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(54) Title: COMPOUNDS FOR TREATMENT OF EMOTIONAL/PSYCHOLOGICAL SYMPTOMS IN FRAGILE X SYNDROME

(57) Abstract: The invention is directed, in various embodiments, to methods of treatment of the emotional or psychological symptoms of Fragile X Syndrome (FXS) in human patients by administration of an effective dose of a compound that is an inhibitor of the cortisol synthetic enzyme 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) or an effective dose of an antagonist of the corticotropin releasing hormone (CRH) receptor. For instance, an effective dose of one of these two classes of drugs is administered to a patient for treatment when the emotional and psychological symptom of FXS comprises chronic anxiety in any form, social aversion, obsessive compulsive behaviors, aggression, agitation, self injurious behavior, or any combination thereof.

COMPOUNDS FOR TREATMENT OF EMOTIONAL/PSYCHOLOGICAL SYMPTOMS IN FRAGILE X SYNDROME

CLAIM OF PRIORITY

[0001] This application claims the benefit of priority to U.S. Provisional Application Serial No. 62/571,874, filed on October 13, 2017, which is incorporated herein by reference in its entirety.

FIELD

[0002] The present disclosure relates to use of inhibitors of 11β-hydroxysteroid dehydrogenase type 1, or antagonists of corticotropin releasing hormone receptor type 1 in the treatment of the symptoms of Fragile X Syndrome (FXS).

BACKGROUND

[0003] FXS is a prevalent inherited form of mental retardation [1,2] that presents with numerous co-morbid symptoms that compound overall impairment. In addition to low IQ (~40 in males 1,3) and a high rate of autism 3 FXS patients frequently exhibit severe anxiety in many forms (particularly social), social aversion, aggression, obsessive/compulsive disorders, and hyperactivity and attention deficit [4,5,6,7]. This highly debilitating combination of symptom requires lifetime care and support for most afflicted males, and poses enormous emotional, parenting, and financial challenges for families [8,9,10]. Considering the prevalence of FXS (~1:4-5000 males, 1:6-8000 females 2), and mechanistic overlaps that it shares with autism (of which FXS is the leading known cause), drug therapies targeting the most challenging symptoms of FXS at a mechanistic level will have a major impact on the quality of life of children with these disorders and their families.

[0004] Anxiety in many forms (including social), social withdrawal/avoidance, and other emotional problems are extremely common features of FXS symptomology [4,5,6,7]. In a recent analysis, over 80% of males with FXS exhibited one or more anxiety disorders [7]; it is notable that this cohort included many subjects that were already on medications that exhibit anxiolytic activity in the normal population, but nevertheless manifested anxiety disorders at a high rate. Indeed, FXS subjects present with an unusually pervasive combination of

anxiety subtypes and do not respond well to traditional therapeutics such as benzodiazapines and SSRIs [4]. Such pervasive and deeply rooted anxiety disorders in FXS are thought to be a core driver of other emotional symptoms (*e.g.* aggression, irritability), and even of autism spectrum phenotypes [4,5,6,7]. A prime example of this is social avoidance – often characterized and quantified by gaze aversion [6,11,12,13] – which correlates with social anxiety in FXS [6] and abnormal activity in brain regions that set expectant fear of social stimuli [14]. In addition, anxiety in FXS may be accompanied by elevated physiological responses to stress. Several studies have documented excessive activation of the hypothalamic-pituitary-adrenal axis (HPA) and increased levels of basal and stressor-induced cortisol in FXS [15,16,17].

[0005] Longitudinal studies of symptom severity in FXS reveal that, while many symptoms improve with age (*e.g.* hyperactivity), anxiety, social avoidance and other emotional problems are remarkably persistent [4,5,18,19]. Parent surveys highlight that these stable aspects of FXS symptomology are particularly disruptive and difficult to manage [20], and they are a major contributor to the greatly increased health care expenditures and overall economic hardship faced by parents of FXS children [5,8,10]. The extremely persistent, disruptive, costly and thus far intractable nature of anxiety and related emotional problems in FXS constitutes an area of great unmet need in FXS research: that being the need to identify the neurobiological basis of such symptoms and to find molecular pathways that offer opportunities for mechanism-based pharmacological intervention.

[0006] FXS results from the absence of an mRNA-binding protein, FMRP, that regulates the translation, transport and stability of many dendritic and axonal mRNAs [21,22,23,24,25]. Efforts to find a pharmacological therapy for FXS have focused mainly on identifying specific mRNA targets of FMRP (but see [26]) and on defining the neurobiological contexts in which FMRP-regulated translation is critical [23,27]. These studies reveal that FMRP may directly bind ~800 mRNAs [24], acting largely as a translational suppressor [24,25,28,29], and that its absence in FXS has comparably scaled effects on the synaptic proteome [25,29] that are in part due to increases in global translation rates [30,31]. FMRP's neurobiological roles are accordingly broad, having pleiotropic functions in regulating neurogenesis [23,32],

the formation [33,34,35,36], plasticity [37,38,39], and morphology [40,41,42,43] of synapses, intrinsic neural excitability/plasticity [38,44,45], and the synchronized activity of neural networks [46,47,48].

[0007] A theory of FXS that emerged from much of this work and guided drug development is the "mGluR theory", which holds that exaggerated translation downstream of group I metabotropic glutamate receptors (mGluRs) leads to changes in synaptic form, function, and plasticity that are the proximal causes of symptoms [27]. Prompted initially by three findings [49,50,51], this theory accommodates many observations that collectively supported the use of mGluR antagonists in FXS [27,46,52,53,54]. However, subsequent work revealed that FMRP gates translation downstream of many receptors [37,39,55,56,57], suggesting that targeting a single receptor type may not be therapeutically optimal [58]. Accordingly, recent Phase III clinical trials of mGluR5 antagonists did not meet their endpoints. Nevertheless, a strong rationale remains for considering mGluR5 antagonists (or targeting the pathway by other means) as part of combo therapies and it is likely that dosing, tolerance, and outcome measure limitations contributed to trial failure [59,60].

[0008] A key question to arise from this work is whether optimal therapies will involve drugs acting on (*i*) receptors that induce FMRP-gated translation, (*ii*) signaling pathways that link these receptors to FMRP-gated and/or global translation, or (*iii*) one or more critical FMRP targets. Most emerging therapeutic approaches focus on the latter two strategies. Studies on translational control pathways in FXS have implicated the mechanistic target of rapamycin (mTOR) [56,57,61], its upstream kinase phosphatidylinositol 3-kinase (PI3K) [24,56,57], and the extracellular signal regulated kinase (ERK1/2) pathway [31,62,63,64,65] as being overactive. Inhibitors of mTOR, PI3K, or ERK1/2 signaling rescue excessive global translation and some phenotypes of the *Fmr1* KO mouse [31,57,62,63,66,67,68,69], and early trials of the ERK inhibitor lovastatin are promising [70,71]. Several specific, phenotypically relevant FMRP targets are also being pursued [71,72,73,74]. The most advanced of these is MMP9, which is overactive in the *Fmr1* KO and FXS, and can be inhibited with the drug minocycline [75,76]. Newer programs focus on specific K^+ channels [72,77,78], GABA receptors [79,80], and ion transporters [81,82] that are dysregulated in the *Fmr1* KO and can be targeted

with specific drugs to normalize several network level and behavioral features of FXS. Emerging from this recent work is an appreciation that neural excitability changes in FXS, as determined by altered levels or activity of K^+ channels, GABAergic tone, and ionic gradients, and endocannabinoid (eCB) signaling may underlie several phenotypes and provide a valuable new focus for development of mechanism-based therapeutics [72,83,84,85,86].

[0009] However, despite these and other promising lines of research [29,52,72,87,88,89], there are no approved mechanism-based treatments for FXS and none in the pipeline that are being explicitly developed to target what is perhaps the most disruptive constellation of symptoms in FXS: extremely persistent anxiety, social aversion, and other emotional problems.

SUMMARY

[0010] Disclosed herein, in various embodiments, are methods for the treatment of the emotional or psychological symptoms of Fragile X Syndrome (FXS) in a human patient in need thereof which method comprises administering to the patient an effective amount of a compound that is an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1, also known as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1)), or an effective amount of an antagonist of corticotropin releasing hormone receptor type 1 (CRHR1).

[0011] In some embodiments, the emotional and psychological symptom of FXS comprises chronic anxiety, social aversion, self-injurious behavior, aggression or perseverative behavior, hyperactivity or any combination thereof. In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) inhibitor is AMG-221, PF915275, BVT-2733, UE-2343, BI-135585 or UE-2316. In some embodiments, the corticotropin releasing hormone receptor (CRHR1) antagonist is SN003, LWH-234, CP-154,526, NBI-27914, NBI-35965, R-121,919, pexacerfont, or GSK561679.

BRIEF DESCRIPTION OF THE FIGURES

[0012] **Figure 1** is a simplified view of aBNST anatomy and Type III, I and II neuron physiology. **(A)** Photomicrograph of a brain slice including the BNST showing the general localization of different nuclei relative to neuroanatomical

landmarks – the anterior commissure (AC), the internal capsule (IC) – and the broader anterolateral (BNST-AL) and anteromedial (BNST-AM) divisions of BNST: juxtacapslar (jcBNST, yellow), oval of the BNST (ovBNST, blue). Type III GABAergic projection neurons are concentrated in the jcBNST, whereas locally projecting GABAergic and Type I/II neurons are in the oval and broader anterodorsal aspect of the BNST. (**B**) Voltage traces of typical BNST neuron responses to hyperpolarizing and depolarizing current pulses. Type III neurons are characterized by a strong inward rectification current (I_{Kir}) in the hyperpolarized region, and respond to threshold depolarization pulses with a delayed action potential near the end of depolarizing ramp. This delayed spike is due to the activation of I_D current. Type I/II neurons are characterized by voltage sag in the hyperpolarizing region due to the activation of Ih current. The voltage sag is more pronounced in Type II than in Type I. Type II are also characterized by a strong depolarization bump at the end of hyperpolarizing pulses. This depolarization is induced by the activation of type T Ca^{++} channels. (**C**) Typical event traces of AMPA receptor-mediated spontaneous mini excitatory postsynaptic currents (mEPSCs) recorded from jcBNST Type III neurons in WT and *Fmr1* KO slices. Neurons were clamped at a RMP of -70 mV. The frequency values represent mean frequencies of the AMPA mEPSCs.

[0013] Figure 2 shows decreased excitability and presynaptic excitatory drive of P17 *Fmr1* KO jcBNST Type III neurons. (**A**) Table of Type III neuron intrinsic properties (Rin, Input resistance; I/O, slope I/O curve; Rheo, rheobase (nA); RMP, resting membrane potential (mV); Vth, spike threshold (mV); SpW, spike width (msec)). (**B** & **C**) Rheobase currents and I/O slopes in 7 WT and 9 KO Type III neurons. (**D** & **E**) Mean (±SEM) sEPSC frequencies and amplitudes in 9 WT and 10 KO Type III neurons. (* $p < 0.05$, 2-tailed t test). Reduced sEPSC frequency without changes in amplitude is indicative of reduced release probability.

[0014] Figure 3 shows upregulation of an HSD11β1-to-CRH signaling cascade in the Fmr1 KO mouse model of FXS. (**A** & **B**) Schematics showing relative levels of HSD11b1, cortisol, and CRH in normal and Fmr1 KO synapses. Upregulation of HSD11b1 in the Fmr1 KO BNST leads to excessive local conversion of inactive cortisone to active cortisol at synapses. This leads to

increased levels of CRH, which by binding to CRHR1 triggers changes in synaptic glutamate release and intrinsic neural excitability in jcBNST that are anxiogenic. (**C**) Fluorescence deconvolution imaging of HSD11β1 and PSD95 in Fmr1 KO, and corresponding frequency distribution of HSD11β1 immunoreactive puncta intensities in WT and KO jcBNST. (**D**) Representative Western blots of HSD11β1 and phosphorylated glucocorticoid receptor (p-GR) in WT and Fmr1 KO jcBNST, normalized to β-actin and total GR, respectively. (**E**) Group Western blot data (mean±SEM) for HSD11β1, the ratio of p-GR total GR, and CRH in jcBNST from 3 WT and 5 Fmr1 KO mice (* $p < 0.05$, ** $p < 0.001$).

[0015] Figure 4 shows normalization of glutamate release probability in Fmr1 KO jcBNST by the CRHR1 antagonist NBI-35965. A follow up study of glutamate release probability onto jcBNST Type III neurons replicated the finding that release probability is reduced in the Fmr1 KO jcBNST. In addition, injection of the CRHR1 antagonist NBI-35965 i.p. for 3 days prior to recording rescued this synaptic phenotype, returning mEPSC rates to values seen in WT mice. * $p < 0.05$; n.s. not significant.

[0016] Figure 5 shows rescue of a trait anxiety phenotype in *Fmr1* KO mice by pharmacological inhibition of HSD11β1 and antagonism of CRHR1. *Fmr1* KO mice exhibit exaggerated hyponeophagia, a form of trait anxiety in which rodents are hesitant to eat new food. This form of anxiety involves the BNST and mPFC. The level of apprehension to eat new food is quantified in terms of the latency (in seconds) to try a new food when it is presented. (**A-C**) Performance of wild type (WT) and *Fmr1* KO (KO) mice in the hyponeophagia paradigm under control (vehicle treated) conditions and during treatment with three structurally distinct inhibitors of HSD11β1: (**A**) AMG-221 (30mg/kg) dosed p.o. for 10 days; (**B**) PF 915275 (10mg/kg) dosed p.o. for 3 days; (**C**) BVT2733 (30mg/kg) dosed i.p. for 3 days. *Fmr1* KO mice exhibit much greater apprehension to eat new food, manifest as a longer latency to sample the food. Administration of CRHR1 antagonists greatly reduce this form of anxiety, reducing the latency to eat new food to a level not different from vehicle-treated controls. (**D-E**) Performance of wild type and *Fmr1* KO mice in the hyponeophagia paradigm under control conditions and during treatment with

three structurally distinct antagonists of CRHR1: (**D**) NBI 35965 (10mg/kg) dosed p.o. for 3 days; (**E**) Antalarmin (30mg/kg) dosed i.p. for 3 days; (**F**) SSR125543A (30mg/kg) dosed i.p. for 3 days. As with the HSD11b1 inhibitors, CRHR1 antagonists greatly reduced anxiety. (n.s.= not significant; *** $p<0.0001$, ** $p<0.01$, * $p<0.05$ by unpaired, 2-tailed t-tests; when analyzed by ANOVA with multiple comparisons to vehicle-treated WT controls, only vehicle-treated KO mice were significantly different from vehicle treated WT mice by ANOVA with multiple comparisons.)

[0017] Figure 6 is a diagram of jcBNST function and how its dysregulation in FXS leads to a chronically anxiogenic changes analogous to those occurring in normal individuals during chronic stress. (**A**) jcBNST function in normal individuals under low stress states. jcBNST integrates excitatory inputs from corticolimbic structures including the insula, mPFC, and BLA that synapse onto Type III GABAergic projection neurons of the jcBNST. Type III neurons project to the LH and PVN regions of the hypothalamus and other areas to directly inhibit autonomic, behavioral, and endocrine (*i.e.* cortisol) responses to stress. jcBNST Type III neurons also project to the BLA and the CeA to limit amygdalar activation during stress, thus also indirectly inhibiting LH, PVN, and other amygdalar targets that mediate psychological, autonomic, and endocrine responses to stress. During low stress, expression of CRH, a factor that suppresses Type III neuron output and plasticity and produces anxiogenic shifts in BNST function, is relatively low in jcBNST, as are levels of cortisol, the downstream effector of CRH in the hypothalamic-pituitary-adreneal (HPA) axis that paradoxically increases CRH expression in jcBNST. (**B**) jcBNST function in normal individuals under chronic high stress conditions. CRH is released into the jcBNST during chronic stress by BLA terminals and other inputs; CRH expression is further increased by cortisol that comes largely from HPA axis activation. CRH reduces the output and LTP-IE of Type III neurons, leading to anxiogenic disinhibition of jcBNST targets and greater amygdalar activation. (**C**) jcBNST function in FXS. Upregulation of HSD11β1 – an enzyme that converts cortisone to active cortisol – in the jcBNST leads to greatly elevated local synthesis of cortisol. This promotes excessive CRH signaling, thereby reducing

jcBNST activity and predisposing it and the amygdala to anxiogenic output at baseline.

