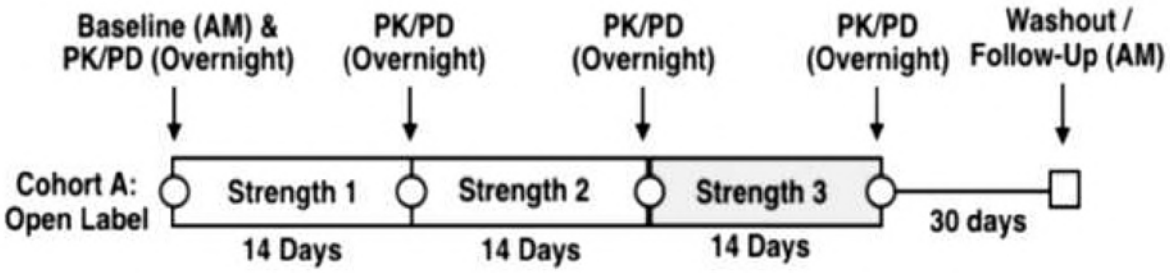

Baseline (AM) & PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
Washout / Follow-Up (AM)
Cohort A: Open Label
Strength 1
Strength 2
Strength 3
14 Days
14 Days
14 Days
30 days

FIG. 1A

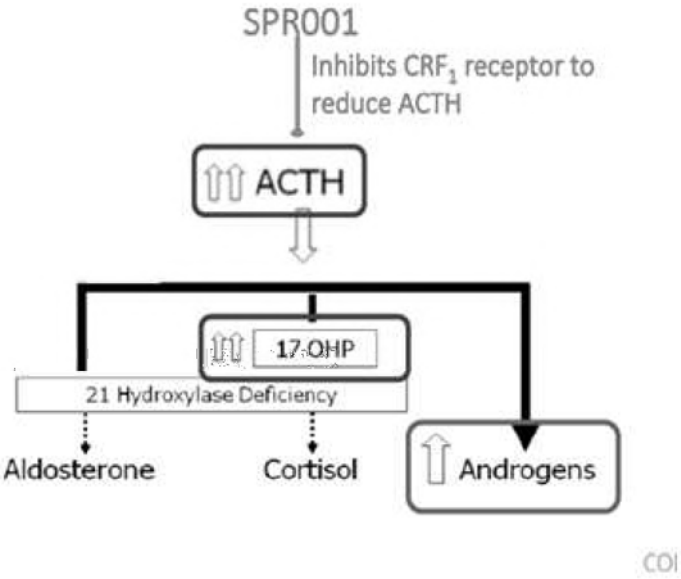

SPR001
Inhibits CRF1 receptor to reduce ACTH
ACTH
17-OHP
21 Hydroxylase Deficiency
Aldosterone
Cortisol
Androgens

FIG. 1B

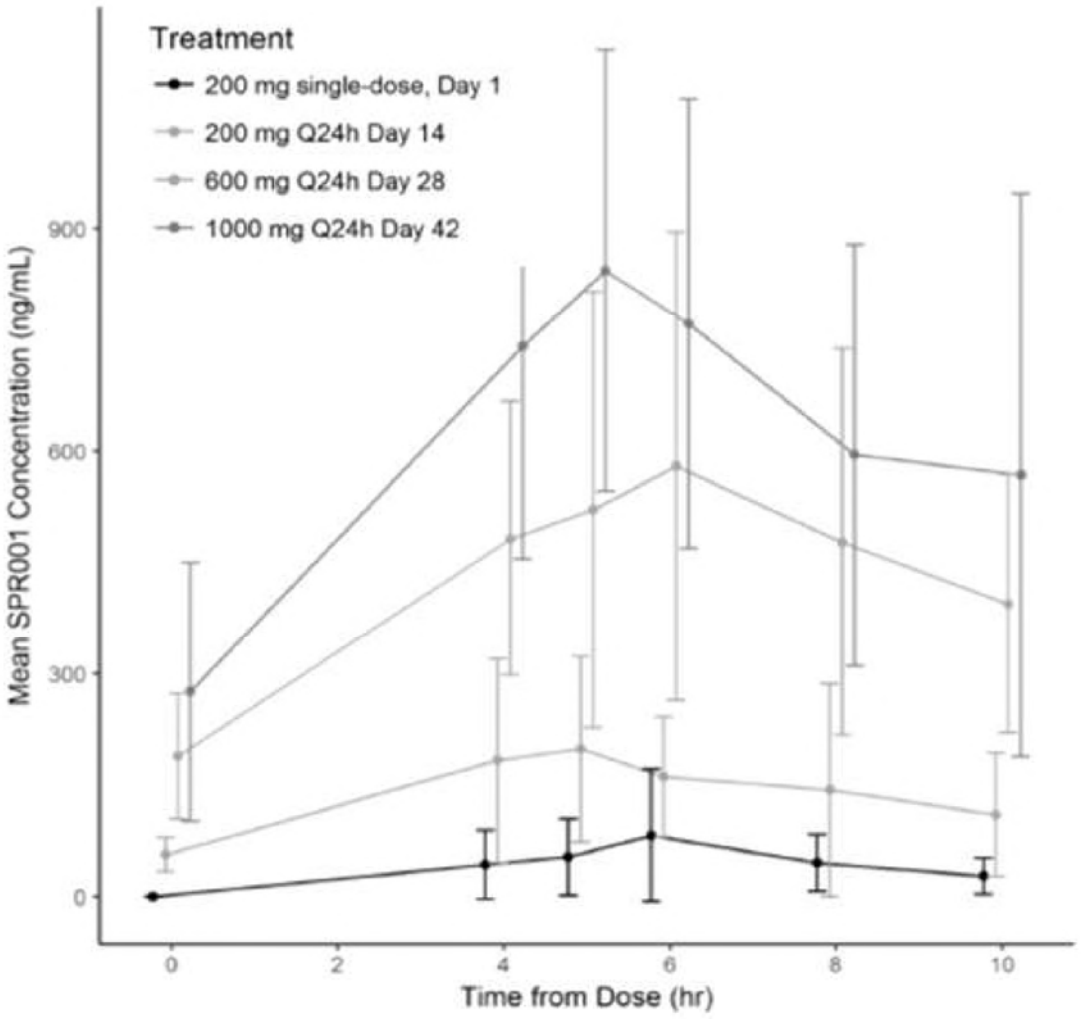

Treatment
200 mg single-dose, Day 1
200 mg Q24h Day 14
600 mg Q24h Day 28
1000 mg Q24h Day 42
Mean SPR001 Concentration (ng/mL)
900
600
300
0
0
2
4
6
8
10
Time from Dose (hr)

FIG. 2

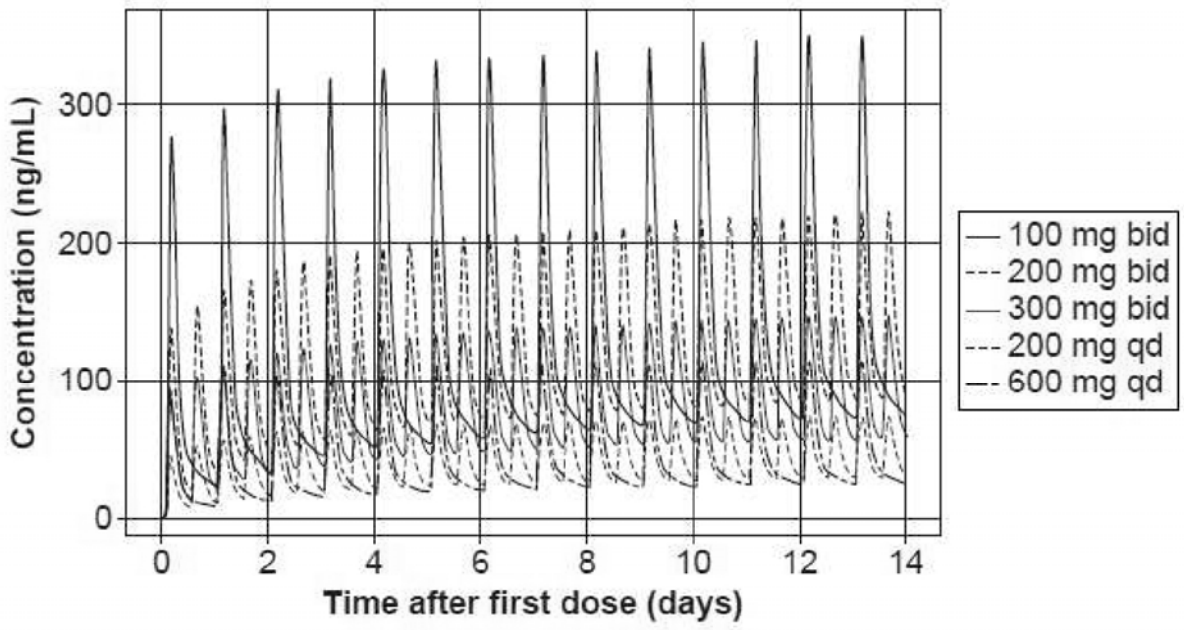

Concentration (ng/mL)
300
200
100
0
0
2
4
6
8
10
12
14
Time after first dose (days)
100 mg bid
200 mg bid
300 mg bid
200 mg qd
600 mg qd

FIG. 3

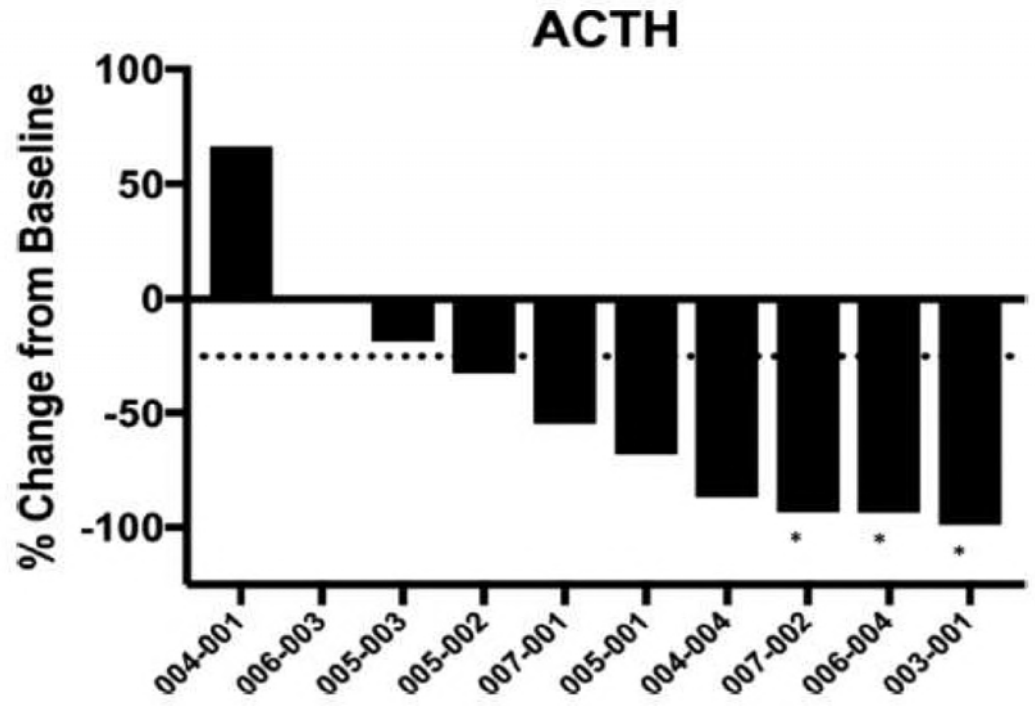

ACTH
% Change from Baseline
100
50
0
-50
-100
*
*
*
004-001
006-003
005-003
005-002
007-001
005-001
004-004
007-002
006-004
003-001