DETAILED DESCRIPTION

[0018] Disclosed herein are methods for the treatment of an emotional or psychological symptom of Fragile X Syndrome (FXS) in a patient which method comprises administering to the patient an effective amount of a compound that is an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1, also known as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1)), or an effective amount of an antagonist of corticotropin releasing hormone receptor type 1 (CRHR1). The methods of using an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 or an antagonist of corticotropin releasing hormone receptor type 1 in the treatment of an emotional or psychological symptom of FXS are based on a new view of the neurobiological origins of the unusually persistent chronic anxiety and related emotional symptoms in FXS presented herein.

[0019] In some embodiments, the emotional and psychological symptom of FXS is selected from chronic anxiety in any form (e.g. generalized, social, novelty, specific phobias and others), social aversion, self-injurious behavior, aggression or perseverative behavior, hyperactivity, and any combination thereof.

Definitions

[0020] The term "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to." "Consisting essentially of" or its grammatic variants when used to define compositions and methods, shall mean excluding other elements of any essential significance to the compositions and methods for the intended use, but not excluding elements that do not materially affect the characteristic(s) of the compositions or methods. "Consisting of" or its grammatic variants shall mean excluding elements not specifically recited. Embodiments defined by each of these transition terms are within the scope of this disclosure. For example, when a composition is described as comprising

ingredients A, B and C, a composition consisting essentially of A, B and C, and a composition consisting of A, B and C are independently within the scope of this disclosure.

[0021] As used in this specification and the appended claims, the singular forms "a" "an" and "the" and the like include plural referents unless the context clearly dictates otherwise. For example, the term "a pharmaceutically acceptable carrier" includes reference to one and more than one pharmaceutically acceptable carriers.

[0022] The term "about" means within ± 20%, ± 15%, ± 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, or 0.05% of a given value or range. In some embodiments, about means ± 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, or 0.05% of a given value or range. In some embodiments, about means ± 5% of a given value or range. In some embodiments, about means ± 4% of a given value or range. In some embodiments, about means ± 3% of a given value or range. In some embodiments, about means ± 2% of a given value or range. In some embodiments, about means ± 1% of a given value or range. In some embodiments, about means ± 0.5% of a given value or range. In some embodiments, about means ± 0.05% of a given value or range. The term "about x" includes the value "x."

[0023] The term "treating" refers to preventing, curing, reversing, attenuating, alleviating, minimizing, suppressing, halting or reducing the severity of a disease, condition or a symptom of a disease or condition.

[0024] The term "administration" refers to introducing an agent into a patient. A therapeutic amount can be administered. "Administration" and related terms "administer" and "administering," when used in connection with a compound or composition (and grammatical equivalents) refer both to direct administration, which may be administration to a patient by a medical professional or by self-administration by the patient, and/or to indirect administration, which may be the act of prescribing a drug.

[0025] "Pharmaceutically acceptable" refers to a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a

pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable vehicles (*e.g.*, carriers, adjuvants, and/or other excipients) have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0026] "Pharmaceutically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. Examples of salts may include hydrochlorate, phosphate, diphosphate, hydrobromate, sulfate, sulfinate, nitrate, malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, mesylate, p-toluenesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate (such as acetate, $HOOC-(CH_2)_n-COOH$ where n is 0-4). In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts.

[0027] Certain compounds can exist in unsolvated forms, including anhydrous forms, as well as solvated forms, including hydrated forms. As used herein, the term "solvate" refers to a crystal form with either a stoichiometric or non-stoichiometric amount of solvent incorporated into the crystal structure. Similarly, the term "hydrate" refers specifically to a crystal form with either a stoichiometric or non-stoichiometric amount of water incorporated into the crystal structure.

[0028] "Prodrugs" means any compound which releases an active parent drug in vivo when such prodrug is administered to a patient. Prodrugs may be 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. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), amides, guanidines, carbamates (e.g., N,N-dimethylaminocarbonyl) of a hydroxy functional group in a compound, and the like.

[0029] "Tautomer" means compounds produced by the phenomenon wherein a proton of one atom of a molecule shifts to another atom. The tautomers also refer to one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Examples of include keto-enol tautomers, such as acetone/propen-2-ol, imine-enamine tautomers and the like, ring-chain tautomers, such as glucose/2,3,4,5,6-pentahydroxy-hexanal and the like, the tautomeric forms of heteroaryl groups containing a -N=C(H)-NH- ring atom arrangement, such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles. Certain compounds may have one or more tautomers and therefore include various isomers. All such isomeric forms of these compounds are expressly included in the present disclosure.

[0030] "Isomers" mean compounds having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. "Stereoisomer" and "stereoisomers" refer to compounds that exist in different stereoisomeric forms if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Stereoisomers include enantiomers and diastereomers. Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers." When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture."

Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures.

[0031] The terms "effective amount", "pharmaceutically effective amount", and "therapeutically effective amount" refer to an amount that may be effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The effective amount may vary depending on the compound, the disease or condition being treated and its severity, the subject including the age, weight, etc., of the subject to be treated, and the manner of administering, which can readily be determined by one of ordinary skill in the art. The effective amount can include a range of amounts. A pharmaceutically effective amount includes amounts of an agent which are effective when combined with other agents.

[0032] The term "patient" or "subject" refers to a mammal that is treated with a method as described herein, including but not limited to, a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats. In some embodiments, the patient is a human.

11β-hydroxysteroid dehydrogenase type 1 inhibitors

[0033] Hydroxysteroid dehydrogenases (HSDs) regulate the occupancy and activation of steroid hormone receptors by converting steroid hormones into their inactive metabolites. There are many classes of HSDs. The 11-beta-hydroxysteroid dehydrogenases (11βHSDs) catalyze the interconversion of active glucocorticoids (such as cortisol and corticosterone), and their inert forms (such as cortisone and 11-dehydrocorticosterone). 11β-Hydroxysteroid dehydrogenase type 1 (11βHSD or HSD11β1) converts inactive cortisone to active cortisol at a greater rate than it converts cortisol to cortisone. Thus, increased HSD11b1 levels lead to more active cortisol. HSD11b1 is expressed in liver, adipose tissue, brain and lung.

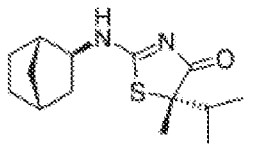
[0034] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is a compound described in U.S. Patent No. 7,807,700. In some

embodiments, the compound is selected from 2-(bicyclo[2.2.1]hept-2-ylamino)-5-isopropyl-1,3-thiazol-4(5H)-one, 2-(bicyclo[2.2.1]hept-2-ylamino)-5-ethyl-1,3-thiazol-4(5H)-one, 2-(bicyclo[2.2.1]hept-2-ylamino)-5-phenyl-1,3-thiazol-4(5H)-one, 2-(cyclohexylamino)-5-ethyl-1,3-thiazol-4(5H)-one, 2-(bicyclo[2.2.1]hept-2-ylamino)-5,5-dimethyl-1,3-thiazol-4(5H)-one, 5-isopropyl-2-(tricyclo[3.3.1.0~3,7~]non-3-ylamino)-1,3-thiazol-4(5H)-one, 6-(tricyclo[3.3.1.0~3,7~]non-3-ylamino)-5-thia-7-azaspiro[3.4]oct-6-en-8-one, 2-(tricyclo[3.3.1.0~3,7~]non-3-ylamino)-1,3-thiazol-4(5H)-one, 6-(cyclooctylamino)-5-thia-7-azaspiro[3.4]oct-6-en-8-one, 6-(cycloheptylamino)-5-thia-7-azaspiro[3.4]oct-6-en-8-one, 6-(bicyclo[2.2.1]hept-2-ylamino)-5-thia-7-azaspiro[3.4]oct-6-en-8-one, 6-[(2,2,3,3-tetramethylcyclopropyl)amino]-5-thia-7-azaspiro[3.4]oct-6-en-8-one, 6-[(2-methylphenyl)amino]-5-thia-7-azaspiro[3.4]oct-6-en-8-one, 2-[(cyclohexylmethyl)amino]-5,5-dimethyl-1,3-thiazol-4(5H)-one, 2-[(2-fluorophenyl)amino]-5-isopropyl-1,3-thiazol-4(5H)-one, 2-[(cyclohexylmethyl)amino]-5-(2-hydroxyphenyl)-1,3-thiazol-4(5H)-one, (5S)-2-(cycloheptylamino)-5-methyl-1,3-thiazol-4(5H)-one, (5R)-2-(cycloheptylamino)-5-methyl-1,3-thiazol-4(5H)-one, 2-(cycloheptylamino)-5-ethyl-1,3-thiazol-4(5H)-one, 2-(cycloheptylamino)-5-isopropyl-1,3-thiazol-4(5H)-one, 5-tert-butyl-2-(cycloheptylamino)-1,3-thiazol-4(5H)-one, 2-(cyclooctylamino)-5-ethyl-1,3-thiazol-4(5H)-one, 5-isopropyl-2-[(2-isopropylphenyl)amino]-1,3-thiazol-4(5H)-one, 5-ethyl-2-[(2-isopropylphenyl)amino]-1,3-thiazol-4(5H)-one, 2-[(2-chlorophenyl)amino]-5-ethyl-1,3-thiazol-4(5H)-one, 5-ethyl-2-[(2-methylphenyl)amino]-1,3-thiazol-4(5H)-one, 5-isopropyl-2-[(2,2,3,3-tetramethylcyclopropyl)amino]-1,3-thiazol-4(5H)-one, 2-(bicyclo[2.2.1]hept-2-ylamino)-5-(4-hydroxybenzyl)-1,3-thiazol-4(5H)-one, 5-[(cyclohexylmethyl)amino]-4-thia-6-azaspiro[2.4]hept-5-en-7-one, 2-(cycloheptylamino)-5-(3,4-dihydroxybenzyl)-1,3-thiazol-4(5H)-one, 2-(cycloheptylamino)-5-(1H-imidazol-4-ylmethyl)-1,3-thiazol-4(5H)-one, 2-(cycloheptylamino)-5-isobutyl-1,3-thiazol-4(5H)-one, 2-(cycloheptylamino)-5-(1H-indol-3-ylmethyl)-1,3-thiazol-4(5H)-one, 2-(cycloheptylamino)-5-(4-hydroxybenzyl)-1,3-thiazol-4(5H)-one, (5R)-2-(cycloheptylamino)-5-(cyclohexylmethyl)-1,3-thiazol-4(5H)-one, 2-(cyclooctylamino)-5-(4-hydroxybenzyl)-1,3-thiazol-4(5H)-one, (5S)-2-(cycloheptylamino)-5-(cyclohexylmethyl)-1,3-thiazol-4(5H)-one, [2-(cycloheptylamino)-4-oxo-4,5-

dihydro-1,3-thiazol-5-yl]acetonitrile, 2-(cycloheptylamino)-5-(pyridin-3-ylmethyl)-1,3-thiazol-4(5H)-one, 5-Isopropyl-2-[(2-methylphenyl)amino]-1,3-thiazol-4(5H)-one, 2-(cyclooctylamino)-5,5-dimethyl-1,3-thiazol-4(5H)-one, 2-(cyclooctylamino)-5-isopropyl-1,3-thiazol-4(5H)-one, 2-(bicyclo[2.2.1]hept-2-ylamino)-1-thia-3-azaspiro[4.5]dec-2-en-4-one, 2-(tricyclo[3.3.1.0~3,7~]non-3-ylamino)-1-thia-3-azaspiro[4.5]dec-2-en-4-one, 2-(cycloheptylamino)-1-thia-3-azaspiro[4.5]dec-2-en-4-one, 2-(cyclooctylamino)-1-thia-3-azaspiro[4.5]dec-2-en-4-one, 2-{[1-(4-chlorophenyl)cyclobutyl]amino}-5-isopropyl-1,3-thiazol-4(5H)-one, 6-{[1-(4-chlorophenyl)cyclobutyl]amino}-5-thia-7-azaspiro[3.4]oct-6-en-8-one, 2-(cycloheptylamino)-5,5-diethyl-1,3-thiazol-4(5H)-one, (5S)-5-isopropyl-2-{[(2S)-2-phenylpropyl]amino}-1,3-thiazol-4(5H)-one, (5R)-5-ethyl-2-{[(2S)-2-phenylpropyl]amino}-1,3-thiazol-4(5H)-one, (5S)-5-ethyl-2-{[(2S)-2-phenylpropyl]amino}-1,3-thiazol-4(5H)-one, (5R)-5-isopropyl-2-{[(2R)-2-phenylpropyl]amino}-1,3-thiazol-4(5H)-one, (5S)-5-isopropyl-2-{[(2R)-2-phenylpropyl]amino}-1,3-thiazol-4(5H)-one, (5R)-5-ethyl-2-{[(2R)-2-phenylpropyl]amino}-1,3-thiazol-4(5H)-one, (5S)-5-ethyl-2-{[(2R)-2-phenylpropyl]amino}-1,3-thiazol-4(5H)-one, 2-anilino-5-isopropyl-1,3-thiazol-4(5H)-one, 5-isopropyl-2-[(2-morpholin-4-ylethyl)amino]-1,3-thiazol-4(5H)-one, 2-(bicyclo[2.2.1]hept-2-ylamino)-1-thia-3-azaspiro[4.4]non-2-en-4-one, 2-(cycloheptylamino)-1-thia-3-azaspiro[4.4]non-2-en-4-one, 2-(cyclooctylamino)-1-thia-3-azaspiro[4.4]non-2-en-4-one, 2-[(2,2,3,3-tetramethylcyclopropyl)amino]-1-thia-3-azaspiro[4.4]non-2-en-4-one, 2-[(2-chlorobenzyl)amino]-5-isopropyl-1,3-oxazol-4(5H)-one, 2-[(4-chlorobenzyl)amino]-5-isopropyl-1,3-oxazol-4(5H)-one, 5-isopropyl-2-[(2,2,6,6-tetramethylpiperidin-4-yl)amino]-1,3-oxazol-4(5H)-one, 5-isopropyl-2-[(2-morpholin-4-ylethyl)amino]-1,3-oxazol-4(5H)-one, 5-benzyl-2-[(cyclohexylmethyl)amino]-1,3-oxazol-4(5H)-one, 2-(cycloheptylamino)-5-isopropyl-1,3-oxazol-4(5H)-one, 2-(bicyclo[2.2.1]hept-2-ylamino)-5-isopropyl-1,3-oxazol-4(5H)-one, 2-(bicyclo[2.2.1]hept-2-ylamino)-5-isobutyl-1,3-oxazol-4(5H)-one, 2-(cycloheptylamino)-5-isobutyl-1,3-oxazol-4(5H)-one, 5-isobutyl-2-[(2-methylphenyl)amino]-1,3-oxazol-4(5H)-one, 2-(bicyclo[2.2.1]hept-2-ylamino)-5-isopropyl-5-methyl-1,3-thiazol-4(5H)-one, 5-ethyl-2-[(3-methylphenyl)amino]-1,3-thiazol-4(5H)-one, 5-isopropyl-2-morpholin-4-yl-1,3-oxazol-4(5H)-one, 2-(4-benzylpiperidin-1-yl)-5-isopropyl-1,3-oxazol-4(5H)-one,

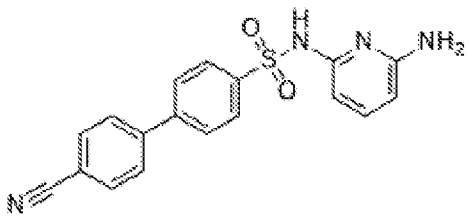
2-azocan-1-yl-5-isopropyl-1,3-oxazol-4(5H)-one, 2-[(cyclohexylmethyl)amino]-5-phenyl-1,3-oxazol-4(5H)-one, and 2-(cycloheptylamino)-5-phenyl-1,3-oxazol-4(5H)-one, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0035] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is AMG-221 (or BVT-83370), which is of the formula:



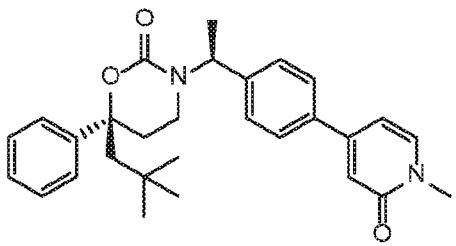
or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0036] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is PF915275, of the formula:



or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0037] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is BI-135585, of the formula:



or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0038] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is a compound described in U.S. Patent Application Publication No.