FIG. 4

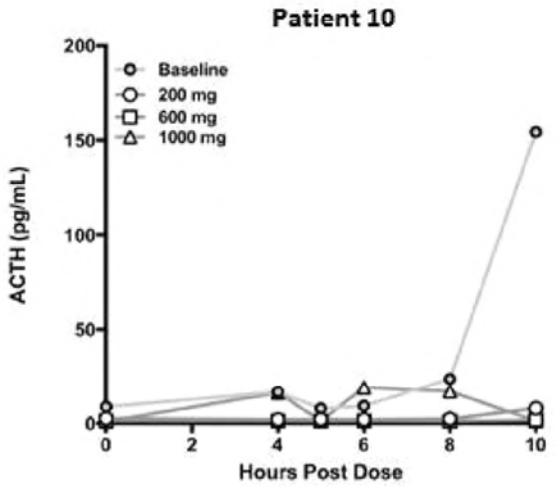


FIG. 5A

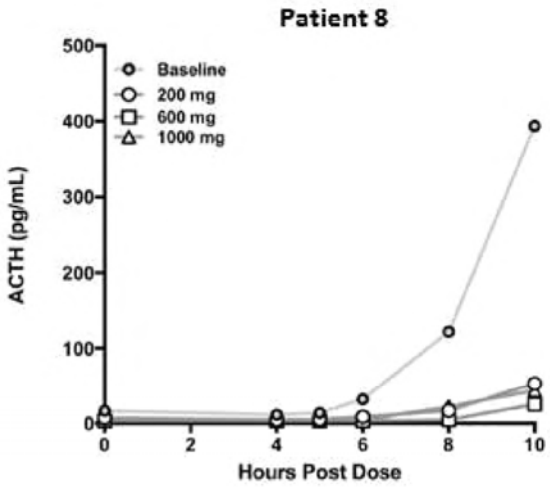


FIG. 5B

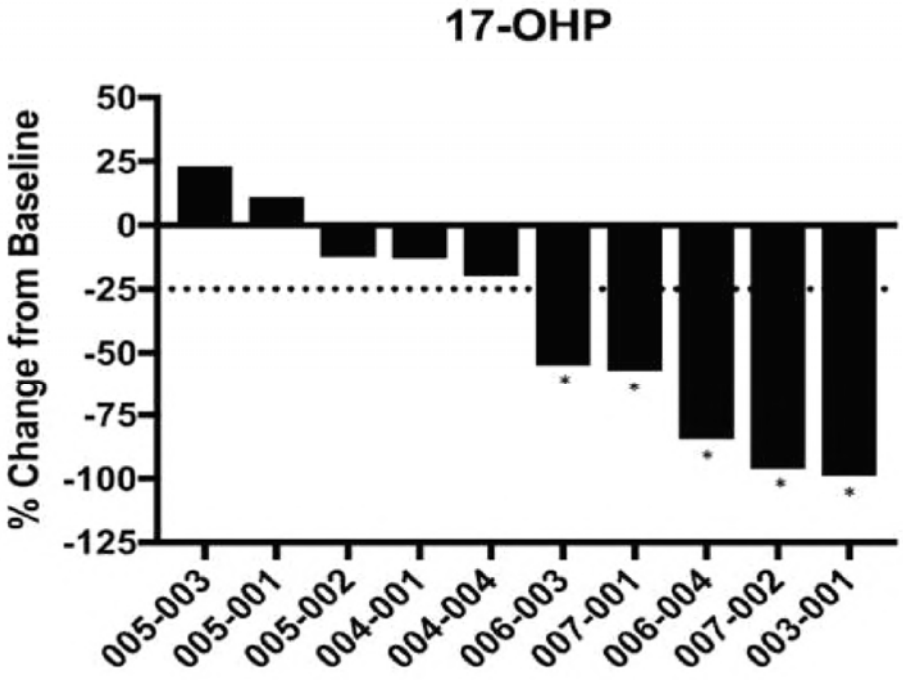


FIG. 6

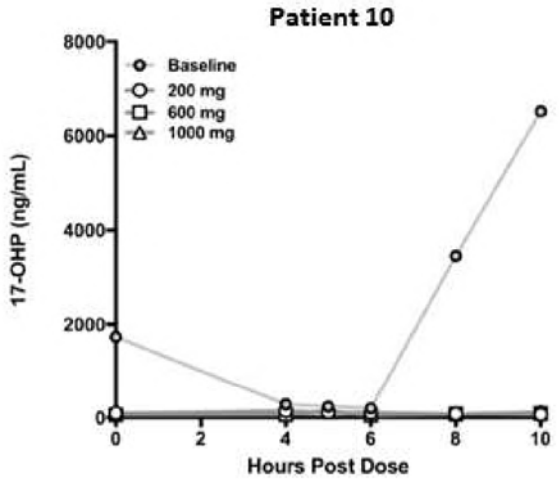


FIG. 7A

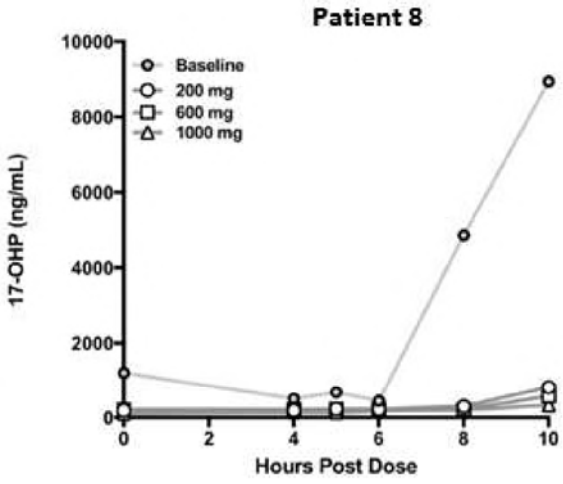


FIG. 7B

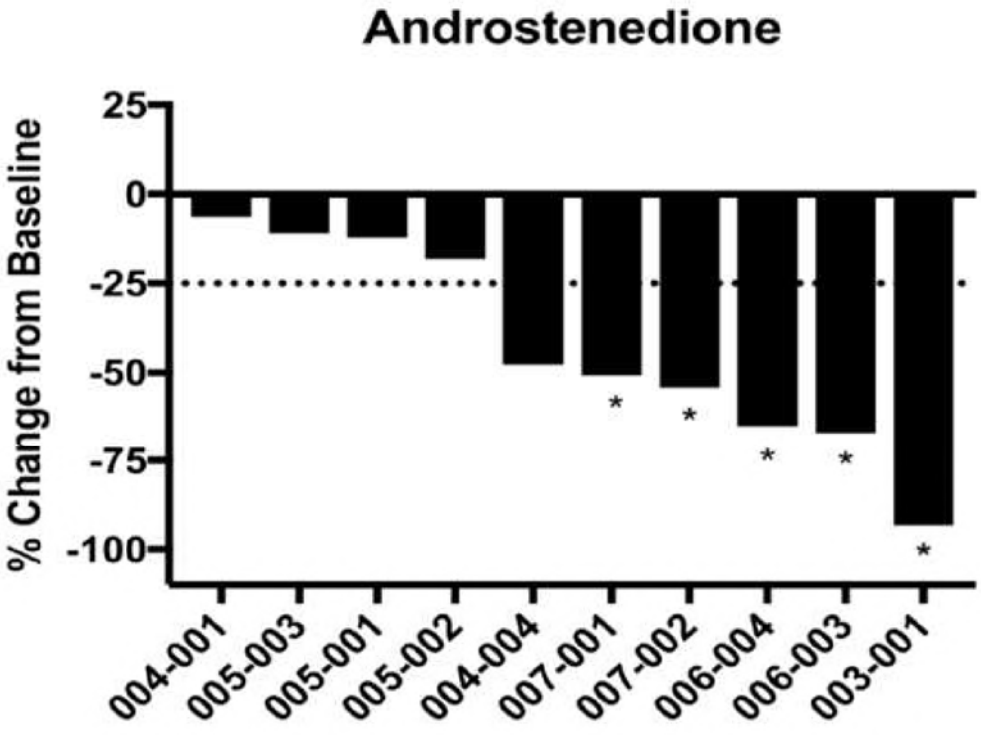


FIG. 8

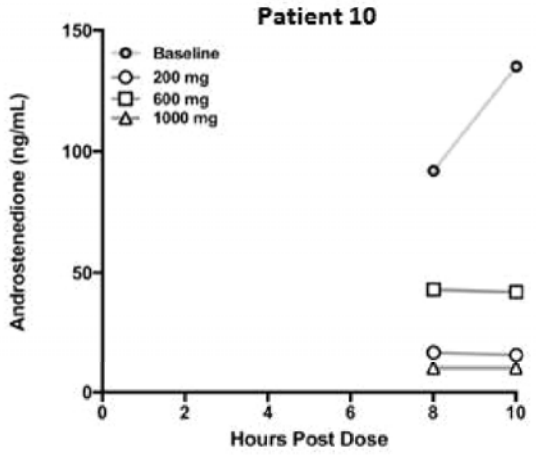


FIG. 9A

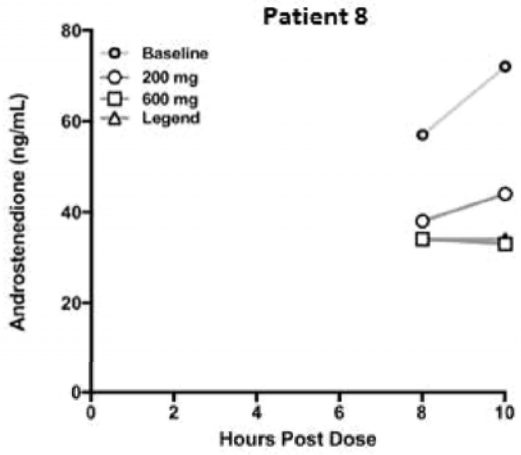


FIG. 9B

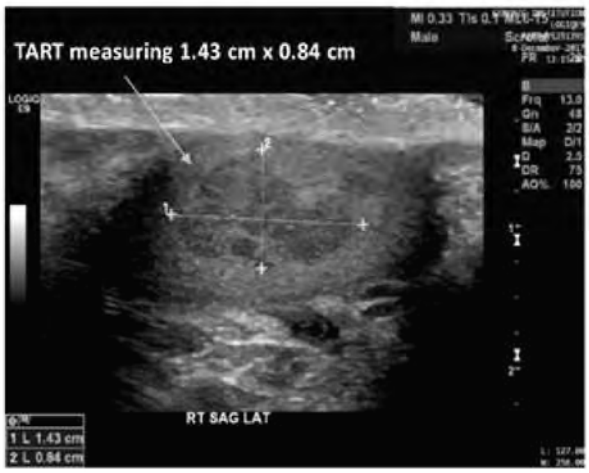


FIG. 10A