2010/0113435. In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is selected from the group consisting of Ethyl 2-(2-(((4-methylphenyl)sulfonyl)amino)-1,3-thiazol-4-yl)acetate, Ethyl 2-(2-{[(2,5-dichloro-3-thienyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2-chlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl 2-{2-[([1'-biphenyl]-4-ylsulfonyl)amino]-1,3-thiazol-4-yl}acetate, Ethyl 2-(2-{[(3-bromophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-nitrophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-methoxyphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(3-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(3-chlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-fluorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(3-fluorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-isopropylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[3-({[4-(2-ethoxy-2-oxoethyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl-]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl [2-({[4-({[4-(2-ethoxy-2-oxoethyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl (2-{[(2-methylphenyl)sulfonyl]amino)}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[2-(trifluoromethyl)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl [2-({[3-(trifluoromethyl)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl [2-({[4-(trifluoromethyl)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl 2-(2-{[(4-bromophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2-nitrophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetat- e, Ethyl (2-{[(2,4,6-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2,4-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(5-fluoro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-propylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2-methoxy-4-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(3,5-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[4-(3-chloro-2-cyanophenoxy)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl (2-{[(3,4-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-butoxyphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-

chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[4-(acetylamino)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl {2-[(8-quinolinylsulfonyl)amino]-1,3-thiazol-4-yl}acetate, Ethyl (2-{[(3,4-dimethoxyphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-iodophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(3-chloro-4-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[5-(dimethylamino)-1-naphthyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl (2-{[(1-methyl-1H-imidazol-4-yl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(5-bromo-2-methoxyphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2,5-dimethoxyphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl {2-[(2-naphthylsulfonyl)amino]-1,3-thiazol-4-yl}acetate, Ethyl {2-[(mesitylsulfonyl)amino]-1,3-thiazol-4-yl}acetate, Ethyl (2-{[(3-bromo-5-chloro-2-thienyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl {2-[({5-[(benzoylamino)methyl]-2-thienyl}sulfonyl)amino]-1,3-thiazol-4-yl}acetate, Ethyl {2-[({5-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-2-thienyl}sulfonyl)amino]-1,3-thiazol-4-yl}acetate, Ethyl (2-{[(4-cyanophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl {2-[({5-[2-(methylsulfanyl)-4-pyrimidinyl]-2-thienyl}sulfonyl)amino]-1,3-thiazol-4-yl}acetate, Ethyl (2-{[(3-cyanophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2,4,5-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[(E)-2-phenylethenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl (2-{[(2,3,4-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-bromo-2,5-difluorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl (2-{[(2,3-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2-bromophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4,5-dichloro-2-thienyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[4-(phenylsulfonyl)-2-thienyl]sulfonyl}amino)-1,3-thiazol-4-yl-]acetate, Ethyl [2-({[5-(phenylsulfonyl)-2-thienyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl (2-{[(2,6-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2-cyanophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[4-(acetylamino)-3-chlorophenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl (2-{[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(3-methoxyphenyl)sulfonyl]amino}-1,3-thiazol-4-

yl)acetate, Ethyl (2-{[(4-bromo-5-chloro-2-thienyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl 2-{2-[(1-naphthylsulfonyl)amino]-1,3-thiazol-4-yl}acetate, Ethyl (2-{[(2,5-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[4-(methylsulfonyl)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl [2-({[2-(methylsulfonyl)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl (2-{[(4-bromo-2-fluorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2,3,4-trifluorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(7-chloro-2,1,3-benzoxadiazol-4-yl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2,4,6-trifluorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, 2-Chloro-5-({[4-(2-ethoxy-2-oxoethyl)-1,3-thiazol-2-yl]amino}sulfonyl)-4-fluorobenzoic acid, Ethyl (2-{[(5-chloro-2-thienyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(2-chloro-4-fluorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl [2-({[5-(3-isoxazolyl)-2-thienyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl (2-{[(4-bromo-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-phenoxyphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(4-chloro-2,6-dimethylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)- acetate, Ethyl [2-({[2-methyl-4-(trifluoromethoxy)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl [2-({[2,4-bis(trifluoromethyl)phenyl]sulfonyl}amino)-1,3-thiazol-4-yl]acetate, Ethyl 2-{2-[[(3-chloro-2-methylphenyl)sulfonyl](methyl)amino]-1,3-thiazol-4-yl}acetate, Ethyl oxo(2-{[(4-propylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl (2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)(oxo)acetate, Ethyl oxo(2-{[(2,4,6-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Ethyl {2-[([1,1'-biphenyl]-4-ylsulfonyl)amino]-1,3-thiazol-4-yl}(oxo)acetate, Ethyl (2-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)(oxo)acetate, 2-(2-{[(4-Methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetic acid, 2-(2-{[(2,5-Dichloro-3-thienyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetic acid, (2-{[(2-Chlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetic acid, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetic acid, Isopropyl 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Phenyl 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Methyl (2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Methyl {2-[([1,1'-biphenyl]-4-ylsulfonyl)amino]-5-methyl-1,3-thiazol-4-yl}acetate, Methyl (2-

{[(4-chlorophenyl)sulfonyl]amino}-5-methyl-1,3-thiazol-4-yl)acetate, Methyl (2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-5-methyl-1,3-thiazol-4-yl)acetate, Methyl [2-({[4-(3-chloro-2-cyanophenoxy)phenyl]sulfonyl}amino)-5-methyl-1,3-thiazol-4-yl]acetate; Methyl (5-methyl-2-{[(4-propylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Methyl (5-methyl-2-{[(2,4,6-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetate, Methyl (2-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}-5-methyl-1,3-thiazol-4-yl)acetate, N-(2-Methoxyethyl)-2-(2-{[(4-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-y- l)acetamide, 2-(2-{[(2,5-Dichloro-3-thienyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-methyl- acetamide, N-(1,3-Benzodioxol-5-ylmethyl)-2-{2-[(1-naphthylsulfonyl)amino]-1,3-thiazol-4-yl}acetamide, N-(2-Furylmethyl)-2-{2-[(1-naphthylsulfonyl)amino]-1,3-thiazol-4-yl}acetamide, 2-(2-{[(2,4-Difluorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-ethyl- acetamide, N-Isopropyl-2-{2-[(1-naphthylsulfonyl)amino]-1,3-thiazol-4-yl}acetamide, N-[2-(1H-Indol-3-yl)ethyl]-2-{2-[(1-naphthylsulfonyl)amino]-1,3-thiazol-4-yl}acetamide, N-(Cyclohexylmethyl)-2-{2-[(phenylsulfonyl)amino]-1,3-thiazol-4-yl}acetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-methylacetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-ethylacetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-phenylacetamide, 2-(2-{[(4-Chlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-(2-furylmethyl)acetamide, N-Benzhydryl-2-(2-{[(4-chlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetamide, 2-(2-{[(4-Chlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-(tetrahydro-2-furanylmethyl)acetamide, Ethyl 4-{[2-(2-{[(4-chlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetyl]amino)}-1-piperidinecarboxylate, N-Benzhydryl-2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetamide, 2-(2-{[(4-Chlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-phenylacetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino)}-1,3-thiazol-4-yl)-N,N-diethylacetamide, 2-{2-[([1,1'-Biphenyl]-4-ylsulfonyl)amino]-1,3-thiazol-4-yl}-N,N-diethylacetamide, N,N-diethyl-2-(2-{[(4-propylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetamide, 2-(2-{[(2,4-Dichloro-6-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N,N-diethylacetamide, N,N-

diethyl-2-(2-{[(2,4,6-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetamide, 2-{2-[([1,1'-Biphenyl]-4-ylsulfonyl)amino]-1,3-thiazol-4-yl}-N,N-diisopropylacetamide, N,N-diisopropyl-2-(2-{[(4-propylphenyl)sulfonyl]amino)}-1,3-thiazol-4-yl)acetamide, 2-(2-{[(2,4-Dichloro-6-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N,N-diisopropylacetamide, N,N-diisopropyl-2-(2-{[(2,4,6-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N,N-diisopropylacetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N,N-dipropylacetamide, N-benzyl-2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-methylacetamide, N-benzyl-2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-ethylacetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N,N-dimethylacetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-cyclohexyl-N-methylacetamide, 3-Chloro-N-{4-[2-(3,4-dihydro-2(1H)-isoquinolinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-2-methylbenzenesulfonamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-methyl-N-phenylacetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-isopropyl-N-methylacetamide, 2-{2-[([1,1'-Biphenyl]-4-ylsulfonyl)amino]-1,3-thiazol-4-yl}-N-isopropyl-N-methylacetamide, N-ethyl-N-methyl-2-(2-{[(2,4,6-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetamide, 2-(2-{[(2,4-Dichloro-6-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-ethyl-N-methylacetamide, N-ethyl-N-methyl-2-(2-{[(4-propylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetamide, 2-{2-[([1,1'-Biphenyl]-4-ylsulfonyl)amino}-1,3-thiazol-4-yl]-N-ethyl-N-methylacetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-ethyl-N-methylacetamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-methyl-N-[(1S)-1-phenylethyl]acetamide, 3-Chloro-2-methyl-N-{4-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-oxo-2-(1-piperidinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-oxo-2-(1-piperidinyl)ethyl]-1,3-thiazol-2-yl}[1,1'-biphenyl]-4-sulfonamide, N-{4-[2-oxo-2-(1-piperidinyl)ethyl]-1,3-thiazol-2-yl}-4-propylbenzenesulfonamide, 2,4-Dichloro-6-methyl-N-{4-[2-oxo-2-(1-

piperidinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2,4,6-Trichloro-N-{4-[2-oxo-2-(1-piperidinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2,4,6-Trichloro-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2,4-Dichloro-6-methyl-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}[1,1'-biphenyl]-4-sulfonamide, N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-propylbenzenesulfonamide, 2,4-Dichloro-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 4-Chloro-2,6-dimethyl-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-phenoxybenzenesulfonamide, 2-Methyl-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-(trifluoromethoxy)benzenesulfonamide, N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-2,4-bis(trifluoromethyl)benzenesulfonamide, 4-Bromo-2-methyl-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 4-(2-Furyl)-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3'-Fluoro-6'-methoxy-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}[1,1'-biphenyl]-4-sulfonamide, 4-(5-Methyl-2-thienyl)-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3'-Acetyl-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}[1,1'-biphenyl]-4-sulfonamide, N-{4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4'-(trifluoromethoxy)[1,1'-biphenyl]-4-sulfonamide, 3',4'-Dichloro-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}[1,1'-biphenyl]-4-sulfonamide, 4-(1,3-Benzodioxol-5-yl)-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 4-(5-chloro-2-thienyl)-N-{4-[2-(4-morphinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-(4-pyridinyl)benzenesulfonamide, N-{4'-[({4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}amino)sulfonyl][1,1'-biphenyl]-3-yl}acetamide, N-{4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-(3-thienyl)benzenesulfonamide, N-{4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-(2-thienyl)benzenesulfonamide, 4'-[({4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}amino)sulfonyl][1,1'-biphenyl]-4-carboxylic acid, 4'-(Methylsulfanyl)-N-{4-[2-(4-morpholinyl)-2-

oxoethyl]-1,3-thiazol-2-yl}-[1,1'-biphenyl]-4-sulfonamide, N-{4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-4-sulfonamide, 4'-Chloro-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}[1,1'-biphenyl]-4-sulfonamide, N-{4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-3'-nitro[1,1'-biphenyl]-4-sulfonamide, 4-(1-Benzofuran-2-yl)-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-(1-pyrrolidinyl)benzenesulfonamide, 4-(4-Methyl-1-piperidinyl)-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 4-Anilino-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 4-(Benzylamino)-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-[(2-thienylmethyl)amino]benzenesulfonamide, 4-(4-Morpholinyl)-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 4-(4-Methyl-1-piperazinyl)-N-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-(4-Morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-[(3-pyridinylmeth-yl)amino]benzenesulfonamide, 2,4-Dichloro-6-methyl-N-{5-methyl-4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{5-methyl-4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}[1,1'-biphenyl]-4-sulfonamide, 2,4,6-Dichloro-N-{5-methyl-4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-chloro-2-methyl-N-{5-methyl-4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-N-(4-{2-[(2R,6S)-2,6-dimethylmorpholinyl]-2-oxoethyl}-1,3-thiazol-2-yl)-2-methylbenzenesulfonamide, 3-Chloro-2-methyl-N-(4-{2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]-2-oxoethyl}-1,3-thiazol-2-yl)benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-oxo-2-(4-thiomorpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-oxo-2-(4-thiomorpholinyl)ethyl]-1,3-thiazol-2-yl}[1,1'-biphenyl]-4-sulfonamide, N-{4-[2-oxo-2-(4-thiomorpholinyl)ethyl]-1,3-thiazol-2-yl}-4-propylbenzenesulfonamide, 2,4-Dichloro-6-methyl-N-{4-[2-oxo-2-(4-thiomorpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2,4,6-Trichloro-N-{4-[2-oxo-2-(4-thiomorpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-(1,1-dioxido-4-thiomorpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-propylbenzenesulfonamide, Tert-butyl 4-[(2-1{[(3-chloro-2-

methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)acetyl]-1-piperazinecarboxylate, N-{4-[2-(4-Acetyl-1-piperazinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-3-chloro-2-methylbenzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide trifluoroacetate, 3-Chloro-2-methyl-N-{4-[2-oxo-2-(1-piperazinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide trifluoroacetate, 2-Methyl-N-{4-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-(trifluoromethoxy)benzenesulfonamide, 2,4-Dichloro-6-methyl-N-{4-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2,4-Dichloro-N-{4-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-chloro-N-(4-{2-[(2R)-2,4-dimethylpiperazinyl]-2-oxoethyl}-1,3-thiazol-2-yl)-2-methylbenzenesulfonamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)-N-methoxy-N-methylacetamide, 3-Chloro-2-methyl-N-[4-(2-oxopentyl)-1,3-thiazol-2-yl]benzeliesulfonamide, 4-Chloro-N-[4-(2-hydroxyethyl)-1,3-thiazol-2-yl]benzenesulfonamide, 3-Chloro-N-[4-(2-hydroxyethyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, 3-Chloro-N-[4-(3-hydroxypropyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, 3-Chloro-N-[4-(2-ethoxyethyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, 3-Chloro-N-[4-(2-isopropoxyethyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, N-{4-[2-(benzyloxy)ethyl]-1,3-thiazol-2-yl}-3-chloro-2-methylbenzenesulfonamide, 3-Chloro-N-[4-(2-methoxyethyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, 3-Chloro-N-{4-[2-(2-fluoroethoxy)ethyl]-1,3-thiazol-2-yl}-2-methylbenzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(2,2,2-trifluoroethoxy)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(2-pyridinylsulfanyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(3-pyridinyloxy)ethyl]-1,3-thiazol-2-yl}benzene- sulfonamide, Methyl 2-[2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethoxy]benzoate, 3-Chloro-N-[5-[(dimethylamino)methyl]-4-(2-ethoxyethyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethylmethanesulfonate, 3-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)propylmethanesulfonate, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl acetate, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl