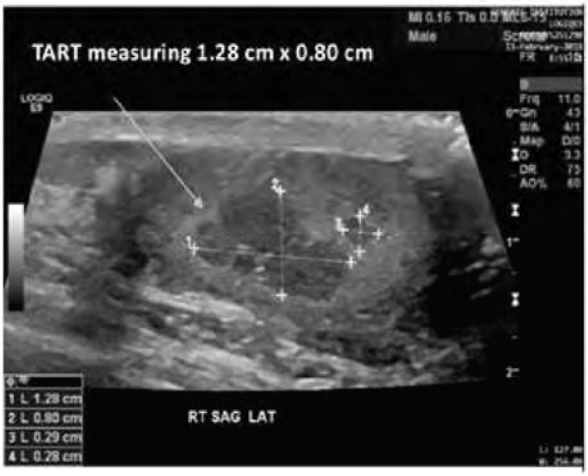


FIG. 10B

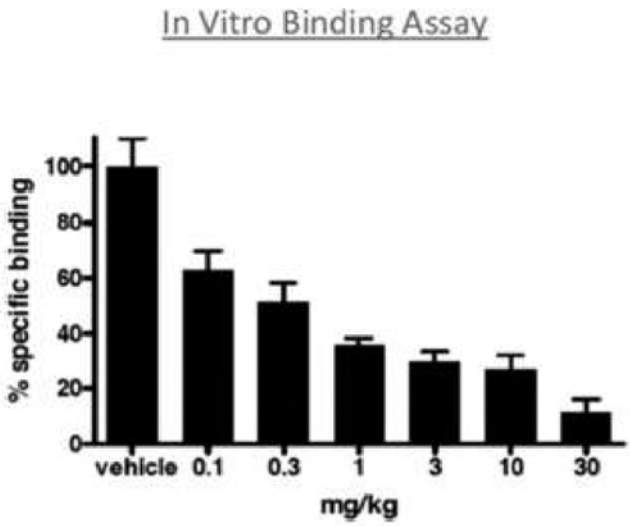


FIG. 11A

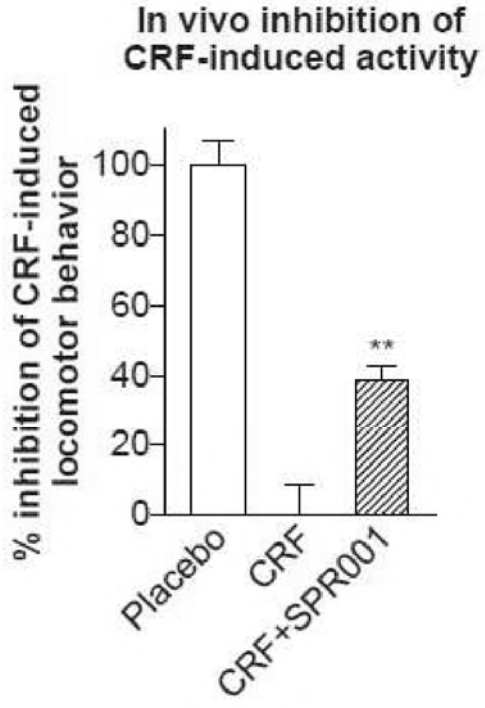


FIG. 11B

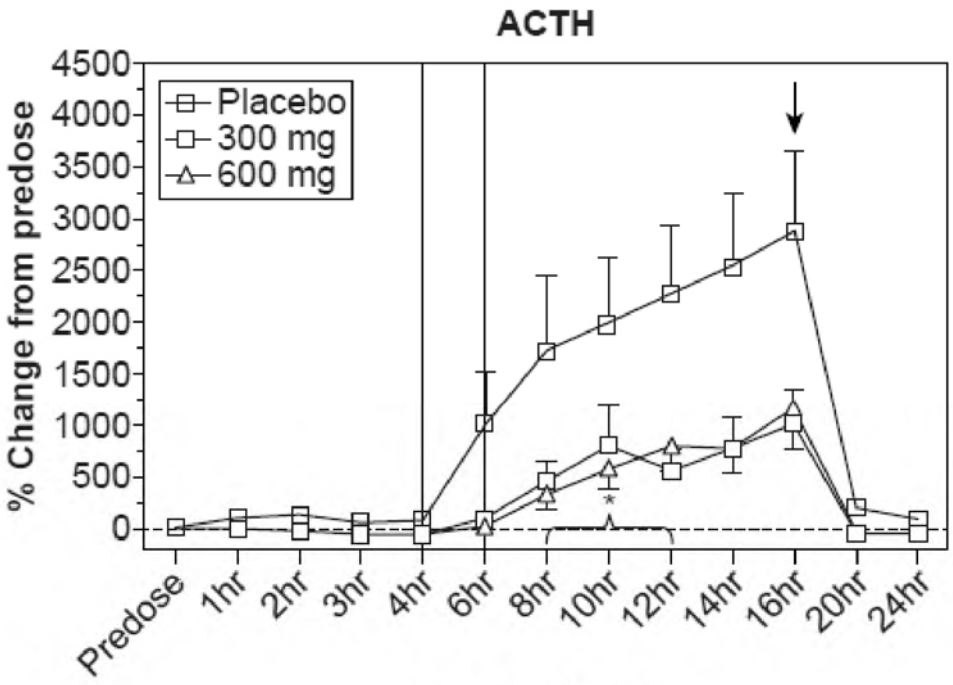


FIG. 12A

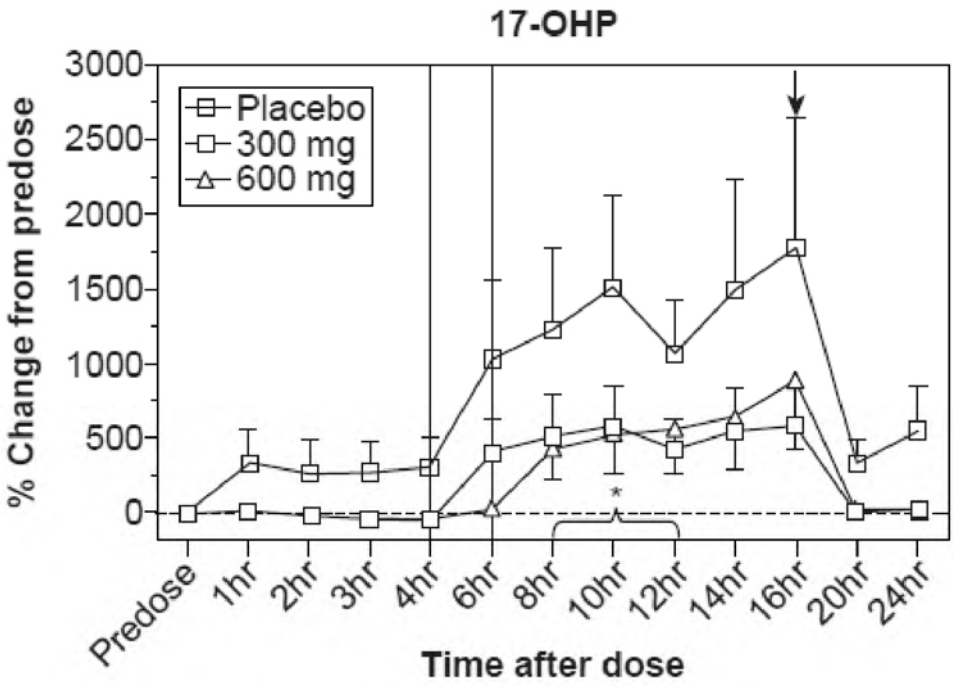


FIG. 12B

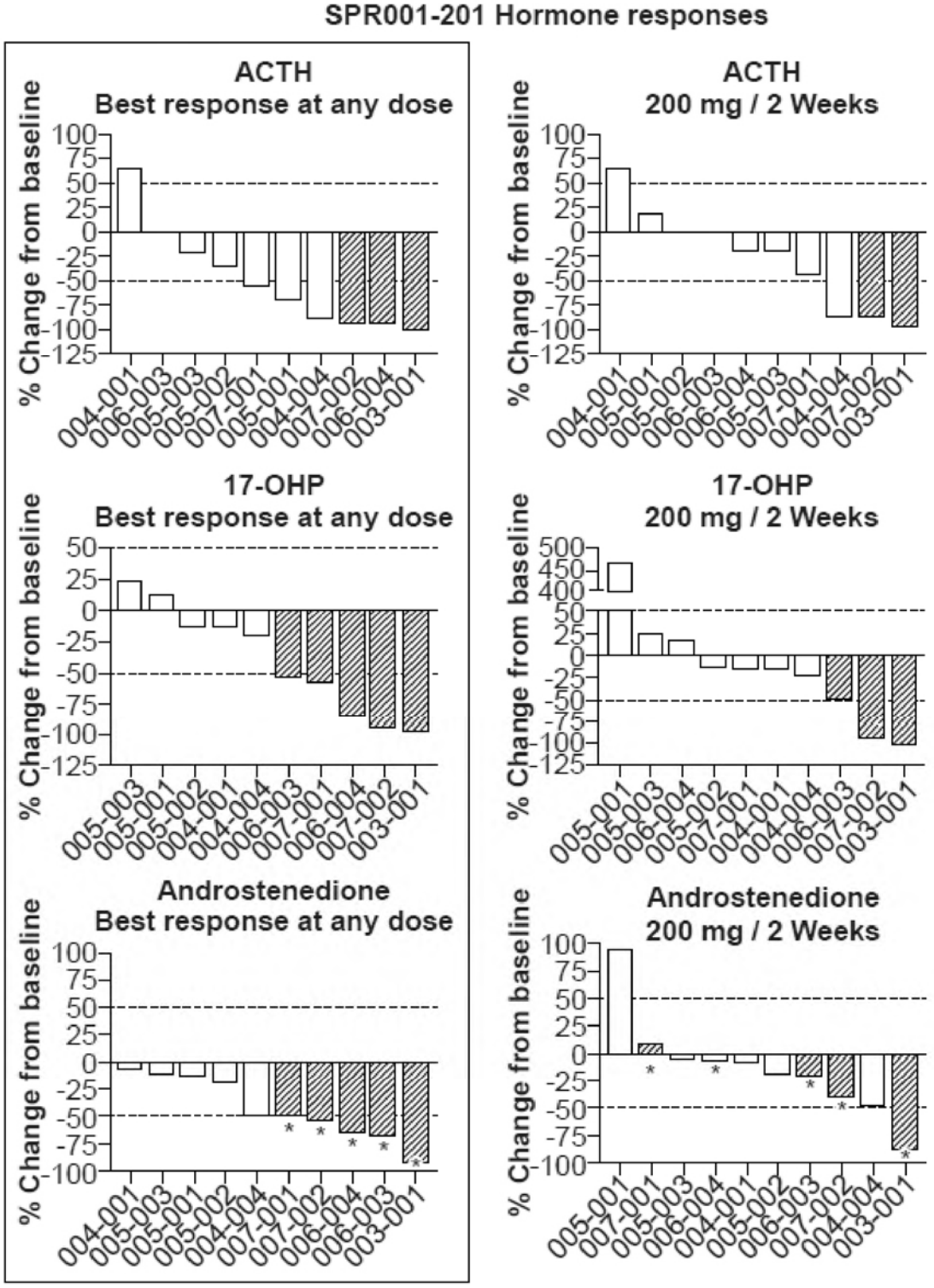


FIG. 13

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

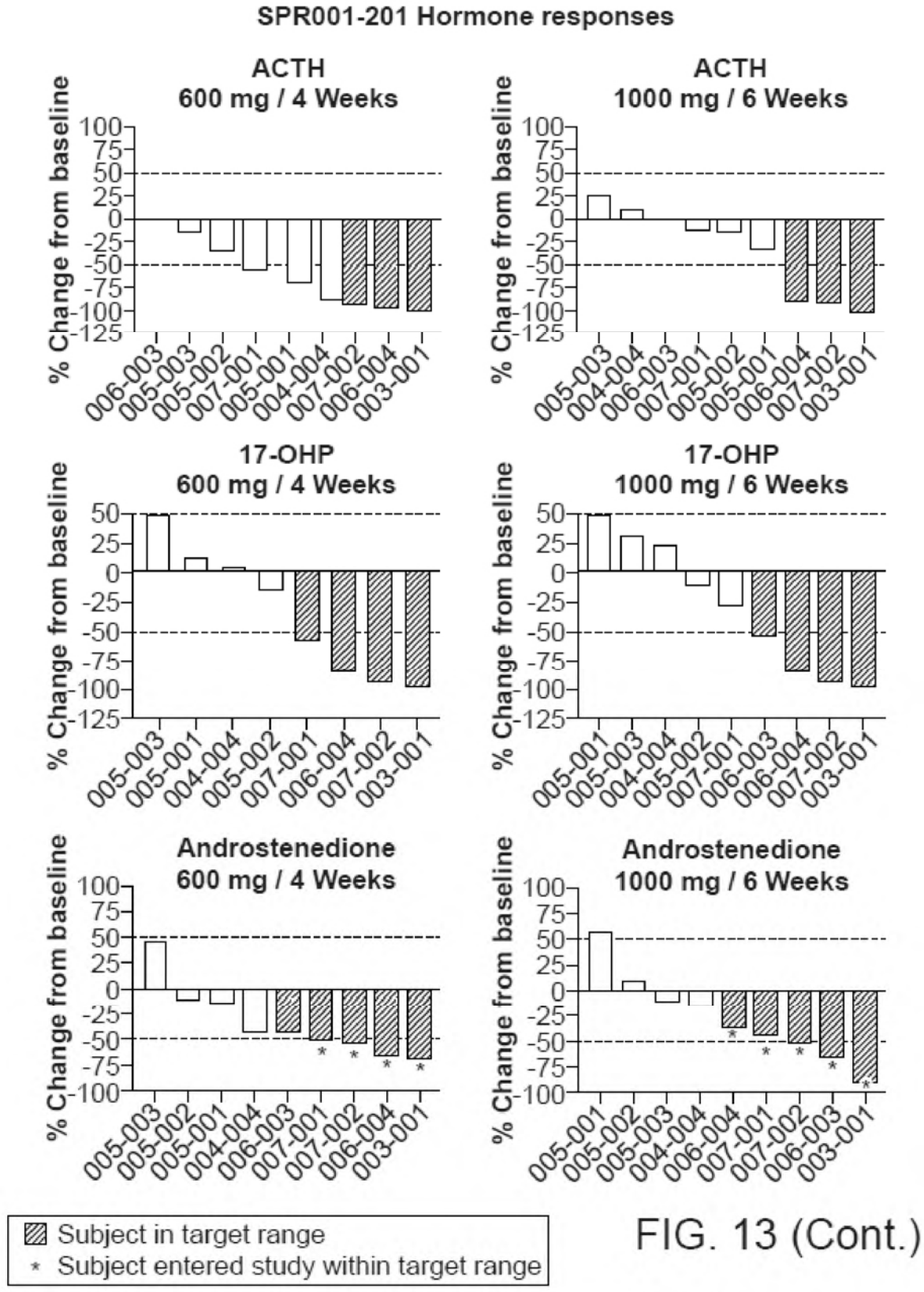


FIG. 13 (Cont.)

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

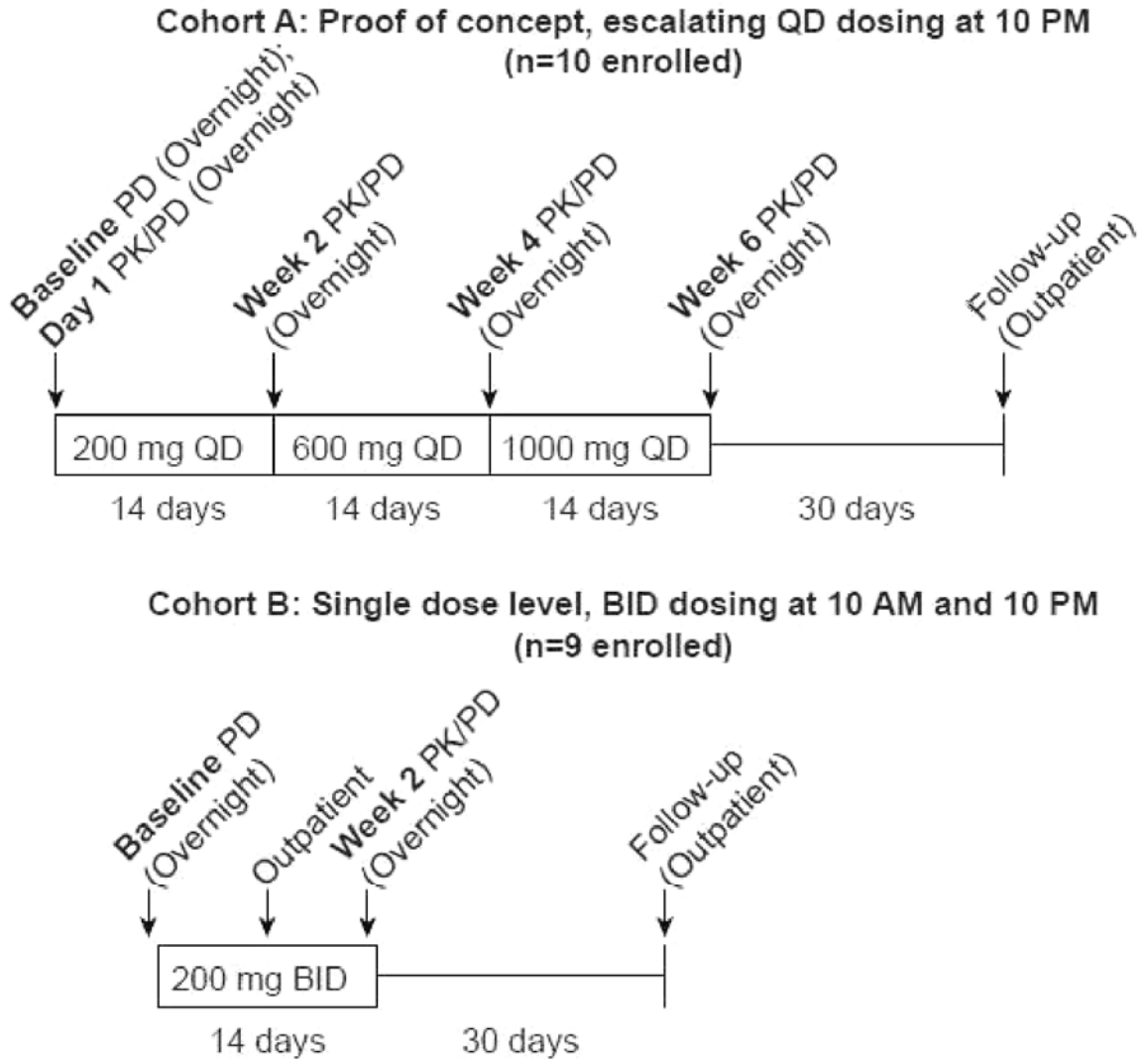

Cohort A: Proof of concept, escalating QD dosing at 10 PM
(n=10 enrolled)
Baseline PD (Overnight);
Day 1 PK/PD (Overnight)
Week 2 PK/PD
(Overnight)
Week 4 PK/PD
(Overnight)
Week 6 PK/PD
(Overnight)
Follow-up
(Outpatient)
200 mg QD
600 mg QD
1000 mg QD
14 days
14 days
14 days
30 days
Cohort B: Single dose level, BID dosing at 10 AM and 10 PM
(n=9 enrolled)
Baseline PD
(Overnight)
Outpatient
Week 2 PK/PD
(Overnight)
Follow-up
(Outpatient)
200 mg BID
14 days
30 days