propionate, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl 2-methylpropanoate, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl 2-furoate, 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl benzoate, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl 4-morpholinecarboxylate, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl diethylcarbamate, 2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl ethylcarbamate, N-[4-(2-azidoethyl)-1,3-thiazol-2-yl]-3-chloro-2-methylbenzenesulfonamide, N-[4-(2-aminoethyl)-1,3-thiazol-2-yl]-3-chloro-2-methylbenzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(methylamino)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 4-Chloro-N-{4-[2-(diethylamino)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide hydrochloride, 3-Chloro-N-{4-[2-(diethylamino)ethyl]-1,3-thiazol-2-yl}-2-methylbenzenesulfonamide hydrochloride, 3-Chloro-N-{4-[2-(1H-imidazol-1-yl)ethyl]-1,3-thiazol-2-yl}-2-methylbenzenesulfonamide dihydrate, 3-Chloro-2-methyl-N-{4-[2-(4-methyl-1-piperazinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide dihydrochloride, 3-Chloro-2-methyl-N-{4-[2-(4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide hydrochloride, 3-Chloro-2-methyl-N-[4-(4-morpholinylmethyl)-1,3-thiazol-2-yl]benzenesulfonamide hydrochloride, 2,4,6-Trichloro-N-{4-[2-(4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide hydrochloride, 2,4-Dichloro-N-{4-[2-(4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide hydrochloride, 2,4-Dichloro-6-methyl-N-{4-[2-(4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide hydrochloride, N-{4-[2-(4-Morpholinyl)ethyl]-1,3-thiazol-2-yl}-4-propylbenzenesulfonamide hydrochloride, 3-Chloro-N-{4-[2-(ethylamino)ethyl]-1,3-thiazol-2-yl}-2-methylbenzenesulfonamide, 3-Chloro-N-(4-{2-[(2-hydroxyethyl)amino]ethyl}-1,3-thiazol-2-yl)-2-methylbenzenesulfonamide, 3-Chloro-N-(4-{(3-[(2-hydroxyethyl)amino]propyl}-1,3-thiazol-2-yl)-2-methylbenzenesulfonamide hydrochloride hydrate, N-[2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino)}-1,3-thiazol-4-yl)ethyl]-N-ethylacetamide, 3-Chloro-2-methyl-N-{4-[2-(3-oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-N-{4-[2-(2-hydroxy-3-oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}-2-methylbenzenesulfonamide, 2,4-Dichloro-N-{4-[2-(3-oxo-4-morpholinyl)ethyl]-

1,3-thiazol-2-yl}benzenesulfonamide, 2,4-Dichloro-6-methyl-N-{4-[2-(3-oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2,4,6-Trichloro-N-{4-[2-(3-oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 4,5-Dichloro-N-{4-[2-(3-oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}-2-thiophenesulfonamide, N-{4-[2-(3-Oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}-4-phenoxybenzenesulfonamide, 3-Fluoro-N-{4-[2-(3-oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-{4-[2-(3-Oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}-5-(2-pyridinyl)-2-thiophenesulfonamide, N-{2-Chloro-4-[({4-[2-(3-oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}amino)sulfonyl]phenyl}acetamide, 3-Chloro-2-methyl-N-{4-[(3-oxo-4-morpholinyl)methyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[3-(3-oxo-4-morpholinyl)propyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-N,2-dimethyl-N-{4-[2-(3-oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(2-methyl-3-oxo-4-morpholinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-[2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl]acetamide, 3-Chloro-2-methyl-N-{4-[2-(3-oxo-1,4-oxazepan-4-yl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(2-oxo-1-pyrrolidinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(2-oxo-1-imidazolidinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-Chloro-2-methyl-N-{4-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, N-[2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl]-N-(2-hydroxyethyl)-2-furamide, N-[2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl]-N-methylcyclopropanecarboxamide, 3-Chloro-2-methyl-N-{4-[2-(4-methyl-2-oxo-1-piperazinyl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide hydrochloride, 3-Chloro-2-methyl-N-(4-{2-[(methylsulfonyl)amino]ethyl}-1,3-thiazol-2-yl)benzenesulfonamide, 3-Chloro-2-methyl-N-(4-{2-[methyl(methylsulfonyl)amino]ethyl}-1,3-thiazol-2-yl)benzenesulfonamide, 3-Chloro-2-methyl-N-[4-(2-{[(trifluoromethyl)sulfonyl]amino}ethyl)-1,3-thiazol-2-yl]benzenesulfonamide, 3-Chloro-2-methyl-N-[4-(2-{methyl[(trifluoromethyl)sulfonyl]amino}ethyl)-1,3-thiazol-2-yl]benzenesulfonamide, N-[2-(2-{[(3-Chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)ethyl]-1-methyl-1H-imidazole-4-sulfonamide, 3-Chloro-N-(4-

{2-[[(3-chloro-2-methylphenyl)sulfonyl](methyl)amino]ethyl}-1,3-thiazol-2-yl)-2-methylbenzenesulfonamide, N-[4-(2-bromoethyl)-1,3-thiazol-2-yl]-3-chloro-2-methylbenzenesulfonamide, 3-Chloro-N-[4-(2-chloroethyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, 3-Chloro-2-methyl-N-{4-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-1,3-thiazol-2-yl}benzenesulfonamide, and Ethyl 3-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-4-yl)propanoate.

[0039] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is a compound described in U.S. Patent Application Publication No. 2005/0250776. In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is selected from the group consisting of ethyl (2-{[(2,4-dichloro-5-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(4-chlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(2,4-difluorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(2,5-dichlorothien-3-yl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(2-chlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl {2-[(1-naphthylsulfonyl)amino]-1,3-thiazol-5-yl}acetate, ethyl (2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl {2-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1,3-thiazol-5-yl}acetate, ethyl (2-{[(4-nitrophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(4-methoxyphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(2,5-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, 3-chloro-N-[5-(2-hydroxyethyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, 3-chloro-N-[5-(2-ethoxyethyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, ethyl (2-{[(3-chlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(4-fluorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(4-isopropylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl [2-({[4-({[4-(2-ethoxy-2-oxoethyl)-1,3-thiazol-2-yl]amino}carbonyl)phenyl]sulfonyl}amino)-1,3-thiazol-5-yl]acetate, ethyl [2-({[2-(trifluoromethyl)phenyl]sulfonyl}amino)-1,3-thiazol-5-yl]acetate, ethyl [2-({[3-(trifluoromethyl)phenyl]sulfonyl)amino)-1,3-thiazol-5-yl]acetate, ethyl [2-({[4-(trifluoromethyl)phenyl]sulfonyl)amino)-1,3-thiazol-5-yl]acetate, methyl (2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, 3-chloro-N-[5-(2-isopropoxyethyl)-1,3-thiazol-2-yl]-2-methylbenzenesulfonamide, 3-chloro-N-[5-(2-methoxyethyl)-1,3-thiazol-2-yl]-

2-methylbenzenesulfonamide, 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)ethylmethanesulfonate, 3-chloro-N-{5-[2-(2-fluoroethoxy)ethyl]-1,3-thiazol-2-yl}-2-methylbenzenesulfonamide, 3-chloro-2-methyl-N-{5-[2-(2,2,2-trifluoroethoxy)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)ethyl acetate, 3-chloro-2-methyl-N-[5-(2-morpholin-4-ylethyl)-1,3-thiazol-2-yl]benzenesulfonamide, N-[5-(2-bromoethyl)-1,3-thiazol-2-yl]-3-chloro-2-methylbenzenesulfonamide, 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)ethyl morpholine-4-carboxylate, 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)ethyl diethylcarbamate, 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)ethyl propionate, 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)ethyl2-methylpropanoate, 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)ethyl 2-furoate, 2-(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)ethyl benzoate, 2-(2{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol5-yl)ethyl ethylcarbamate, 3-chloro-2-methyl-N-[5-(2-oxopentyl)-1,3-thiazol-2-yl]benzenesulfonamide, N-{5-[2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethyl]-1,3-thiazol-2-yl}-4-propylbenzenesulfonamide, 2,4-dichloro-6-methyl-N-{5-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-chloro-2-methyl-N-{5-[2-(3-oxomorpholin-4-yl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2,4-dichloro-6-methyl-N-(5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]benezenesulfonamide, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-1,1'-biphenyl-4-sulfonamide, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-4-propylbenzenesulfonamide, N-[5-(2-oxo-2-thiomorpholin-4-ylethyl)-1,3-thiazol-2-yl]-1,1'-biphenyl-4-sulfonamide, N-[5-(2-oxo-2-thiomorpholin-4-ylethyl)-1,3-thiazol-2-yl]-4-propylbenzenesulfonamide, 2,4-dichloro-6-methyl-N-[5-(2-oxo-2-thiomorpholin-4-ylethyl)-1,3-thiazol-2-yl]benzenesulfonamide, N-[5-(2-oxo-2-piperidin-1-ylethyl)-1,3-thiazol-2-yl]-1,1'-biphenyl-4-sulfonamide, N-[5-(2-oxo-2-piperidin-1-ylethyl)-1,3-thiazol-2-yl]-4-propylbenzenesulfonamide, 2,4-dichloro-6-methyl-N-[5-(2-oxo-2-piperidin-1-ylethyl)-1,3-thiazol-2-yl]benzenesulfonamide, ethyl oxo(2-{[(4-propylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(3-chloro-2-

methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)(oxo)acetate. ethyl oxo(2-{[(2,4,6-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl {2-[(1,1'-biphenyl-4-ylsulfonyl)amino]-1,3-thiazol-5-yl}(oxo)acetate, 3-chloro-2-methyl-N-[4-methyl-5-(- 2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]benzenesulfonamide, 2,4,6-trichloro-N-[4-methyl-5-(2-molpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]benzenesulfonamide, N-[4-methyl-5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-1,1'-biphenyl-4-sulfonamide, ethyl (2-{[(4-bromo-5-chlorothien-2-yl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(3-bromo-5-chlorothien-2-yl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl {2-[({5-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]thien-2-yl)sulfonyl)amino]-1,3-thiazol-5-yl)acetate, ethyl {2-[({5-[2-(methylthio)pyrimidin-4-yl]thien-2-yl}sulfonyl)amino]-1,3-thiazol-5-yl}acetate, methyl (4-methyl-2-{[(2,4,6-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate; 3-chloro-2-methyl-N-[5-(2-oxo-2-piperazin-1-ylethyl)-1,3-thiazol-2-yl]benzenesulfonamide, 4-bromo-2-methyl-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]benzenesulfonamide, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-2,4-bis(trifluoromethyl)benzenesulfonamide, 2-methyl-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-4-(trifluoromethoxy)benzenesulfonamide, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-4-phenoxybenzenesulfonamide, ethyl (2-{[(2,3,4-trichlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(4-bromo-2,5-difluorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl [2-({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)-1,3-thiazol-5-yl]acetate, ethyl [2-({[4-(phenylsulfonyl)thien-2-yl]sulfonyl}amino)-1,3-thiazol-5-yl]acetate, ethyl [2-({[5-(phenylsulfonyl)thien-2-yl]sulfonyl)amino)-1,3-thiazol-5-yl]acetate, ethyl (2-{[(2,6-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(2,4-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, tert-butyl 4-[(2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetyl]piperazine-1-carboxylate, 3-chloro-2-methyl-N-{5-[2-(pyridine-3-yloxy)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-chloro-2-methyl-N-[5-(2-oxo-2-thiomorpholin-4-ylethyl)-1,3-thiazol-2-yl]benzenesulfonamide, ethyl (2-{[(4-bromo-2-fluorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, 3-chloro-2-methyl-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]benzenesulfonamide, methyl (2-{[(4-chlorophenyl)sulfonyl]amino}-4-methyl-

1,3-thiazol-5-yl)acetate, methyl (2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-4-methyl-1,3-thiazol-5-yl)acetate, 3-chloro-2-methyl-N-[5-(2-oxo-2-pyrrolidin-1-ylethyl)-1,3-thiazol-2-yl]benzenesulfonamide, ethyl (2-{[(3-methoxyphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(5-fluoro-2-methylphenyl)sulfonyl]amino)}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(4-propylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, 3-chloro-2-methyl-N-[5-(2-oxo-2-piperidin-1-yl-ethyl)-1,3-thiazol-2-yl]benzenesulfonamide, ethyl (2-{[(3,5-dichlorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(3,4-dichlorophenyl)- sulfonyl]amino}-1,3-thiazol-5-yl)acetate. ethyl (2-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, 3-chloro-2-methyl-N-[5-(morpholin-4-ylmethyl)-1,3-thiazol-2-yl]benzenesulfonamide, 3-chloro-N-{5-[2-(1H-imidazol-1-yl)ethyl]-1,3-thiazol-2-yl}-2-methylbenzenesulfonamide, ethyl [2-({[2-methyl-4-(trifluoromethoxy)phenyl]sulfonyl}am-ino)-1,3-thiazol-5-yl]acetate, ethyl (2-{[(2,3,4-trifluorophenyl)sulfonyl]-amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(2,4,6-trifluorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(5-chlorothien-2-yl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(2-chloro-4-fluorophenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(5-isoxazol-3-ylthien-2-yl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl (2-{[(4-phenoxyphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, ethyl [2-({[2,4-bis(trifluoromethyl)phenyl]sulfonyl)amino)-1,3-thiazol-5-yl]acetate, 3-chloro-2-methyl-N-{5-[2-(3-oxo-1,4-oxazepan-4-yl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-chloro-2-methyl-N-{5-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 3-chloro-2-methyl-N-{5-[2-(4-methyl-2-oxopiperazin-1-yl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2,4-dichloro-N-{5-[2-(3-oxomorpholin-4-yl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 2,4-dichloro-6-methyl-N-{5-[2-(3-oxomorpholin-4-yl)ethyl]-1,3-thiazol-2-yl}benzenesulfonamide, 4-(2-furyl)-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]benzenesulfonmide, 5'-fluoro-2'-methoxy-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-1,1'-biphenyl-4-sulfonamide, 4-(5-methylthien-2-yl)-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]benzenesulfonamide, 3'-acetyl-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-1,1'-biphenyl-4-sulfonamide, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-4'-(trifluoromethoxy)-1,1'-biphenyl-4-sulfonamide, 3',4'-