FIG. 14

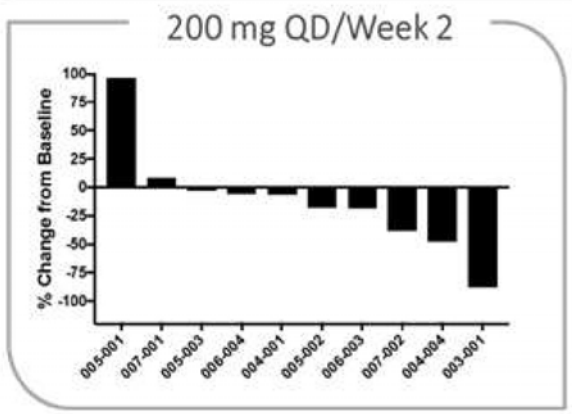


FIG. 15A

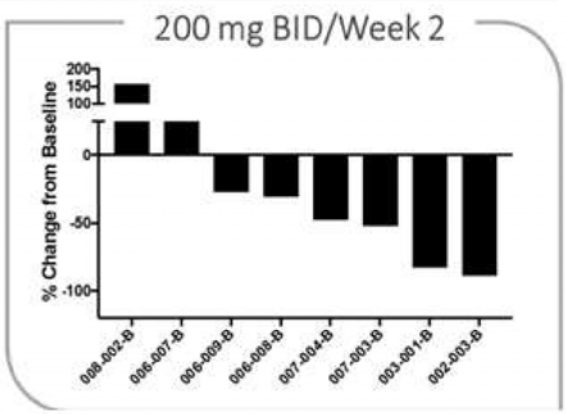


FIG. 15B

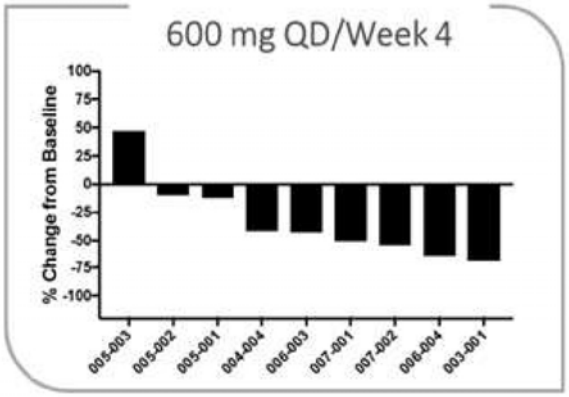


FIG. 15C

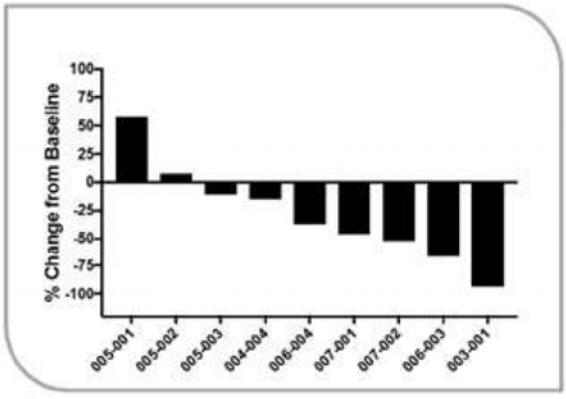


FIG. 15D

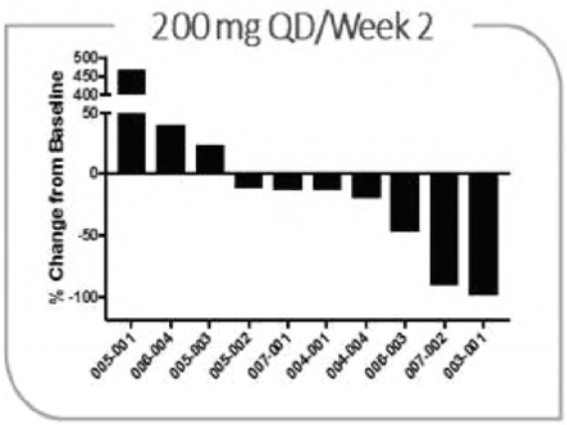


FIG. 16A

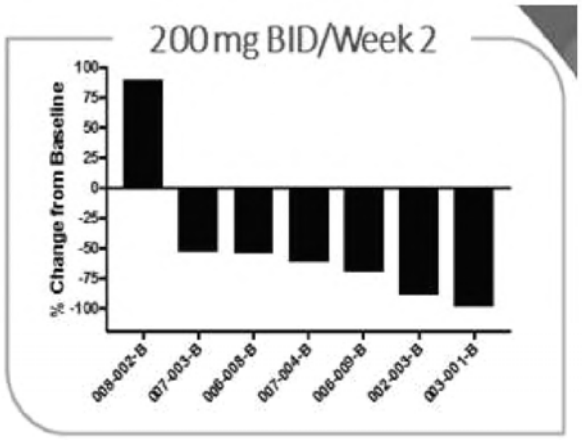


FIG. 16B

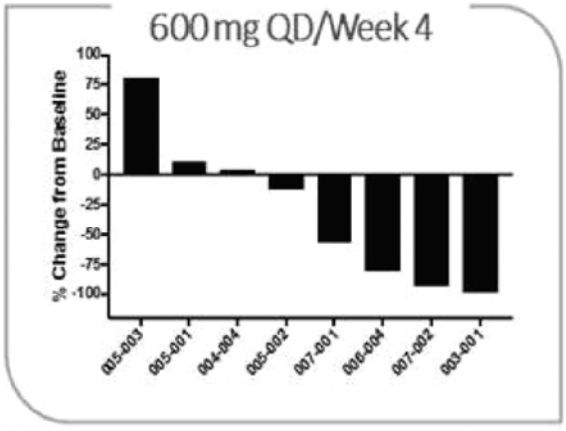


FIG. 16C

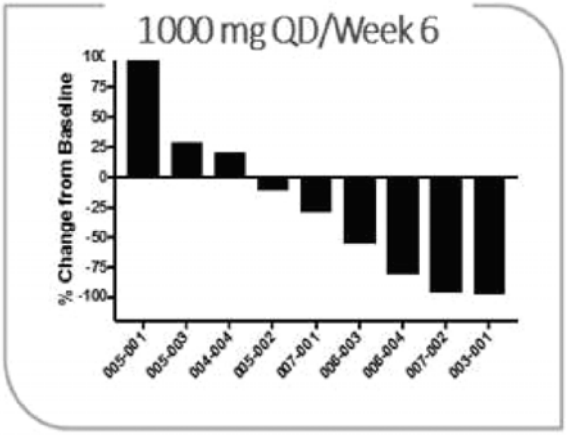


FIG. 16D

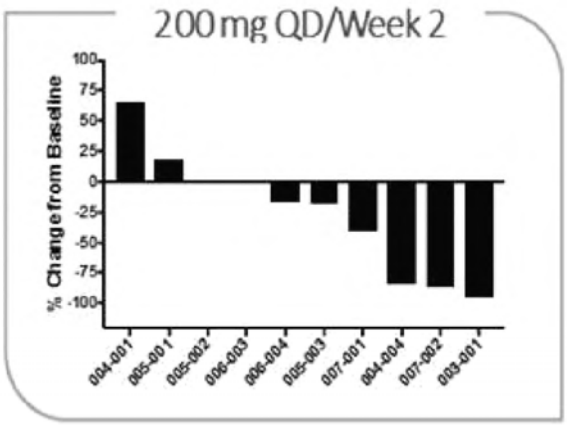


FIG. 17A

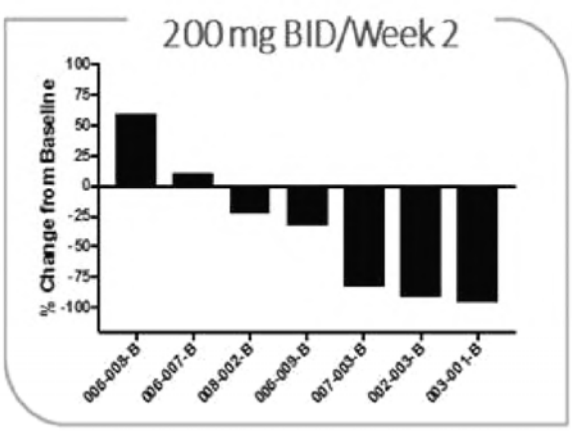


FIG. 17B

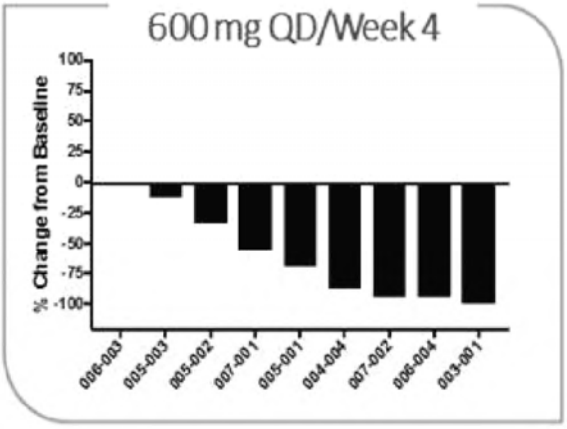


FIG. 17C

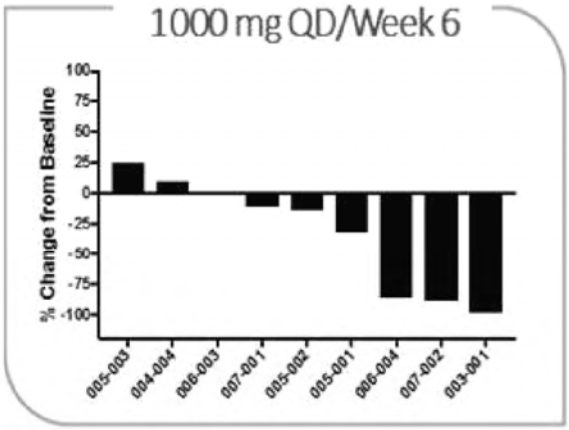


FIG. 17D

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

CROSS-REFERENCE

This application is a continuation of U.S. application Ser. No. 18/941,832, filed Nov. 8, 2024, which is a continuation of U.S. application Ser. No. 17/667,285, filed on Feb. 8, 2022, which is a continuation of U.S. application Ser. No. 17/081,694 filed on Oct. 27, 2020, which issued as U.S. Pat. No. 11,304,950 on Apr. 19, 2022, and which is a continuation of International Application No. PCT/US2019/029486 filed on Apr. 26, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed Apr. 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed Mar. 23, 2019, each of which is entirely incorporated herein by reference.

BACKGROUND

Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, inter alia, are solutions to these and other problems in the art.

SUMMARY

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

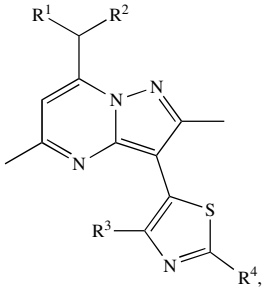
Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):

(I)



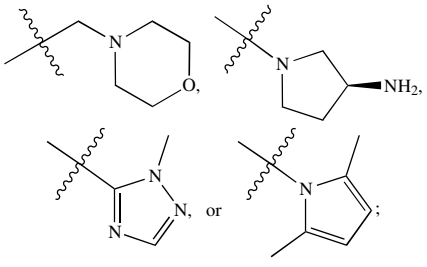
or a pharmaceutically acceptable salt thereof,

wherein:

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

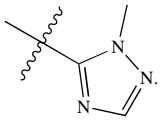
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

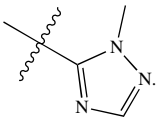


R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

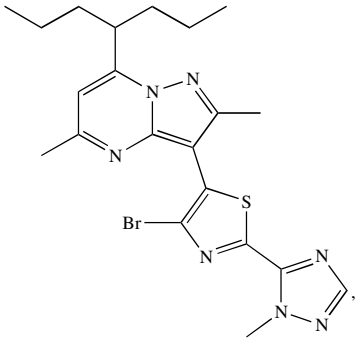
In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl. In some embodiments, R^4 is Br, R^aR^bN—, pyridin-4-yl, morpholin-4-yl, or



In some embodiments, R^4 is morpholin-4-yl or

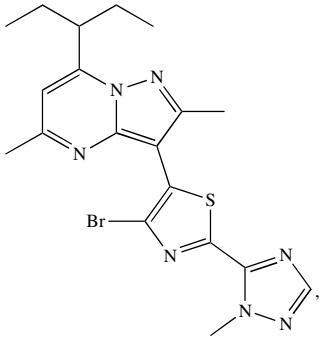


In some embodiments, R^4 is hydrogen, Br, R^aR^bN— and R^a and R^b are independently C_1-C_3alkyl. In some embodiments, the compound is



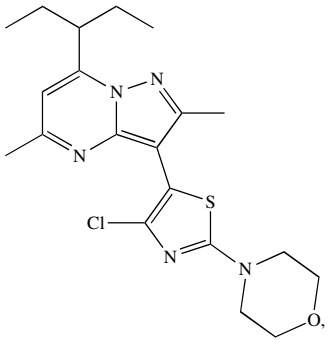
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

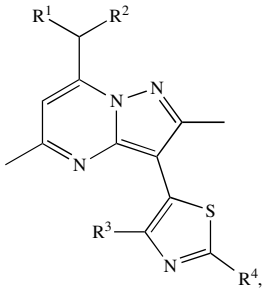
In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:



(I)

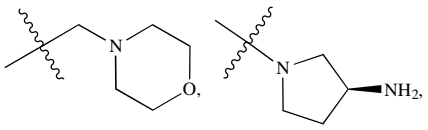
or a pharmaceutically acceptable salt thereof,

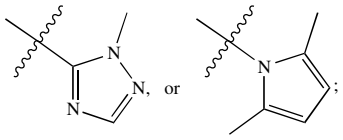
wherein:

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

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

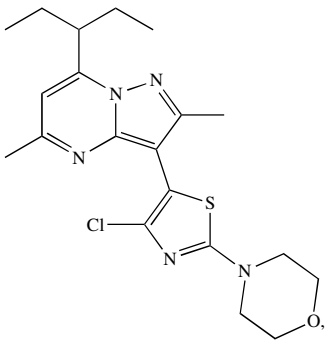
R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl





R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

In some embodiments, the compound of Formula (I) has the structure:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

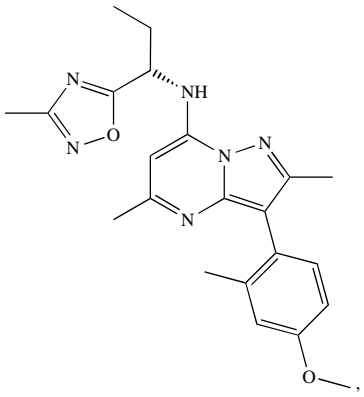
In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

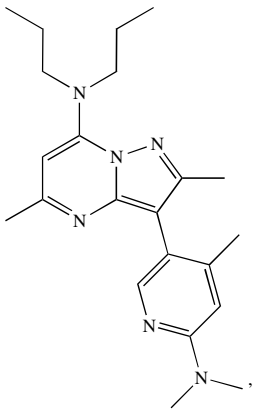
In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

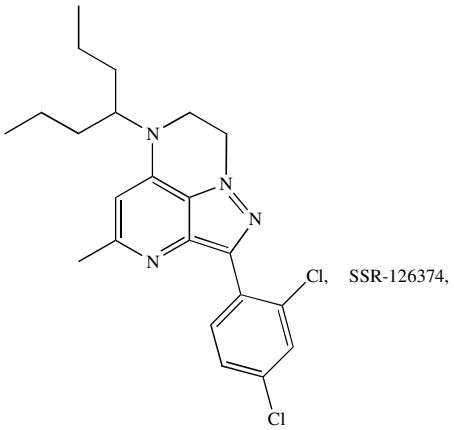
In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

In some embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist.

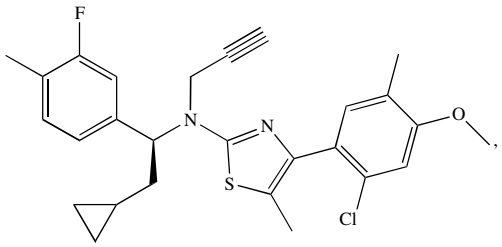
In some embodiments, the CRF_1 antagonist is



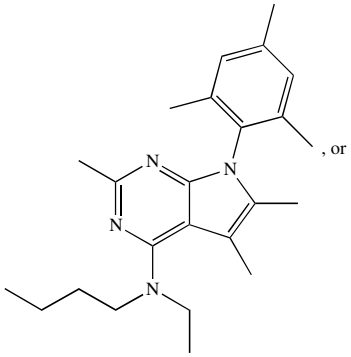




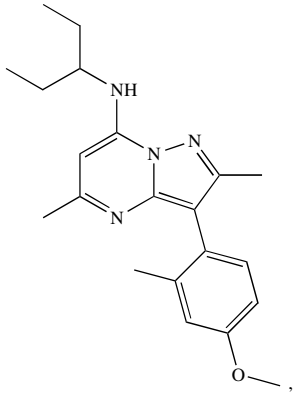
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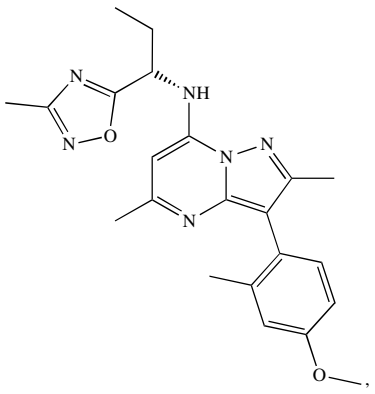


, or



or a pharmaceutically acceptable salt thereof.

In some embodiments, the CRF1 antagonist is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt

thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure.

Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

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

To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

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

FIG. **1**A-**1**B. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics (A). A schematic representation of inhibition of CRF_1 with a CRF_1 antagonist (Compound 1) (B).

FIG. **2**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

FIG. **3**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF1 antagonist (Compound 1).

FIG. **4**. Graphic representation of patient-level response (measuring ACTH levels) to a CRF_1 antagonist (Compound 1).

FIG. **5**A-**5**B. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a CRF_1 antagonist [Patient 10 (A); Patient 8 (B)].

FIG. **6**. Graphic representation of patient-level response (measuring 17-OHP levels) to a CRF_1 antagonist (Compound 1).

FIG. **7**A-**7**B. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a CRF_1 antagonist [Patient 10 (A); Patient 8 (B)].

FIG. **8**. Graphic representation of patient-level response (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1).

FIG. **9**A-**9**B. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1) [Patient 10 (A); Patient 8 (B)].

FIG. **10**A-**10**B. Images of a patient with TART pre-treatment with a CRF_1 antagonist (Compound 1) (A) and 6-weeks post-treatment with a CRF1 antagonist (Compound 1) (B).

FIG. **11**A-**11**B. Graphic representation of an in vitro binding assay of a CRF_1 antagonist (Compound 1); ^{125}I-sauvagine binding to rat cerebellar membranes one hour after oral administration of increasing Compound 1 doses (A) and in vivo inhibition of CRF-induced activity after treatment with a CRF_1 antagonist; Compound 1 (oral, 10 mg/kg) (B).

FIG. **12**A-**12**B. Graphic representation of ACTH levels (A) and 17-OHP levels (B) after treatment with a CRF_1 antagonist.

FIG. **13**. Graphic representation of hormone responses after treatment with a CRF_1 antagonist (Compound 1).

FIG. **14** depicts the proof of concept and escalating QD dosing at 10 pm for Cohort A and the single dose level and BID dosing at 10 am and 10 pm for Cohort B.

FIG. **15**A-**15**D are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

FIG. **16**A-**16**D are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

FIG. **17**A-**17**D are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

DETAILED DESCRIPTION

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

I. Definitions

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., —CH_2O— is equivalent to —OCH_2—.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl) methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (—O—).

The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, —$CH_2CH_2CH_2CH_2$—. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: —CH_2—CH_2—O—CH_3, —CH_2—CH_2—NH—CH_3, —CH_2—CH_2—N(CH_3)—CH_3, —CH_2—S—CH_2—CH_3, —CH_2—CH_2, —S(O)—CH_3, —CH_2—CH_2—S($O)_2$—CH_3, —CH═CH—O—CH_3, —Si($CH_3)_3$, —CH_2—CH═N—OCH_3, —CH═CH—N(CH_3)—CH_3, —O—CH_3, —O—CH_2—CH_3, and —CN. Up to two or three heteroatoms may be consecutive, such as, for example, —CH_2—NH—OCH_3 and —CH_2—O—Si($CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, —CH_2—CH_2—S—CH_2—CH_2— and —CH_2—S—CH_2—CH_2—NH—CH_2—. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula —$C(O)_2$R'— represents both —$C(O)_2$R'— and —R'$C(O)_2$—. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as —C(O)R', —C(O)NR', —NR'R", —OR', —SR', and/or —SO_2R'. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as —NR'R" or the like, it will be understood that the terms heteroalkyl and —NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as —NR'R" or the like.

The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "acyl" means, unless otherwise stated, —C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least

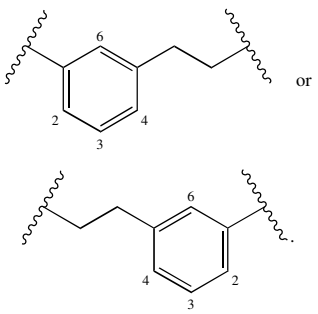
one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be —O— bonded to a ring heteroatom nitrogen.

Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

The symbol "〰" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, —N_3, —CF_3, —CCl_3, —CBr_3, —CI_3, —CN, —CHO, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_2CH_3—SO_3H, —OSO_3H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —$NHC(O)NHNH_2$, substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, —OR', =O, =NR', =N—OR', —NR'R", —SR', -halogen, —SiR'R"R"', —OC(O)R', —C(O)R', —CO_2R', —CONR'R", —OC(O)NR'R", —NR"C(O)R', —NR'—C(O)NR"R"', —NR"$C(O)_2$R', —NR—C(NR'R"R"')=NR"", —NR—C(NR'R")=NR"', —S(O)R', —$S(O)_2$R', —$S(O)_2$NR'R", —$NRSO_2$R', —NR'NR"R"', —ONR'R", —NR'C(O)NR"NR"R"", —CN, —NO_2, —$NR'SO_2$R", —NR'C(O)R", —NR'C(O)—OR", —NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R"', and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, —NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., —CF_3 and —CH_2CF_3) and acyl (e.g., —$C(O)CH_3$, —$C(O)CF_3$, —$C(O)CH_2OCH_3$, and the like).

Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: —OR', —NR'R", —SR',

-halogen, —SiR'R"R'", —OC(O)R', —C(O)R', —CO_2R', —CONR'R", —OC(O)NR'R", —NR"C(O)R', —NR'—C(O)NR"R'", —NR"$C(O)_2$R', —NR—C(NR'R"R'")═NR"", —NR—C(NR'R")═NR'", —S(O)R', —$S(O)_2$R', —$S(O)_2$NR'R", —$NRSO_2$R', —NR'NR"R'", —ONR'R", —NR'C(O)NR"NR"'R"", —CN, —NO_2, —R', —N_3, —$CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, —NR'SO_2R", —NR'C(O)R", —NR'C(O)—OR", —NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)—$(CRR')_q$—U—, wherein T and U are independently —NR—, —O—, —CRR'—, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$—B—, wherein A and B are independently —CRR'—, —O—, —NR—, —S—, —S(O)—, —$S(O)_2$—, —$S(O)_2$NR'—, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula —$(CRR')_s$—X'— $(C"R"R'")_d$—, where s and d are independently integers of from 0 to 3, and X is —O—, —NR'—, —S—, —S(O)—, —$S(O)_2$—, or —$S(O)_2$NR'—. The substituents R, R', R", and R'" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, —CF_3, —CN, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_3H, —SO_4H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —NHC═(O)$NHNH_2$, —NHC═(O)NH_2, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —OCF_3, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, —CF_3, —CN, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_3H, —SO_4H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —NHC═(O)$NHNH_2$, —NHC═(O)NH_2, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —OCF_3, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, —CF_3, —CN, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_3H, —SO_4H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —NHC═(O)$NHNH_2$, —NHC═(O)NH_2, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —OCF_3, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one sub-

stituent selected from: oxo, halogen, —CF_3, —CN, —OH, —NH_2, —COOH, —$CONH_2$, —NO_2, —SH, —SO_3H, —SO_4H, —SO_2NH_2, —$NHNH_2$, —ONH_2, —NHC═(O)$NHNH_2$, —NHC═(O) NH_2, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —OCF_3, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

A "size-limited substituent" or "size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

A "lower substituent" or "lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as

enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid.

It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

"Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R^{13} substituents are present, each R^{13} substituent may be distinguished as R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc. is defined within the scope of the definition of R^{13} and optionally differently.

A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radiolabeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", *Journal of Pharmaceutical Science,* 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (−)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted in vivo after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

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

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it.

Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (e.g. non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, e.g., in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed in vitro or in vivo from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

"Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme.

In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the

agonist. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

The terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms include any recombinant or naturally-occurring form of CRF_1 variants thereof that maintain CRF1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of CRF_1 variants (e.g., frameshift mutations) thereof that maintain CRF1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF_1). In embodiments, the CRF_1 protein encoded by the CRHR1 gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (e.g., ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, etc.).

The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (e.g., Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas.

Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

"Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

"Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatinifomi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

The terms "treating" or "treatment" refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-

being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

"Treating" or "treatment" as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (e.g., ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

"Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

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

An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy,* 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically

effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, e.g., Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each

other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents.

In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

The compounds disclosed herein may be co-administered with an agonist or antagonist of CRF_1 function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

"Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/AZD6244, GSK1120212/trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.), platinum-based compounds (e.g. cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec®), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; daclixmab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflomithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lov-

astatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras famesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic gly cosaminogly cans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflomithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II (including recombinant interleukin II, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol™ (i.e. paclitaxel), Taxotere™, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP—XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1,

Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin Al (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, lnanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, lsoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (−)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR—OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guerin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In, ^{90}Y or ^{131}I, etc.), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

"Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoli-n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli-n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family; (v) an antiangiogenic agent such as one which

inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin.alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax 11-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc, ^{64}Cu ^{67}Cu, ^{89}Sr, ^{86}Y, ^{87}Y, ^{90}Y, ^{105}Rh, ^{111}Ag, ^{111}In, ^{117m}Sn, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi, optionally conjugated to antibodies directed against tumor antigens.

In addition, a CRF_1 inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered once daily until study reached endpoint. The CRF_1 inhibitors/CRF1 antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

The methods disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (e.g., *spodoptera*) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

"Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment.

In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a CRF1 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with CRF_1 (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A CRF_1 modulator is a compound that increases or decreases the activity or function or level of activity or level of function of CRF1. A modulator may act alone, or it may use a cofactor, e.g., a

protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of CRF_1, either directly or indirectly, relative to the absence of the molecule.

The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with CRF_1 activity, a CRF_1 associated disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with CRF1 activity or function may be an endocrine disorder that results (entirely or partially) from aberrant CRF1 function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant CRF1 activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with CRF1 activity or function or a CRF1 associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., CRF1 modulator, CRF1 inhibitor, or CRF1 antagonist), in the instance where increased CRF1 activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with CRF1 activity or function or a CRF1 associated endocrine disorder, may be treated with an CRF1 modulator or CRF1 inhibitor, in the instance where increased CRF1 activity or function (e.g. signaling pathway activity) causes the disease.

The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extracellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a CRF_1 with a compound as described herein may reduce the level of a product of the CRF_1 catalyzed reaction or the level of a downstream derivative of the product or binding may reduce the interactions between the CRF1 or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

As used herein, the terms "corticotropin-releasing factor type-1," "CRF1," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the CRF1 receptor in an in vitro assay, an in vivo model, and/or other means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

"Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In embodiments, the antibody will have an affinity that is greater than about 10^9 liters/mol, as

determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

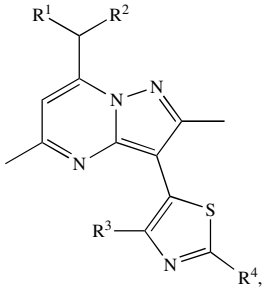
The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA), complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

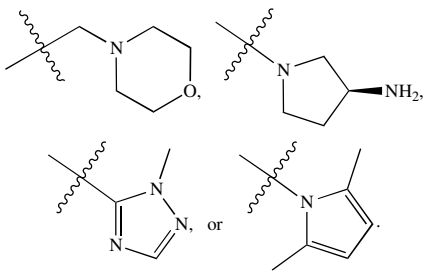
The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

II. Compounds

In an aspect provided herein, is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

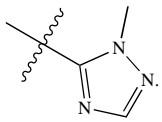


R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

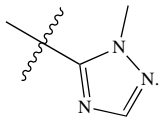
In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

In certain embodiments, R^3 is Cl, Br, or methyl.