dichloro-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-1,1'-biphenyl-4-sulfonamide, 4-(1,3-benzodioxol-5-yl)-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]benzenesulfonamide, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-4-pyridin-4-ylbenzenesulfonamide, N-[4'-({[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]amino}sulfonyl)-1,1'-biphenyl-3-yl]acetamide, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-4-thien-3-ylbenzenesulfonamide, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-4-thien-2-ylbenzenesulfonamide, 4'-({[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]amino}sulfonyl)-1,1'-biphenyl-4-carboxylic acid, 4'-(methylthio)-N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-1,1'-biphenyl-4-sulfonamide, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-3',5'-bis(trifluoromethyl)-1,1'-biphenyl-4-sulfonamide, 4'-chloro-N-[5-(2-morpholin-4-yl-2-oxo-ethyl)-1,3-thiazol-2-yl]-1,1'-biphenyl-4-sulfonamides, N-[5-(2-morpholin-4-yl-2-oxoethyl)-1,3-thiazol-2-yl]-3'-nitro-1,1'-biphenyl-4-sulfonamide, and isopropyl (2-{[(3-chloro-2-methylphenyl)sulfonyl]amino}-1,3-thiazol-5-yl)acetate, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0040] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is a compound described in U.S. Patent Application Publication No. 2010/0113435. In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is selected from the group consisting of ethyl (4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)acetate, (4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)acetic acid, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)-N-methylacetamide, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)-N-ethylacetamide, 2,5-dichloro-N-(3-chloro-2,3'-bithien-4'-yl)benzenesulfonamide, isopropyl (4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)acetate, 3-chloro-N-[4-(2-hydroxyethyl)thien-3-yl]-2-methylbenzenesulfonamide, 3-chloro-N-[4-(2-ethoxyethyl)thien-3-yl]-2-methylbenzenesulfonamide, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)-N,N-diethylacetamide, methyl (4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)acetate, 3-chloro-N-[4-(2-isopropoxyethyl)thien-3-yl]-2-methylbenzenesulfonamide, 3-chloro-N-[4-(2-methoxyethyl)thien-3-yl]-2-methylbenzenesulfonamide, 2-(4-{[(3-chloro-2-

methylphenyl)sulfonyl]amino}thien-3-yl)ethyl methanesulfonate, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)acetamide, 3-chloro-N-{4-[2-(2-fluoroethoxy)ethyl]thien-3-yl}-2-methylbenzenesulfonamide, 3-chloro-2-methyl-N-{4-[2-(2,2,2-trifluoroethoxy)ethyl]thien-3-yl}benzenesulfonamide, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl acetate, 3-chloro-2-methyl-N-[4-(2-morpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, N-[4-(2-bromoethyl)thien-3-yl]-3-chloro-2-methylbenzenesulfonamide, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl morpholine-4-carboxylate, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl diethylcarbamate, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl propionate, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl 2-methylpropanoate, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl 2-furoate, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl benzoate, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)-N-methoxy-N-methylacetamide, 3-chloro-N-{4-[2-(diethylamino)ethyl]thien-3-yl}-2-methylbenzenesulfonamide, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl ethylcarbamate, N-[2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl]-N-ethylacetamide, 3-chloro-2-methyl-N-[4-(2-oxopentyl)thien-3-yl]benzenesulfonamide, N-{4-[2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethyl-]thien-3-yl}-4-propylbenzenesulfonamide, 2,4,6-trichloro-N-[4-(2-morpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, 2,4-dichloro-N-[4-(2-morpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, 3-chloro-2-methyl-N-{4-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 2,4-dichloro-6-methyl-N-[4-(2-morpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, N-[4-(2-morpholin-4-ylethyl)thien-3-yl]-4-propylbenzenesulfonamide, 2,4-dichloro-6-methyl-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 2,4,6-trichloro-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-propylbenzenesulfonamide, N-[4-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[4-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]-4-propylbenzenesulfonamide, 2,4-dichloro-6-methyl-N-[4-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, N-[4-(2-oxo-2-

piperidin-1-ylethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[4-(2-oxo-2-piperidin-1-ylethyl)thien-3-yl]-4-propylbenzenesulfonamide, 2,4-dichloro-6-methyl-N-[4-(2-oxo-2-piperidin-1-ylethyl)thien-3-yl]benzenesulfonamide, 2,4,6-trichloro-N-[4-(2-oxo-2-piperidin-1-ylethyl)thien-3-yl]benzenesulfonamide, N-(4-phenylthien-3-yl)-4-propylbenzenesulfonamide, ethyl (4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)(oxo)acetate, 3-chloro-2-methyl-N-(4-phenylthien-3-yl)benzenesulfonamide, 3-chloro-N-[4-(4-fluoro-3-methylphenyl)thien-3-yl]-2-methylbenzenesulfonamide, 2,4,6-trichloro-N-(4-phenylthien-3-yl)benzenesulfonamide, N-(4-phenylthien-3-yl)-1,1'-biphenyl-4-sulfonamide, 2,4-dichloro-6-methyl-N-(4-phenylthien-3-yl)benzenesulfonamide, 2-{4-[(1,1'-biphenyl-4-ylsulfonyl)amino]thien-3-yl}-N-ethyl-N-methylacetamide, N-ethyl-N-methyl-2-(4-{[(4-propylphenyl)sulfonyl]amino}thien-3-yl)acetamide, 2-(4-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}thien-3-yl)-N-ethyl-N-methylacetamide, N-ethyl-N-methyl-2-(4-{[(2,4,6-trichlorophenyl)sulfonyl]amino}thien-3-yl)acetamide, 2,4,6-trichloro-N-[4-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, 2-{4-[(1,1'-biphenyl-4-ylsulfonyl)amino]thien-3-yl}-N-isopropyl-N-methylacetamide, 2-{4-[(1,1'-biphenyl-4-yl-sulfonyl)amino]thien-3-yl}-N,N-diethylacetamide, N,N-diethyl-2-(4-{[(4-propylphenyl)sulfonyl]amino}thien-3-yl)acetamide, 2-(4-{[(2,4-dichloro-6-methyl- phenyl)sulfonyl]amino}thien-3-yl)-N,N-diethylacetamide, N,N-diethyl-2-(4-{[(2,4,6-trichlorophenyl)sulfonyl]amino}thien-3-yl)acetamide, 2-{4-[(1,1'-biphenyl-4-ylsulfonyl)amino]thien-3-yl}-N,N-diisopropylacetamide, N,N-diisopropyl-2-(4-{[(4-propylphenyl)sulfonyl]amino}thien-3-yl)acetamide, 2-(4-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}thien-3-yl)-N,N-diisopropylacetamide, N,N-diisopropyl-2-(4-{[(2,4,6-trichlorophenyl)sulfonyl]amino}thien-3-yl)acetamide, N-[4-(4-{[(4-propylphenyl)sulfonyl]amino}thien-3-yl)phenyl]acetamide, 4-propyl-N-(4-pyridin-3-ylthien-3-yl)benzenesulfonamide, N-[4-(2-chloro-5-nitrophenyl)thien-3-yl]-4-propylbenzenesulfonamid- e N-[4-(2-chlorophenyl)thien-3-yl]-4-propylbenzenesulfonamide, 3-chloro-N-[4-(2-chloro-5-nitrophenyl)thien-3-yl]-2-methylbenzenesulfonamide, 3-chloro-N-(5-chloro-2,3'-bithien-4'-yl)-2-methylbenzenesulfonamide, 3-chloro-N-[4-(2-chlorophenyl)thien-3-yl]-2-methylbenzenesulfonamide, N-[4-(4-{[(2,4,6-

trichlorophenyl)sulfonyl]amino}thien-3-yl)phenyl]acetamide, 2,4,6-trichloro-N-(4-pyridin-3-ylthien-3-yl)benzenesulfonamide, 2,4,6-trichloro-N-[4-(2-chloro-5-nitrophenyl)thien-3-yl]benzenesulfonamide, 2,4,6-trichloro-N-(5-chloro-2,3'-bithien-4'-yl)benzenesulfonamide, 2,4,6-trichloro-N-[4-(2-chlorophenyl)thien-3-yl]benzenesulfonamide, N-(4-{4-[(1,1'-biphenyl-4-ylsulfonyl)amino]thien-3-yl}phenyl)acetamide N-(4-pyridin-3-ylthien-3-yl)-1,1'-biphenyl-4-sulfonamide, N-[4-(2-chloro-5-nitrophenyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[4-(2-chlorophenyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[4-(4-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}thien-3-yl)phenyl]acetamide 2,4-dichloro-6-methyl-N-(4-pyridin-3-ylthien-3-yl)benzenesulfonamide, 2,4-dichloro-N-[4-(2-chloro-5-nitrophenyl)thien-3-yl]-6-methylbenzenesulfonamide, 2,4-dichloro-N-(5-chloro-2,3'-bithien-4'-yl)-6-methylbenzenesulfonamide 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)-N,N-dipropylacetamide, 3-chloro-2-methyl-N-[4-(2-oxo-2-piperazin-1-ylethyl)thien-3-yl]benzenesulfonamide, 2,4-dichloro-N-[4-(2,5-dimethyl-3-furyl)thien-3-yl]-6-methylbenzenesulfonamide, N-(3-chloro-2,3'-bithien-4'-yl)-4-propylbenzenesulfonamide 3-chloro-N-(3-chloro-2,3'-bithien-4'-yl)-2-methylbenzenesulfonamide, 2,4,6-trichloro-N-(3-chloro-2,3'-bithien-4'-yl)benzenesulfonamide, 2,4-dichloro-N-(3-chloro-2,3'-bithien-4'-yl)-6-methylbenzenesulfonamide, 2,4-dichloro-N-[4-(2-chlorophenyl)thien-3-yl]-6-methylbenzenesulfonamide, 4-bromo-2-methyl-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-2,4-bis(trifluoromethyl)benzenesulfonamide, 2-methyl-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-(trifluoromethoxy)benzenesulfonamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-phenoxybenzenesulfonamide, 4-chloro-2,6-dimethyl-N-[4-(2-m- orpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 2,4-dichloro-N-[4-(2-morpholin-4-yl-2-oxothyl)thien-3-yl]benzenesufonamide, tert-butyl 4-[(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)acetyl]piperazine-1-carboxylate, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)-N,N-dimethylacetamide, 3-chloro-2-methyl-N-{4-[2-(pyridin-3-yloxy)ethyl]thien-3-yl}benzenesulfonamide, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)-N-isopropyl-N-methylacetamide, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)-N-ethyl-N-methylacetamide, 3-

chloro-2-methyl-N-[4-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, 3-chloro-2-methyl-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)-N,N-diisopropylacetamide, 3-chloro-2-methyl-N-[4-(2-oxo-2-pyrrolidin-1-ylethyl)thien-3-yl]benzenesulfonamide, 3-chloro-2-methyl-N-[4-(2-oxo-2-piperidin-1-ylethyl)thien-3-yl]benzenesulfonamide, 3-chloro-2-methyl-N-[4-(morpholin-4-ylmethyl)thien-3-yl]benzenesulfonamide, 3-chloro-N-{4-[2-(1H-imidazol-1-yl)ethyl]thien-3-yl}-2-methylbenzenesulfonamide, 2,4,5-trichloro-N-(3-chloro-2,3'-bithien-4'-yl)benzenesulfonamide 2,3,4-trichloro-N-(3-chloro-2,3'-bithien-4'-yl)benzenesulfonamide, 2,3,4-trichloro-N-[4-(2-chlorophenyl)thien-3-yl]benzenesulfonamide, N-[4-(4-{[(4-bromo-2,5-difluorophenyl)sulfonyl]amino}thien-3-yl)phenyl]acetamide, 4-bromo-N-(3-chloro-2,3'-bithien-4'-yl)-2,5-difluorobenzenesulfonamide, 4,5-dichloro-N-[4-(2-chlorophenyl)thien-3-yl]thiophene-2-sulfonamide, N-[4-(4-{[(2,4,5-trichlorophenyl)sulfonyl]amino}thien-3-yl)phenyl]acetamide, 4-bromo-5-chloro-N-(3-chloro-2,3'-bithien-4'-yl)thiophene-2-sulfonamide, 3-bromo-5-chloro-N-[4-(2-chlorophenyl)thien-3-yl]thiophene-2-sulfonamide, N-[4-(4-{[(2,6-dichlorophenyl)sulfonyl]amino}thien-3-yl)phenyl]acetamide, 2,6-dichloro-N-(3-chloro-2,3'-bithien-4'-yl)benzenesulfonamide, N-[2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl]acetamide, 3-chloro-2-methyl-N-(4-{2-[(methylsulfonyl)amino]ethyl}thien-3-yl)benzenesulfonamide, 3-chloro-2-methyl-N-{4-[2-(3-oxo-1,4-oxazepan-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 3-chloro-2-methyl-N-{4-[2-(2-oxopyrrolidin-1-yl)ethyl]thien-3-yl}benzenesulfonamide, 2,3,4-trichloro-N-{4-[2,6-dichloro-4-(trifluoromethyl)phenyl]thien-3-yl}benzenesulfonamide, N-[4-(2-chloro-6-fluorophenyl)thien-3-yl]-4-propylbenzenesulfonamide, 4-bromo-N-{4-[2,6-dichloro-4-(trifluoromethyl)phenyl]thien-3-yl}-2,5-difluorobenzenesulfonamide, 4,5-dichloro-N-[4-(2-chloro-6-fluorophenyl)thien-3-yl]thiophene-2-sulfonamide, 4-bromo-5-chloro-N-{4-[2,6-dichloro-4-(trifluoromethyl)phenyl]thien-3-yl}thiophene-2-sulfonamide, 2,4-dichloro-N-[4-(2-chloro-6-fluorophenyl)thien-3-yl]-6-methylbenzenesulfonamide, 4-bromo-N-[4-(2-chloro-6-fluorophenyl)thien-3-yl]-2-methylbenzenesulfonamide, 3-chloro-2-methyl-N-(4-{2-[methyl(methylsulfonyl)amino]ethyl)thien-3-yl)benzenesulfonamide, N-[2-

(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl]-N-methylcyclopropanecarboxamide, 3-chloro-2-methyl-N-{4-[2-(4-methyl-2-oxopiperazin-1-yl)ethyl]thien-3-yl}benzenesulfonamide, 3-chloro-2-methyl-N-[4-(2-{[(trifluoromethyl)sulfonyl]amino}ethyl)thien-3-yl]benzenesulfonamide, N-[4-(4-{[(4-bromo-5-chlorothien-2-yl)sulfonyl]amino}thien-3-yl)phenyl]acetamide, 2,4-dichloro-N-{4-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 2,4-dichloro-6-methyl-N-{4-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 2,4,6-trichloro-N-{4-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 4-(2-furyl)-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 5'-fluoro-2'-methoxy-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, 4-(5-methylthien-2-yl)-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 3'-acetyl-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4'-(trifluoromethoxy)-1,1'-biphenyl-4-sulfonamide, 3',4'-dichloro-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, 4-(1,3-benzodioxol-5-yl)-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 4-(5-chlorothien-2-yl)-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-pyridin-4-ylbenzenesulfonamide, N-[4'-({[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]amino}sulfonyl)-1,1'-biphenyl-3-yl]acetamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-thien-3-ylbenzenesulfonamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-thien-2-ylbenzenesulfonamide, 4'-(methylthio)-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-3',5'-bis(trifluoromethyl)-- 1,1'-biphenyl-4-sulfonamide, 4'-chloro-N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[4-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-3'-nitro-1,1'-biphenyl-4-sulfonamide, 3-chloro-2-methyl-N-[4-(2-{methyl[(trifluoromethyl)sulfonyl]amino}ethyl)thien-3-yl]benzenesulfonamide, N-[2-(4-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-3-yl)ethyl]-1-methyl-1H-imidazole-4-sulfonamide, 3-chloro-N-{4-[2-(2-hydroxy-3-oxomorpholin-4-yl)ethyl]thien-3-yl}-2-methylbenzenesulfonamide, 4,5-dichloro-N-{4-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}thiophene-2-sulfonamide, N-{4-[2-(3-

oxomorpholin-4-yl)ethyl]thien-3-yl}-4-phenoxybenzenesulfonamide, 3-fluoro-N-{4-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}benzenesulfonamide, N-{4-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}-5-pyridin-2-ylthiophene-2-sulfonamide, N-{2-chloro-4-[({4-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}amino)sulfonyl]phenyl}acetamide, ethyl (3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)acetate, (3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)acetic acid, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)-N-methylacetamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)-N-ethylacetamide, 2,5-dichloro-N-(3'-chloro-2,2'-bithien-3-yl)benzenesulfonamide, isopropyl (3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)acetate, 3-chloro-N-[2-(2-hydroxyethyl)thien-3-yl]-2-methylbenzenesulfonamide, 3-chloro-N-[2-(2-ethoxyethyl)thien-3-yl]-2-methylbenzenesulfonamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)-N,N-diethylacetamide, methyl (3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)acetate, 3-chloro-N-[2-(2-isopropoxyethyl)thien-3-yl]-2-methylbenzenesulfonamide, 3-chloro-N-[2-(2-methoxyethyl)thien-3-yl]-2-methylbenzenesulfonamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl methanesulfonate, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)acetamide, 3-chloro-N-{2-[2-(2-fluoroethoxy)ethyl]thien-3-yl}-2-methylbenzenesulfonamide 3-chloro-2-methyl-N-{2-[2-(2,2,2-trifluoroethoxy)ethyl]thien-3-yl}benzenesulfonamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl acetate, 3-chloro-2-methyl-N-[2-(2-morpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, N-[2-(2-bromoethyl)thien-3-yl]-3-chloro-2-methylbenzenesulfonamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl morpholine-4-carboxylate, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl diethylcarbamate, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl propionate 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl 2-methylpropanoate, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl 2-furoate, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl benzoate, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)-N-methoxy-N-methylacetamide, 3-chloro-N-{2-[2-(diethylamino)ethyl]thien-3-yl}-2-methylbenzenesulfonamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl

ethylcarbamate, N-[2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl]-N-ethylacetamide, 3-chloro-2-methyl-N-[2-(2-oxopentyl)thien-3-yl]benzenesulfonamide, N-{2-[2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethyl]thien-3-yl}-4-propylbenzenesulfonamide, 2,4,6-trichloro-N-[2-(2-morpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, 2,4-dichloro-N-[2-(2-morpholin-4-ylethyl)thien-3-yl]benzenesulfonamide 3-chloro-2-methyl-N-{2-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 2,4-dichloro-6-methyl-N-[2-(2-morpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, N-[2-(2-morpholin-4-ylethyl)thien-3-yl]-4-propylbenzenesulfonamide, 2,4-dichloro-6-methyl-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 2,4,6-trichloro-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-propylbenzenesulfonamide, N-[2-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[2-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]-4-propylbenzenesulfonamide, 2,4-dichloro-6-methyl-N-[2-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, N-[2-(2-oxo-2-piperidin-1-ylethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[2-(2-oxo-2-piperidin-1-ylethyl)thien-3-yl]-4-propylbenzenesulfonamide, 2,4-dichloro-6-methyl-N-[2-(2-oxo-2-piperidin-1-ylethyl)thien-3-yl]benzenesulfonamide, 2,4,6-trichloro-N-[2-(2-oxo-2-piperidin-1-ylethyl)thien-3-yl]benzenesulfonamide, N-(2-phenylthien-3-yl)-4-propylbenzenesulfonamide, ethyl (3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)(oxo)acetate, 3-chloro-2-methyl-N-(2-phenylthien-3-yl)benzenesulfonamide, 3-chloro-N-[2-(4-fluoro-3-methylphenyl)thien-3-yl]-2-methylbenzenesulfonmide, 2,4,6-trichloro-N-(2-phenylthien-3-yl)benzenesulfonamide, N-(2-phenylthien-3-yl)-1,1'-biphenyl-4-sulfonamide 2,4-dichloro-6-methyl-N-(2-phenylthien-3-yl)benzenesulfonamide, 2-{3-[(1,1'-biphenyl-4-ylsulfonyl)amino]thien-2-yl}-N-ethyl-N-methylacetamide, N-ethyl-N-methyl-2-(3-{[(4-propylphenyl)sulfonyl]amino}thien-2-yl)acetamide, 2-(3-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}thien-2-yl)-N-ethyl-N-methylacetamide, N-ethyl-N-methyl-2-(3-{[(2,4,6-trichlorophenyl)sulfonyl]amino}thien-2-yl)acetamide, 2,4,6-trichloro-N-[2-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]benzenesulfonamide 2-{3-[(1,1'-biphenyl-4-ylsulfonyl)amino]thien-2-yl}-N-

isopropyl-N-methylacetamide, 2-{3-[(1,1'-biphenyl-4-ylsulfonyl)amino]thien-2-yl}-N,N-diethylacetamide, N,N-diethyl-2-(3-{[(4-propylphenyl)sulfonyl]amino}thien-2-yl)acetamide, 2-(3-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}thien-2-yl)-N,N-diethylacetamide, N,N-diethyl-2-(3-{[(2,4,6-trichlorophenyl)sulfonyl]amino}thien-2-yl)acetamide, 2-{3-[(1,1'-biphenyl-4-ylsulfonyl)amino]thien-2-yl}-N,N-diisopropylacetamide, N,N-diisopropyl-2-(3-{[(4-propylphenyl)sulfonyl]amino}thien-2-yl)acetamide, 2-(3-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}thien-2-yl)-N,N-diisopropylacetamide, N,N-diisopropyl-2-(3-{[(2,4,6-trichlorophenyl)sulfonyl]amino}thien-2-yl)acetamide, N-[4-(3-{[(4-propylphenyl)sulfonyl]amino}thien-2-yl)phenyl]acetamide, 4-propyl-N-(2-pyridin-3-ylthien-3-yl)benzenesulfonamide, N-[2-(2-chloro-5-nitrophenyl)thien-3-yl]-4-propylbenzenesulfonamide, N-[2-(2-chlorophenyl)thien-3-yl]-4-propylbenzenesulfonamide, 3-chloro-N-[2-(2-chloro-5-nitrophenyl)thien-3-yl]-2-methylbenzenesulfonamide, 3-chloro-N-(5'-chloro-2,2'-bithien-3-yl)-2-methylbenzenesulfonamide, 3-chloro-N-[2-(2-chlorophenyl)thien-3-yl]-2-methylbenzenesulfonamide, N-[4-(3-{[(2,4,6-trichlorophenyl)sulfonyl]amino}thien-2-yl)phenyl]acetamide, 2,4,6-trichloro-N-(2-pyridin-3-ylthien-3-yl)benzenesulfonamide, 2,4,6-trichloro-N-[2-(2-chloro-5-nitrophenyl)thien-3-yl]benzenesulfonamide, 2,4,6-trichloro-N-(5'-chloro-2,2'-bithien-3-yl)benzenesulfonamide, 2,4,6-trichloro-N-[2-(2-chlorophenyl)thien-3-yl]benzenesulfonamide, N-(4-{3-[(1,1'-biphenyl-4-ylsulfonyl)amino]thien-2-yl}phenyl)acetamide, N-(2-pyridin-3-ylthien-3-yl)-1,1'-biphenyl-4-sulfonamide, N-[2-(2-chloro-5-nitrophenyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[2-(2-chlorophenyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[4-(3-{[(2,4-dichloro-6-methylphenyl)sulfonyl]amino}thien-2-yl)phenyl]acetamide 2,4-dichloro-6-methyl-N-(2-pyridin-3-ylthien-3-yl)benzenesulfonamide, 2,4-dichloro-N-[2-(2-chloro-5-nitrophenyl)thien-3-yl]-6-methylbenzenesulfonamide, 2,4-dichloro-N-(5'-chloro-2,2'-bithien-3-yl)-6-methylbenzenesulfonamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)-N,N-dipropylacetamide, 3-chloro-2-methyl-N-[2-(2-oxo-2-piperazin-1-ylethyl)thien-3-yl]benzenesulfonamide, 2,4-dichloro-N-[2-(2,5-dimethyl-3-furyl)thien-3-yl]-6-methylbenzenesulfonamide, N-(3'-chloro-2,2'-bithien-3-yl)-4-propylbenzenesulfonamide, 3-chloro-N-(3'-chloro-2,2'-bithien-3-yl)-2-methylbenzenesulfonamide, 2,4,6-trichloro-N-(3'-

chloro-2,2'-bithien-3-yl)benzenesulfonamide, 2,4-dichloro-N-(3'-chloro-2,2'-bithien-3-yl)-6-methylbenzenesulfonamide, 2,4-dichloro-N-[2-(2-chlorophenyl)thien-3-yl]-6-methylbenzenesulfonamide, 4-bromo-2-methyl-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-2,4-bis(trifluoromethyl)benzenesulfonamide, 2-methyl-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-(trifluoromethoxy)benzenesulfonamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-phenoxybenzenesulfonamide, 4-chloro-2,6-dimethyl-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 2,4-dichloro-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, tert-butyl 4-[(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)- acetyl]piperazine-1-carboxylate, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)-N,N-dimethylacetamide, 3-chloro-2-methyl-N-{2-[2-(pyridin-3-yloxy)ethyl]thien-3-yl}benzenesulfonamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)-N-isopropyl-N-methylacetamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)-N-ethyl-N-methylacetamide, 3-chloro-2-methyl-N-[2-(2-oxo-2-thiomorpholin-4-ylethyl)thien-3-yl]benzenesulfonamide, 3-chloro-2-methyl-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)-N,N-diisopropylacetamide, 3-chloro-2-methyl-N-[2-(2-oxo-2-pyrrolidin-1-ylethyl)thien-3-yl]benzenesulfonamide, 3-chloro-2-methyl-N-[2-(2-oxo-2-piperidin-1-ylethyl)thien-3-yl]benzenesulfonamide, 3-chloro-2-methyl-N-[2-(morpholin-4-ylmethyl)thien-3-yl]benzenesulfonamide, 3-chloro-N-{2-[2-(1H-imidazol-1-yl)ethyl]thien-3-yl}-2-methylbenzenesulfonamide, 2,4,5-trichloro-N-(3'-chloro-2,2'-bithien-3-yl)benzenesulfonamide 2,3,4-trichloro-N-(3'-chloro-2,2'-bithien-3-yl)benzenesulfonamide 2,3,4-trichloro-N-[2-(2-chlorophenyl)thien-3-yl]benzenesulfonamide, N-[4-(3-{[(4-bromo-2,5-difluorophenyl)sulfonyl]amino}thien-2-yl)phenyl]acetamide, 4-bromo-N-(3'-chloro-2,2'-bithien-3-yl)-2,5-difluorobenzenesulfonamide, 4,5-dichloro-N-[2-(2-chlorophenyl)thien-3-yl]thiophene-2-sulfonamide N-[4-(3-{[(2,4,5-trichlorophenyl)sulfonyl]amino}thien-2-yl)phenyl]acetamide, 4-bromo-5-chloro-N-(3'-chloro-2,2'-bithien-3-yl)thiophene-2-sulfonamide, 3-bromo-5-chloro-N-[2-

(2-chlorophenyl)thien-3-yl]thiophene-2-sulfonamide, N-[4-(3-{[(2,6-dichlorophenyl)sulfonyl]amino}thien-2-yl)phenyl]acetamide, 2,6-dichloro-N-(3'-chloro-2,2'-bithien-3-yl)benzenesulfonamide, N-[2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl]acetamide, 3-chloro-2-methyl-N-(2-{2-[(methylsulfonyl)amino]ethyl}thien-3-yl)benzenesulfonamide, 3-chloro-2-methyl-N-{2-[2-(3-oxo-1,4-oxazepan-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 3-chloro-2-methyl-N-{2-[2-(2-oxopyrrolidin-1-yl)ethyl]thien-3-yl}benzenesulfonamide, 2,3,4-trichloro-N-{2-[2,6-dichloro-4-(trifluoromethyl)phenyl]thien-3-yl}benzenesulfonamide, N-[2-(2-chloro-6-fluorophenyl)thien-3-yl]-4-propylbenzenesulfonamide 4-bromo-N-{2-[2,6-dichloro-4-(trifluoromethyl)phenyl]thien-3-yl}-2,5-difluorobenzenesulfonamide, 4,5-dichloro-N-[2-(2-chloro-6-fluorophenyl)thien-3-yl]thiophene-2-sulfonamide, 4-bromo-5-chloro-N-{2-[2,6-dichloro-4-(trifluoromethyl)phenyl]thien-3-yl}thiophene-2-sulfonamide, 2,4-dichloro-N-[2-(2-chloro-6-fluorophenyl)thien-3-yl]-6-methylbenzenesulfonamide, 4-bromo-N-[2-(2-chloro-6-fluorophenyl)thien-3-yl]-2-methylbenzenesulfonamide, 3-chloro-2-methyl-N-(2-{2-[methyl(methylsulfonyl)amino]ethyl}thien-3-yl)benzenesulfonamide, N-[2-(3-[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl]-N-methylcyclopropanecarboxamide, 3-chloro-2-methyl-N-{2-[2-(4-methyl-2-oxopiperazin-1-yl)ethyl]thien-3-yl}benzenesulfonamide, 3-chloro-2-methyl-N-[2-(2-{[(trifluoromethyl)sulfonyl]amino}ethyl)thien-3-yl]benzenesulfonamide, N-[4-(3-{[(4-bromo-5-chlorothien-2-yl)sulfonyl]amino}thien-2-yl)phenyl]acetamide, 2,4-dichloro-N-{2-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 2,4-dichloro-6-methyl-N-{2-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 2,4,6-trichloro-N-{2-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}benzenesulfonamide, 4-(2-furyl)-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 5'-fluoro-2'-methoxy-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, 4-(5-methylthien-2-yl)-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, 3'-acetyl-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4'-(trifluoromethoxy)-1,1'-biphenyl-4-sulfonamide, 3',4'-dichloro-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, 4-(1,3-benzodioxol-5-yl)-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-

yl]benzenesulfonamide, 4-(5-chlorothien-2-yl)-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]benzenesulfonamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-pyridin-4-ylbenzenesulfonamide, N-[4'-({[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]amino}sulfonyl)-1,1'-biphenyl-3-yl]acetamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-thien-3-ylbenzenesulfonamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-4-thien-2-ylbenzenesulfonamide, 4'-(methylthio)-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-3',5'-bis(trifluoromethyl)-1,1'-biphenyl-4-sulfonamide, 4'-chloro-N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-1,1'-biphenyl-4-sulfonamide, N-[2-(2-morpholin-4-yl-2-oxoethyl)thien-3-yl]-3'-nitro-1,1'-biphenyl-4-sulfonamide, 3-chloro-2-methyl-N-[2-(2-{methyl[(trifluoromethyl)sulfonyl]amino}ethyl)thien-3-yl]benzenesulfonamide, N-[2-(3-{[(3-chloro-2-methylphenyl)sulfonyl]amino}thien-2-yl)ethyl]-1-methyl-1H-imidazole-4-sulfonamide, 3-chloro-N-{2-[2-(2-hydroxy-3-oxomorpholin-4-yl)ethyl]thien-3-yl}-2-methylbenzenesulfonamide, 4,5-dichloro-N-{2-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}thiophene-2-sulfonamide, N-{2-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}-4-phenoxybenzenesulfonamide, 3-fluoro-N-{2-[2-(3-oxomorpholin-4-yl)ethyl]-thien-3-yl}benzenesulfonamide, N-{2-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}-5-pyridin-2-ylthiophene-2-sulfonamide, N-{2-chloro-4-[({2-[2-(3-oxomorpholin-4-yl)ethyl]thien-3-yl}amino)sulfonyl]phenyl}acetamide, methyl (3-{[(5-fluoro-2-methylphenyl)sulfonyl]amino}thien-2-yl)acetate, methyl (3-{[(3-cyanophenyl)sulfonyl]amino}thien-2-yl)acetate, methyl (3-{[(4-butoxyphenyl)sulfonyl]amino}thien-2-yl)acetate, methyl (3-{[(2-methylsulfanylpyrimidin-4-ylthiophene)sulfonyl]amino}thien-2-yl)acetate, methyl (3-{[(1-methylimidazol-4-yl)sulfonyl]amino}thien-2-yl)acetate, methyl (3-{[(4-methylphenyl)sulfonyl]amino}thien-2-yl)acetate, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0041] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is a compound described in U.S. Patent Application Publication No.