In certain embodiments, R^4 is Br, R^aR^bN—, pyridin-4-yl, morpholin-4-yl, or

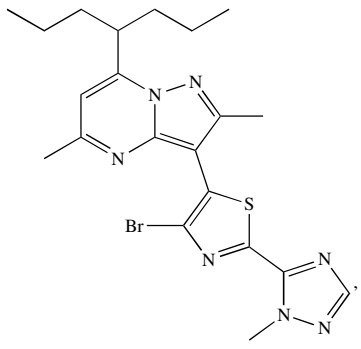


In certain embodiments, R^4 is morpholin-4-yl or



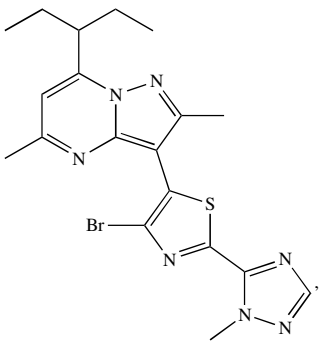
In certain embodiments, R^4 is hydrogen, Br, R^aR^bN- and R^a and R^b are independently C_1-C_3alkyl.

In certain embodiments, the compound is



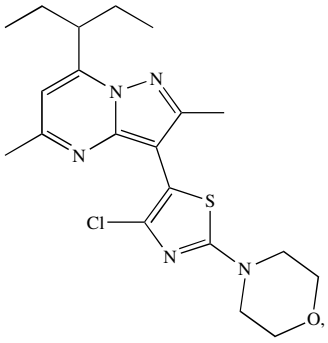
or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

III. Pharmaceutical Compositions

In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

The compounds (e.g., CRF_1 inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., CRF_1 inhibitor(s)/antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., CRF_1 inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be administered ex vivo or in vivo to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of CRF1 function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby

provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly (methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions typically comprise a therapeutically effective amount of a CRF_1 inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a CRF1 inhibitor/antagonist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., CRF1 inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein.

One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol.

Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

The present disclosure contemplates the administration of the compound (e.g., CRF1 inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

The compound (e.g., CRF1 inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

IV. Methods

In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix, uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinemia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhab-

domyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, aligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but not limited to, renal cell cancer, adenocarcinoma, hypemephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (See Fishman et al., 1985, *Medicine,* 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy et al., 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

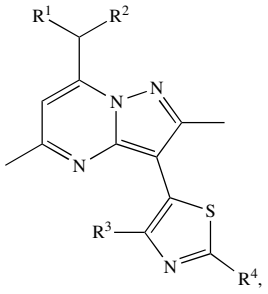
In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

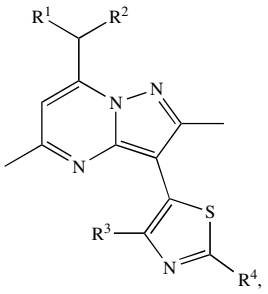
In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof.

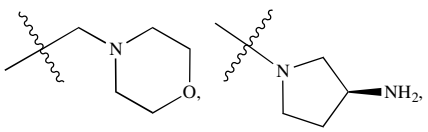
In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof.

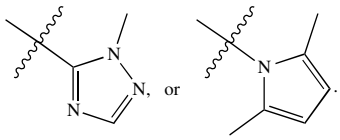
In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):





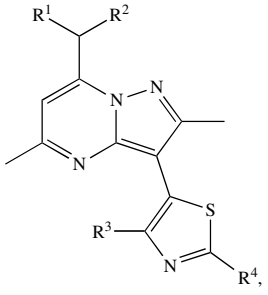
or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,





R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



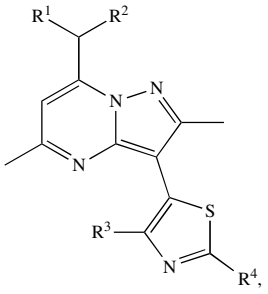
or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments.

In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):

or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 70% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

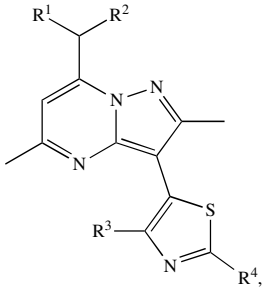
In an aspect provided herein, is a method of decreasing or reducing 17α-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least about 30% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about

40% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

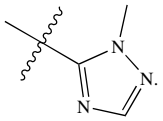


or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

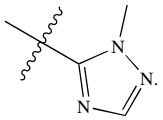
In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

In certain embodiments, R^3 is Cl, Br, or methyl.

In certain embodiments, R^4 is Br, R^aR^bN—, pyridin-4-yl, morpholin-4-yl, or

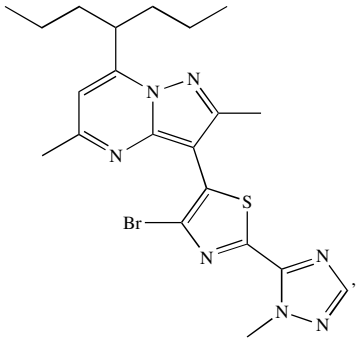


In certain embodiments, R^4 is morpholin-4-yl or



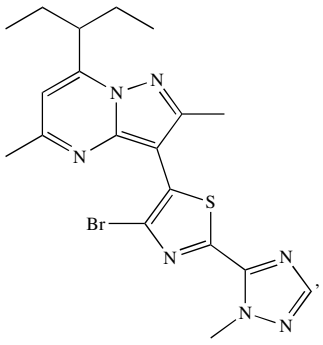
In certain embodiments, R^4 is hydrogen, Br, R^aR^bN- and R^a and R^b are independently C_1-C_3alkyl.

In certain embodiments, the compound is



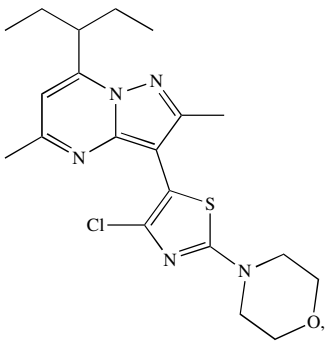
or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is cyclically administered to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg, from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or

a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445

mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg,

about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some

embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In

certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prod-

rug thereof is administered in an amount of about 140 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the com-

pound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg

twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prod-

rug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the com-

pound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

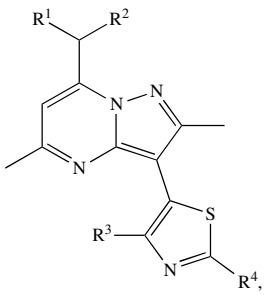
In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is admin-

istered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I); and a pharmaceutically acceptable excipient comprising with a compound as described herein, including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3, and R^4 are as described herein, including embodiments.

In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the pharmaceutical composition is administered orally.

In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the

pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

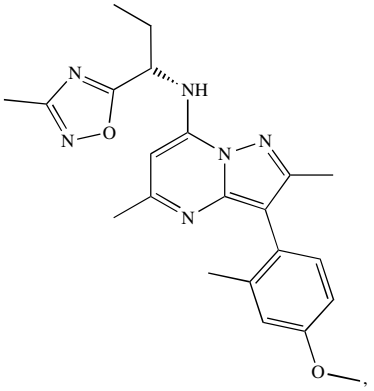
In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

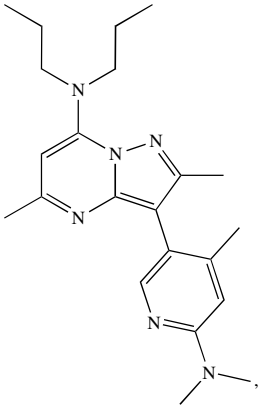
In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

In certain embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In certain embodiments, the CRF_1 antagonist is:

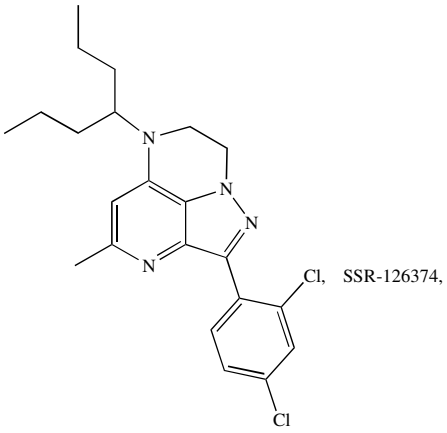


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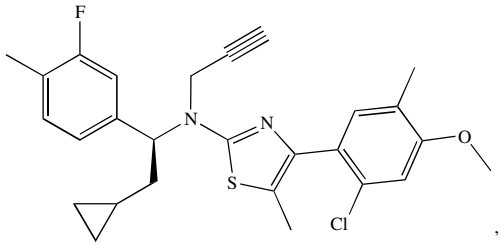
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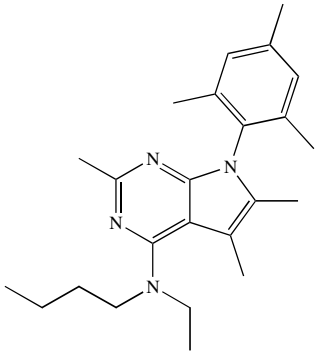
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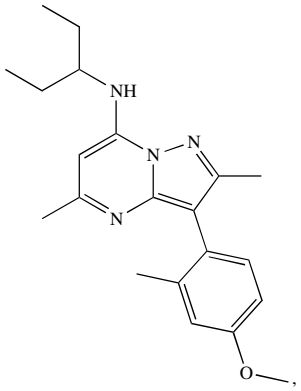


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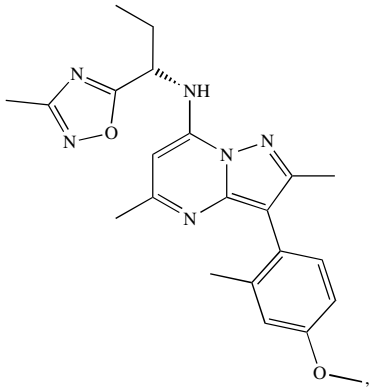


, or

-continued



or a pharmaceutically acceptable salt thereof. In certain embodiments, the CRF_1 antagonist is



or a pharmaceutically acceptable salt thereof.

In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (see, *Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology,* 2nd Edition, Rathbone et al., Eds., Marcel Dekker, Inc.: New York, NY, 2008).

The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form.

Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are

not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

Coloring and flavoring agents can be used in all of the above dosage forms.

The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (see, *Remington: The Science and Practice of Pharmacy*, supra).

The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, N-methyl-2-pyrrolidone, N,N-dimethylacetamide, and dimethyl sulfoxide.

Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride.

Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but

are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and metliacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

V. Examples

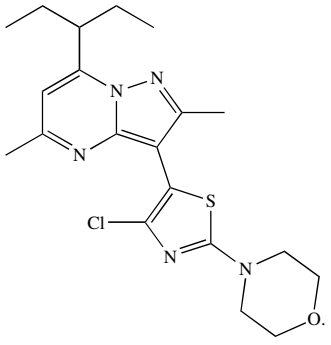
While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing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

Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)-driven overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 (CRF_1) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH (FIG. **12**A-**12**B). Compound 1 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

The structure of Compound 1 is.



Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2

proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

The specification of study drug dosing at 10 μm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma C_{max} (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10 pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. (FIGS. **1**A-**1**B).