2005/0070720. In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is selected from the group consisting of

3-(1-admantyl)-5-(cyanomethyl)-6,6-8-methyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-5,6-diahydro[1,2,4]triazolo[3,4-a]isoquinoline;

3-(1-adamantyl)-8-benzyl-5,6,7,8-tetahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-9-methoxy-5, 6,11,12-tetrahydro-5,12-ethano[1,2,4]triazolo [4,3-c][3]benzazocine;

(+/-)(6aRS,12aSR)-3-(1-adamantyl)-5,6,6a,12a-tetrahydro[1,4]benzodioxino[2,3-c][1,2,4]triazolo[4,3-a]pyridine;

1-(1-adamantyl)-5,5a,6,7,9,9a-hexahydro[1,2,4]triazolo[4,3-a]quinolin-8(4H)-one ethylene ketal;

3-(1-adamantyl)-8-methyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-admnantyl)-6-methyl-6-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyidine;

3-(1-adamantyl)-6-(4-chlorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-6-(2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-8-methyl-6-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-6-(4-fluorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-6-(2-chlorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-6-(1,1'-biphenyl-4-yl)-6-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-6-(1,1'-biphenyl-4-yl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-6-(2,6-dichlorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1 -adamantyl)-6,7-diphenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-6-cyclohexyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyzidine;

3-(1-adamantyl)-7-phenyl-5,6,7,8-tedahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-5,6-diphenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-6-(ethoxycarbonyl)-5,6,7,9-tetrabydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-5-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-6,6-diphenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-5-methyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-7-tert- butyl-5,6,7,8-tetxahydro [1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-8-(3,4methoxybenzyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-9-chloro-5,6-diliydro[1,2,4]triazolo[3,4-a]isoquinoline;

3-(1-adamantyl)-7-benzyl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-d][1,4]diazepine;

(5aR,9aS)-3-(1-adamantyl)-5,5a,6,7,9a,10-hexahydro[1,2,4]triazolo[4,3-b]isoquinolin-8(9H)-one ethylene ketal;

3-(1-adamantyl)-8-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-adamantyl)-8-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-[(3,5,7-trimethyl-1-adamantyl)methyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(1-admlantyl)-5,6,7,8,9,10-hexahydro[1,2,4]triazolo[4,3-a]azocine;

3-(3,5-dimethyl-1-adamantyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole;

3-(1-adamantylmethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-(3,5-dimethyl-1-adamantyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine;

3-[(3,5,7-trimethyl-1-adamantyl)methyl]-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-(3,5-dimethyl-1-adamantyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-(1-adamantylmetyl)-5,6,7,8,9,10-hexahydro[1,2,4]triazolo[4,3-a]azocine;

3-(3,5,7-trimethyl-1-adamantyl-1-methyl]-5,6,7 8,9,10-hexahydro[1,2,4]triazolo[4,3-a]azocine;

3-(3,5-dimemyl-1-adamantyl)-5,6,7,8,9,10-hexahydro[1,2,4]triazolo[4,3-a]azocine;

3-(1-adamantyl)-6,7,8,9,10,11-hexahydro-5H-[1,2,4]triazolo[4,3-a]azonine;

3-(1-adamantylmethyl)-6,7,8,9,10,11-hexahydro-5H-[1,2,4]triazolo[4,3-a]azonine;

3-[(3,5,7-trimefhyl-1-adamantyl)methyl]-6,7,8,9,10,11-hexahydro-5H-[1,2,4]triazolo[4,3-a]azonine;

3-(3,5-dimethyl-1-adamantyl)-6,7,8,9,10,11-hexahydro-5H-[1,2,4]triazolo[4,3-a]azonine;

3-(1-adamantyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-b][1,3]thiazepine;

3-(1-adamantyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4b][1,3,4]thiadiazepine;

3-(1-adamantyl)-6,7,8,9-tetrahydra-5H-[1,2,4] triazolo[3,4-b][1,3]thiazocine;

3-[(3,5-dimethyl-1-adamantyl)methyl]-6,7,8,9,10,11-hexahydro-5H-[1,2,4]triazolo[4,3-a]azonine;

3-(1-adamantylmethyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-(1-adamantyl)-9-fluoro-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-(3,5,7-trimethyl-1-adamantyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)adamantan-1-ol;

3-(3-fluoro-1-adamantyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-[2-(1-adamantyl)ethyl]-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-(3-bromo-1-adamantyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-(3-phenyl-1-adamantyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-(1-adamantyl)-6,7,8,9,10,11,12,13-octahydro-5H-[1,2,4]triazolo[4,3-a]azacycloundecine;

3-(1-adamantyl)-5,6,7,8,9,10,11,12,13,14-decahydro[1,2,4]triazolo[4,3-a]azacyclododecine;

3-(1-admnantyl)-5,6,7,8,9,10,11,12-octahydro[1,2,4]triazolo[4,3-a]azecine;

3-(1-adamantyl)-7-tert-butyl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine;

3-(1-adamantyl)-6,8,8-trimethyl-8,9-dihydro-7H-[1,2,4]triazolo[4,3-a]azepine;

1-(1-adamantyl)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1]benzazepine;

3-(1-adamantyl)-10,11-dihydro-5H-[1,2,4]triazolo[4,3-b][2]benzazepine;

3-(1-adamantyl)-6,6,8-trimethyl-6,7,8,9-tetrahydro-5H-5,7-methano[1,2,4]triazolo[4,3-a]azepine;

3-(1-adamantyl)-5,7a,8,8a-tetrahydro-5,8-ethenocyclopropa[c][1,2,4]tnazolo[4,3-a]azepine;

3-(1-adamantyl)-6,9-dihydro-5H-[1,2,4]triazolo[4,3-a]azepine;

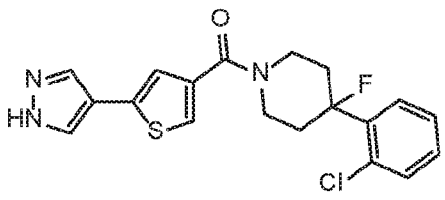
3-(1-adamantyl)-6,7,8,9,10,11-hexahydro-5H-5,9:7,11-dimethano[1,2,4]triazolo[4,3-a]azonine;

3-(1-adamantyl)-7-phenyl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine; and

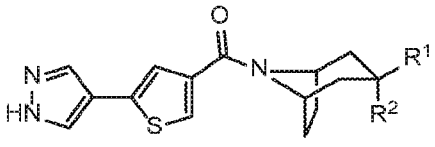
3-adamantanyl-4H,5H,8H,9H-1,2,4-triazolo[4,3-a]azocine;

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0042] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is UE-2343 or UE-2316, of the formula:



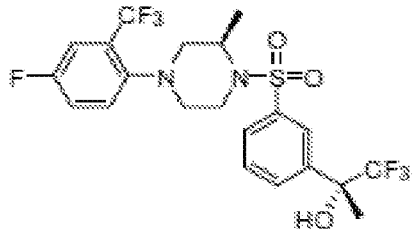
UE-2316



UE-2343

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0043] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is HSD-016, of the formula



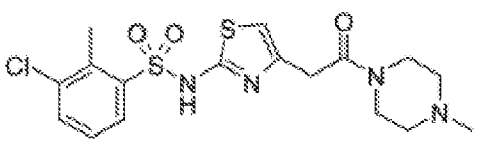
or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0044] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is a compound described in 11β-HSD1 Inhibitors for the Treatment of Type 2 Diabetes and Cardiovascular Disease, Anderson and Walker, Drugs, 2013, 73(13):1385–1393.

[0045] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is INCB-13739 or MK-0916.

[0046] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is selected from those described in Scott, Medicinal Chemistry of Inhibitors of 11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1), J. Med. Chem. 2014, 57:4466–4486.

[0047] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is selected from:



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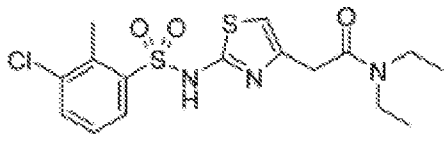

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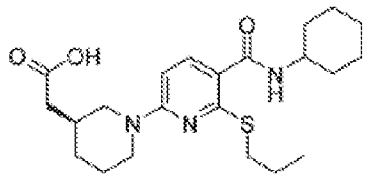

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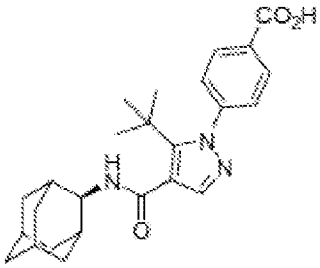

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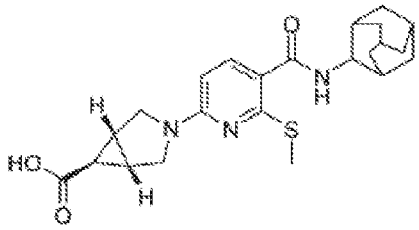

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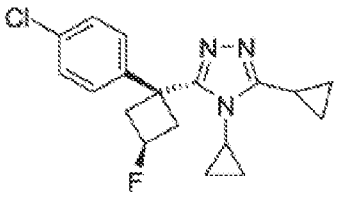

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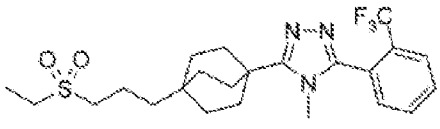

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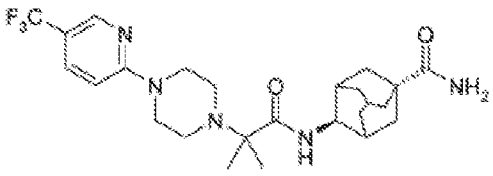

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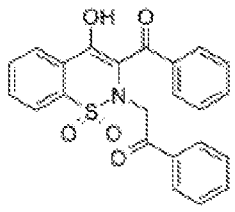

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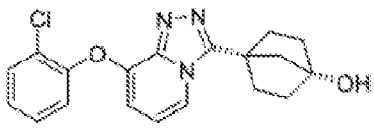
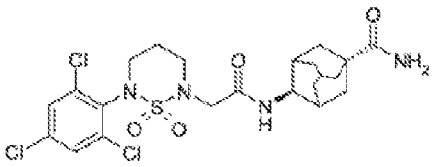
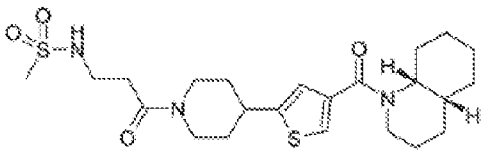


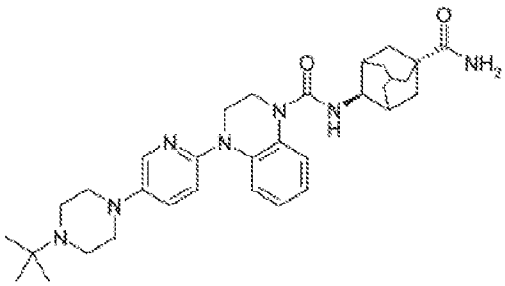
(BMS-770767),



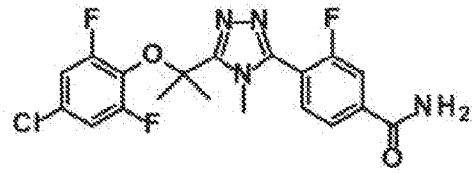
(KR-67183),



(UE1961),



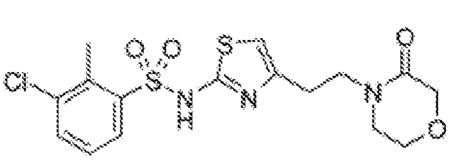
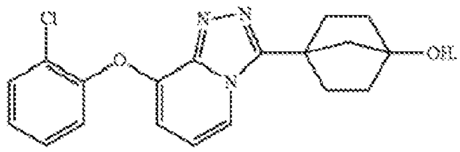
(SAR184841), and

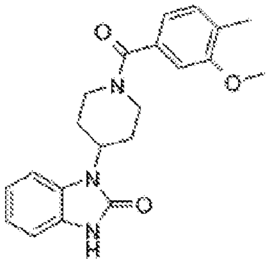
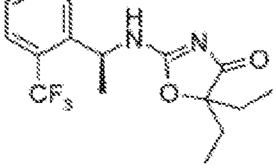
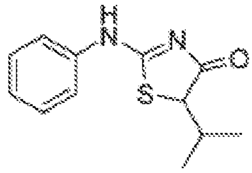


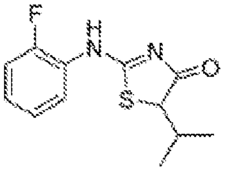
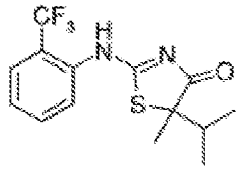
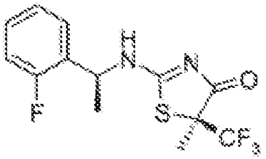
ASP3662.

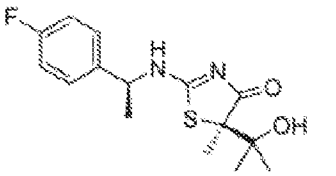
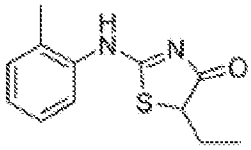
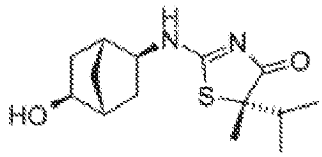
or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

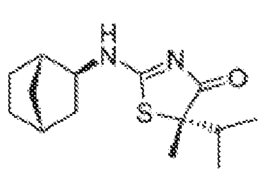
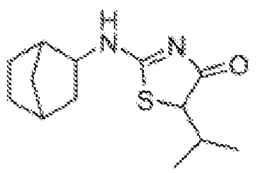
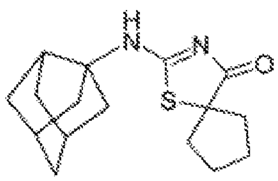
[0048] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is selected from:

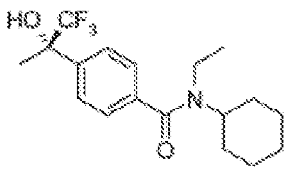
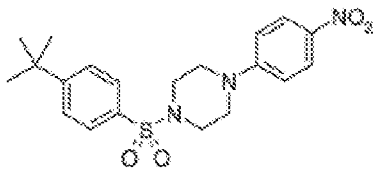
 ,  ,

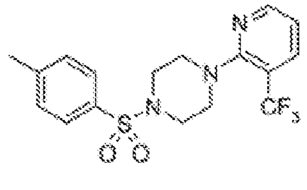
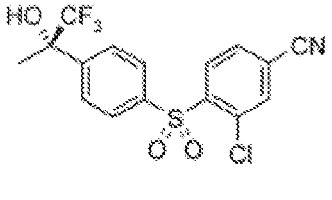
 ,  ,  ,

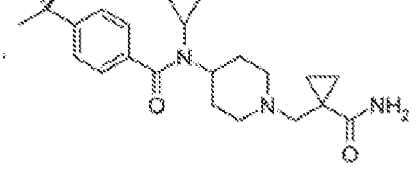
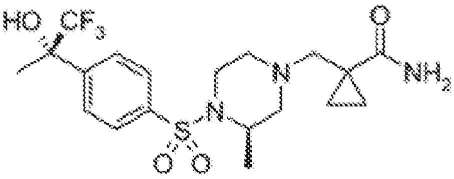
 ,  ,  ,