Objectives	Endpoints
Primary	
To assess the efficacy of Compound 1 in subjects with TART	Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12
Secondary	
To evaluate the safety of Compound 1 in subjects with TART	Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs) Physical examination findings Vital signs Changes in electrocardiogram (ECG) Changes in clinical laboratory values
To assess the pharmacodynamic (PD) biomarker effects of Compound 1	Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, and aldosterone from baseline to Week 12
To assess changes on semen analysis	Changes in sperm count, morphology, and motility from baseline to Week 12
To assess changes in metabolism	Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12 Changes in body weight, body mass index (BMI), waist circumference, and blood pressure
To evaluate changes in quality of life (QoL) and mood	Changes in QoL measured using the Short Form 36 (SF-36) Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS)

Study Population

Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

Eligibility Criteria

Inclusion Criteria

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with >1 lesion(s) measuring>2 cm in diameter
- On a stable regimen of GC replacement for >30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria

- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
  - A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
  - Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2
  - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
  - Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months
- HADS score>12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C—SSRS) conducted at screening and baseline (eg, C—SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:

- Clinically meaningful abnormal ECG results, in the opinion of the Investigator
- Fridericia-corrected QT interval (QTcF)>450 msec
- Alanine aminotransferase (ALT)>2×upper limit of normal (ULN)
- Bilirubin>1.5×ULN (isolated bilirubin>1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
- Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

Study Duration

The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of 54 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

Study Design

This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks. In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

Dose, Route, Regimen

All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10 pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

On mornings of study visits with 8 am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6 am and 8 am).

If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

Investigational Drug

Compound 1 is a small-molecule CRF_1 receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

Example 2

Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a small-molecule antagonist of the CRF_1 receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. **12**A-**12**B). The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

Nonclinical Toxicology of Compound 1

The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70 days before mating, during mating, and <4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

Clinical Experience with Compound 1

To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study 13C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study 13C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each

subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (FIGS. **2**-**3**).

Known Potential Risks

Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to monitor the risk of testicular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

Known Potential Benefits

Early clinical studies suggests that Compound 1 is effective as a CRF1 receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. **12**A-**12**B).

Assessment of Potential Risks and Benefits

The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a CRF1 receptor antagonist, Compound 1 is intended to reduce abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

Example 3. Congenital Andrenal Hyperplasia (CAH)

CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks CRF_1 receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

As shown in FIGS. **4** and **5**A-**5**B, the attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated>25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a CRF_1 receptor antagonist.

FIGS. **6** and **7**A-**7**B demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated>25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a CRF_1 receptor antagonist.

FIGS. **8** and **9**A-**9**B demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess androgen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated>25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a CRF1 receptor antagonist.

FIGS. **10**A-**10**B show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF_1 receptor antagonist.

FIGS. **11**A-**11**B demonstrate Compound 1 is a potent, selective, and functional CRF_1 receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective CRF_1 receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity (CRF_1 receptor-mediated downstream cascade), demonstrating in vitro efficacy as a CRF_1 receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.c.v. administration of CRF (FIG. **11**B).

FIGS. **12**A-**12**B demonstrate single pill of CRF_1 receptor antagonist (i.e., as described in US 2017/0020877 A1) improves ACTH and 17-OHP in CAH patients.

FIG. **13** shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a CRF_1 receptor antagonist.

Example 4. Assess Reduction in Excess ACTH and Adrenal Steroid Production

The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and toler-

ability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

Eligibility Criteria

Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP>800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for >30 days before enrollment

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

Study Design

FIG. **14** depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

Baseline Characteristics

Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 participants were enrolled and received at least 1 dose of Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

TABLE 1

Baseline characteristics of each cohort

Parameter	Cohort A (n = 10)	Cohort B (n = 8)
Demographics		
Age (years), mean (range)	39.3 (24-66)	36.8 (19-66)
Sex	5 M, 5 F	1 M, 7 F
Bmi (kg/m^2), mean ± SD	31.5 ± 12.0	31.1 ± 6.7
Daily GC dose (mg HC equivalents), mean range	28 (13-40)	35 (20-50)
Types of GCs	4 JC, 3 pred, 3 dex	2 HC, 4 pred, 3 dex
17OHP at screening[a] (ng/dl), mean ± SD	5,985 ± 6,347	4,592 ± 4,624

Abbreviations:
17OHP: 17-hydroxyprogesterone;
BMI: body mass index;
dex: dexamethasone;
F: female;
GC: glucocorticoid.
HC: hydrocortisone;
M: male;
pred: prednisone;
SD: standard deviation.
[a]17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females.

Safety

Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

Pharmacokinetics

Over a wide range of doses (200 to 1000 mg QD), Compound 1 exhibited a predictable, dose-dependent PK profile.

Efficacy

FIG. **15**A-**15**D show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

FIG. **16**A-**16**D show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at 1 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

FIG. **17**A-**17**D show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at 1 dose level for 8 out of 10 participants in Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism.

TABLE 2

Percentage change from baseline in ACTH, 17OHP and A4.

	Cohort A			Cohort B
	200 mg QD (Week 2)	600 mg QD (Week 4)	1000 mg QD (Week 6)	200 mg BID (Weed 2)
ACTH	−25.7 (±51.6)	−60.1 (±37.5)	−32.7 (±47.0)	−36.5 (±58.0)
17OHP	+22.2 (±172.3)	−23.7 (±64.2)	−13.8 (±74.7)	−47.8 (±63.3)
A4	−12.1 (±47.4)	−33.2 (±36.5)	−28.6 (±44.6)	−16.0 (±81.4)

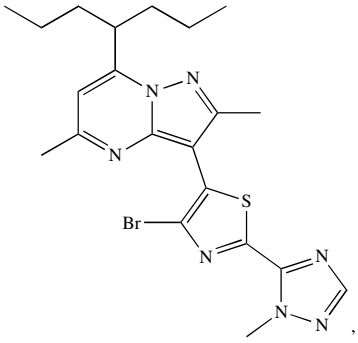
CONCLUSIONS

Compound 1, a potent and selective CRF1 receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAH. Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

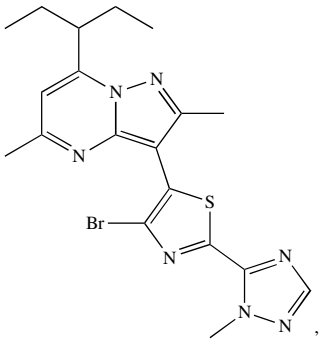
While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed:

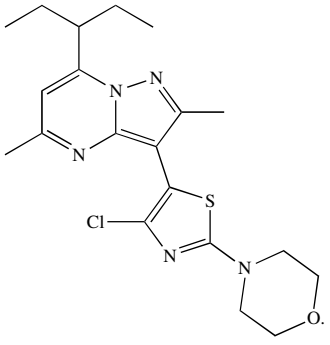
1. A method of treating ovarian adrenal rest tumors (OART) and menstrual irregularity in a subject, comprising administering to the subject a small molecule corticotropin-releasing factor type-1 (CRF1) antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF1 antagonist is:



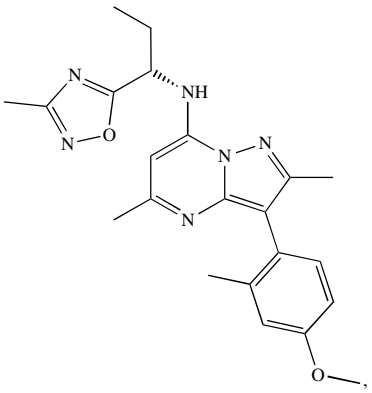
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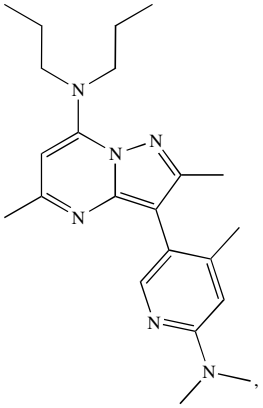


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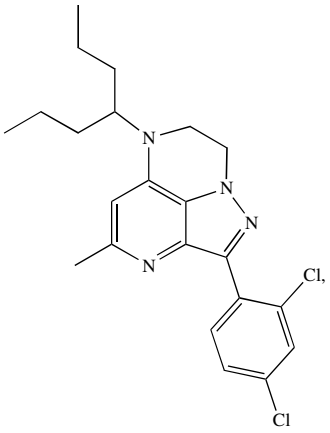
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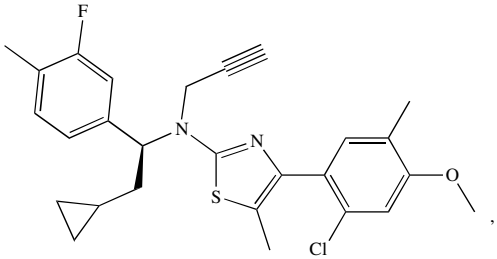


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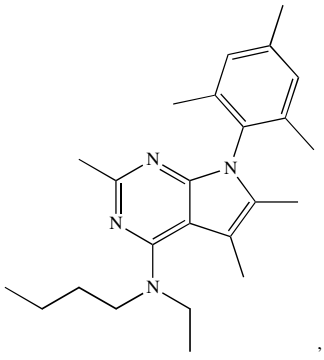
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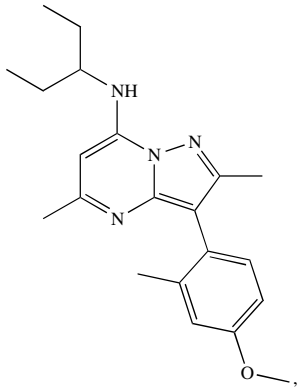


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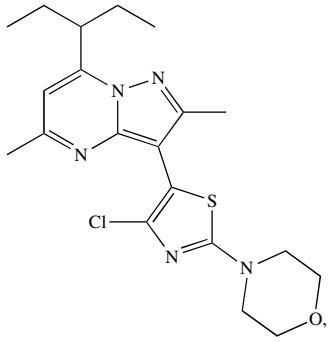
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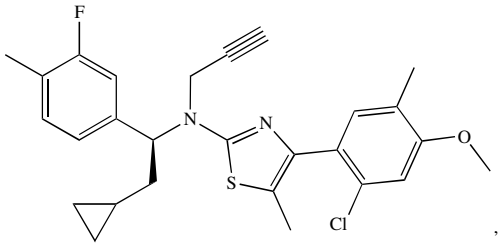
or a pharmaceutically acceptable salt thereof.

2. The method of claim **1**, wherein the small molecule CRF1 antagonist is:



or a pharmaceutically acceptable salt thereof.

3. The method of claim **1**, wherein the small molecule CRF_1 antagonist is:



or a pharmaceutically acceptable salt thereof.

4. The method of claim **1**, further comprising treating ovulatory dysfunction or infertility.

5. The method of claim **1**, wherein the subject has congenital adrenal hyperplasia (CAH).

6. The method of claim **1**, wherein the subject is an adolescent.

7. The method of claim **1**, wherein the subject is at least 18 years or older.

8. The method of claim **1**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.

9. The method of claim **8**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 50 mg.

10. The method of claim **8**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 100 mg.

11. The method of claim **8**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 200 mg.

12. The method of claim **8**, wherein the small molecule CRF_1 antagonist is administered at a dose of about 400 mg.

13. The method of claim **1**, wherein the small molecule CRF_1 antagonist is administered to the subject once per day.

14. The method of claim **1**, wherein the small molecule CRF_1 antagonist is administered to the subject twice per day.

15. The method of claim **13**, wherein the subject is in a fed state.

16. The method of claim **14**, wherein the subject is in a fed state.

17. The method of claim **1**, wherein the small molecule CRF_1 antagonist is administered orally.

18. The method of claim **1**, wherein the small molecule CRF_1 antagonist is formulated as a capsule or tablet.

19. The method of claim **1**, wherein the administering reduces a plasma concentration of a biomarker comprising 17α-hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, androstenedione (A4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, or aldosterone, or a combination thereof.

20. The method of claim **19**, wherein the biomarker is selected from the group consisting of 17-OHP, ACTH, and A4.

21. The method of claim **19**, wherein the plasma concentration of the biomarker is reduced by at least 10% from baseline.

* * * * *

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