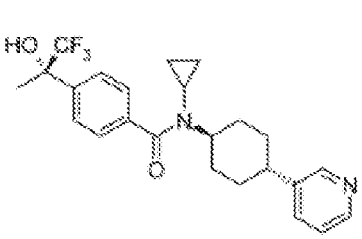
 ,  , 

,  ,  ,  ,

 ,  ,

 ,  ,

 ,  ,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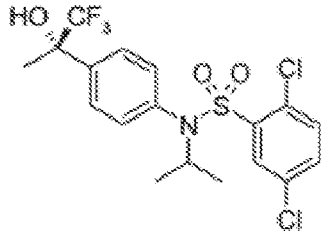
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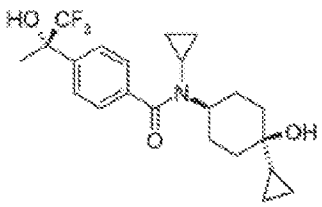
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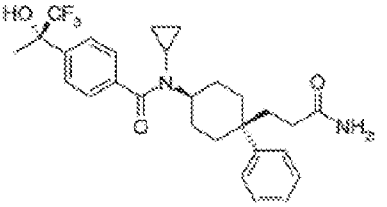
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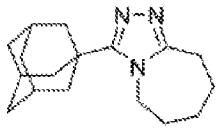
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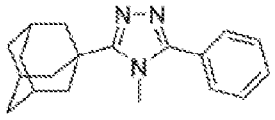
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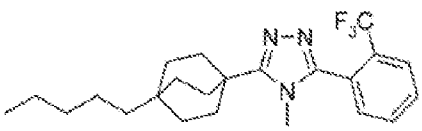
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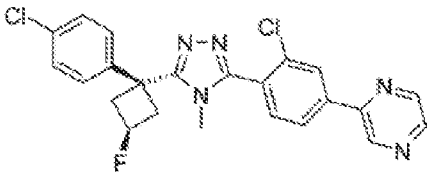
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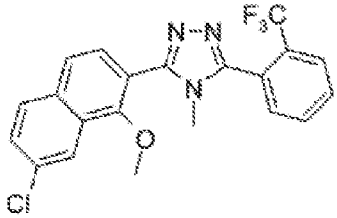
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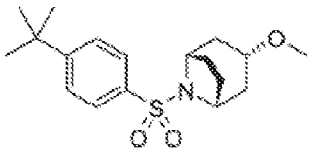
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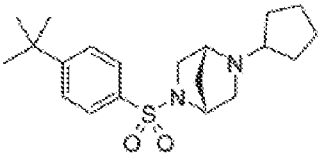
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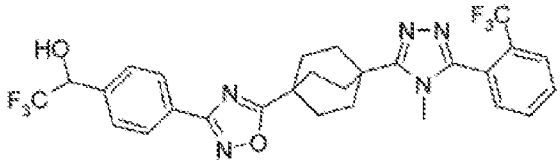
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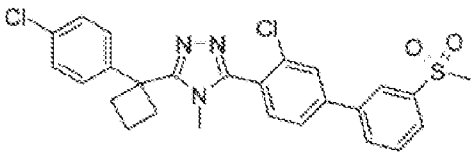
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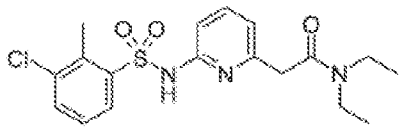
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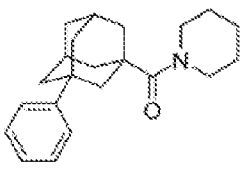
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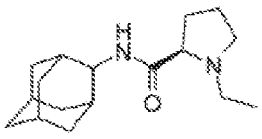
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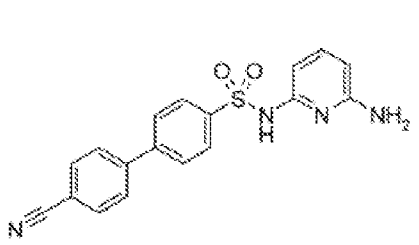
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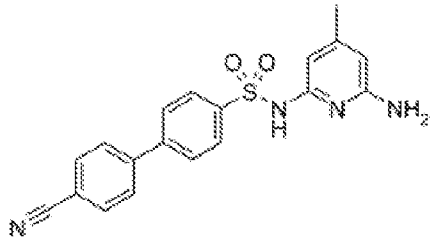
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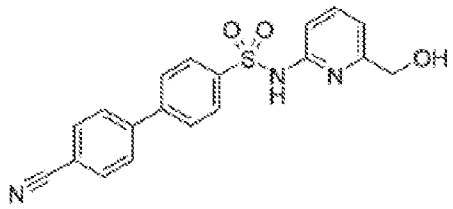
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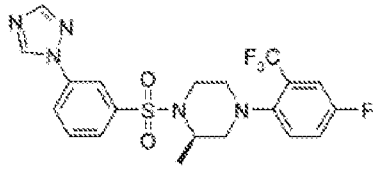
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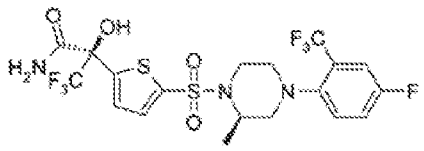
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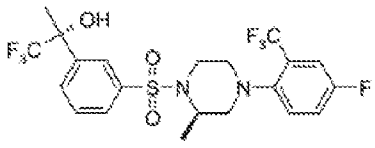
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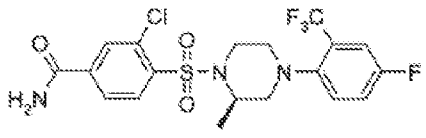
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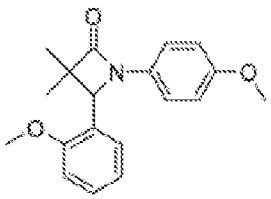
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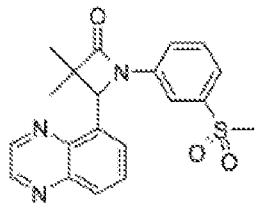
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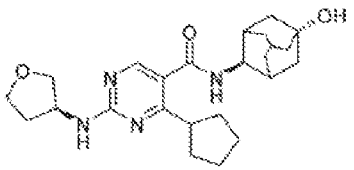
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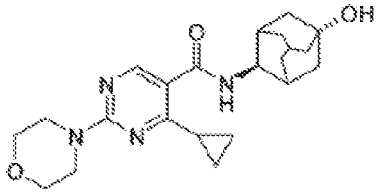
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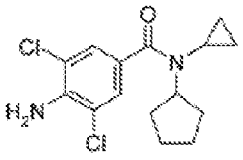
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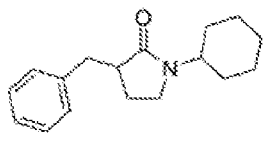
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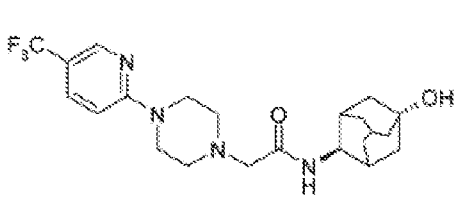
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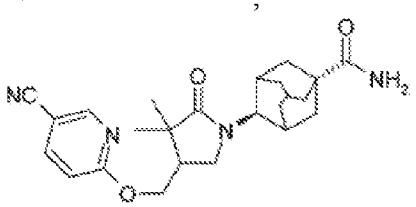
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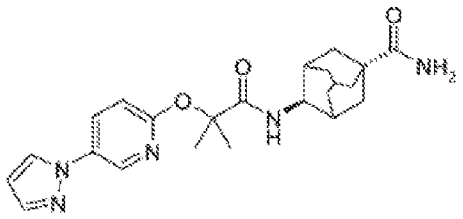
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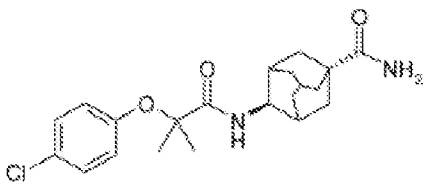
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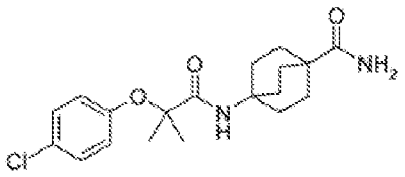
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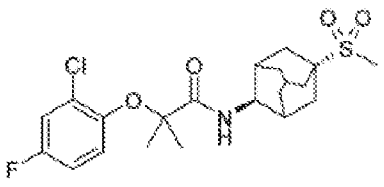
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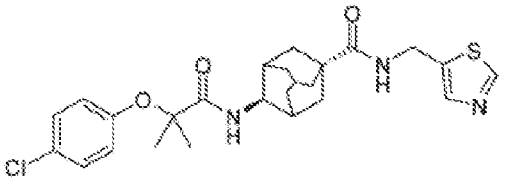
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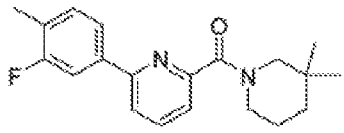
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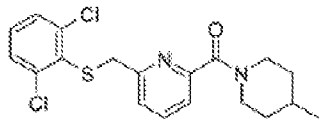
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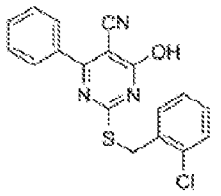
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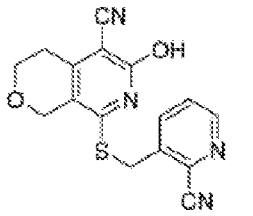
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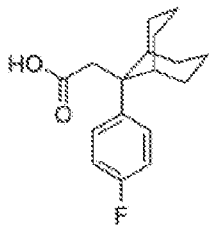
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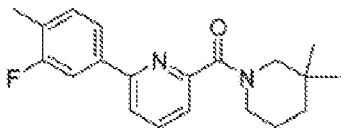
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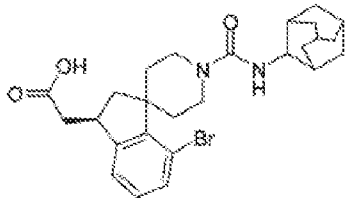
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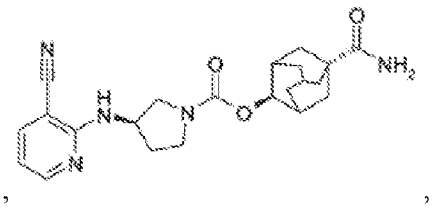
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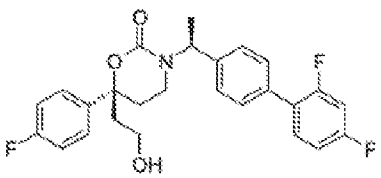
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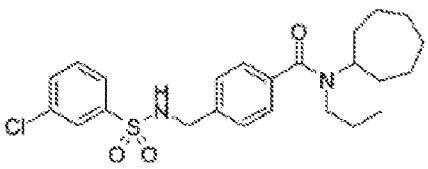
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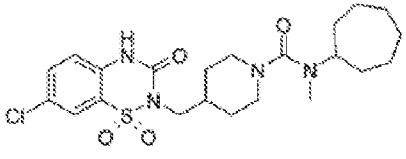
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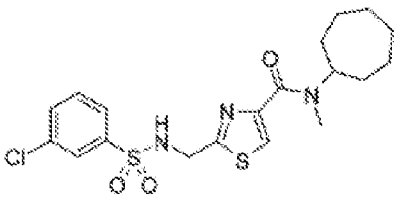
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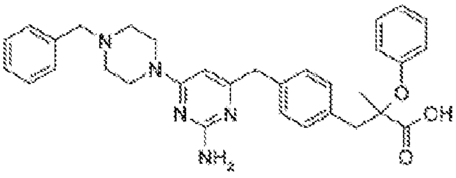
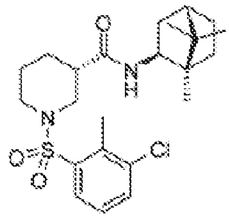
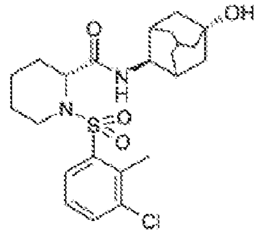
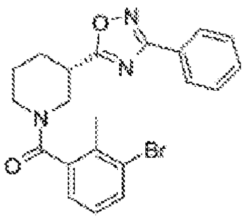
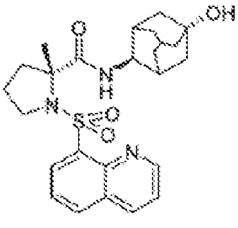
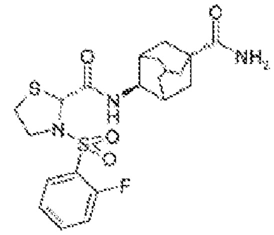
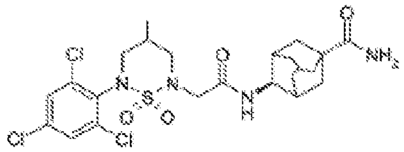
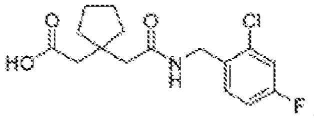
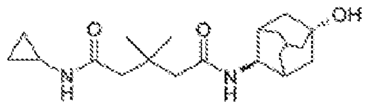
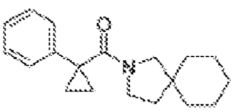
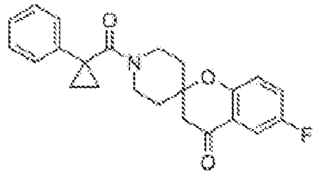
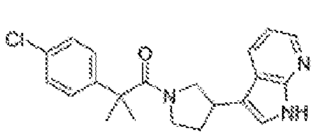
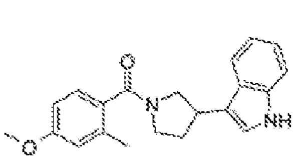
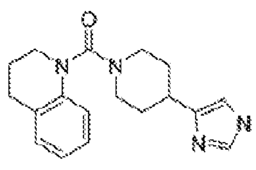
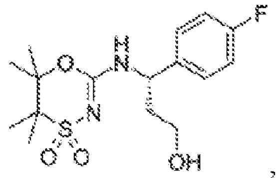
 ,  ,

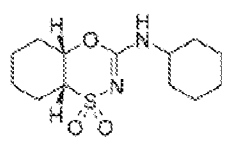
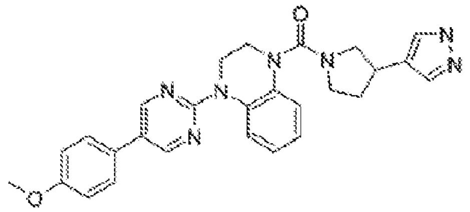
 ,  ,  ,

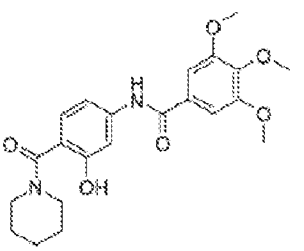
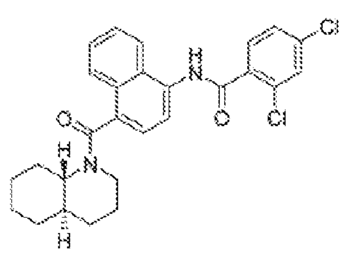
 ,  ,

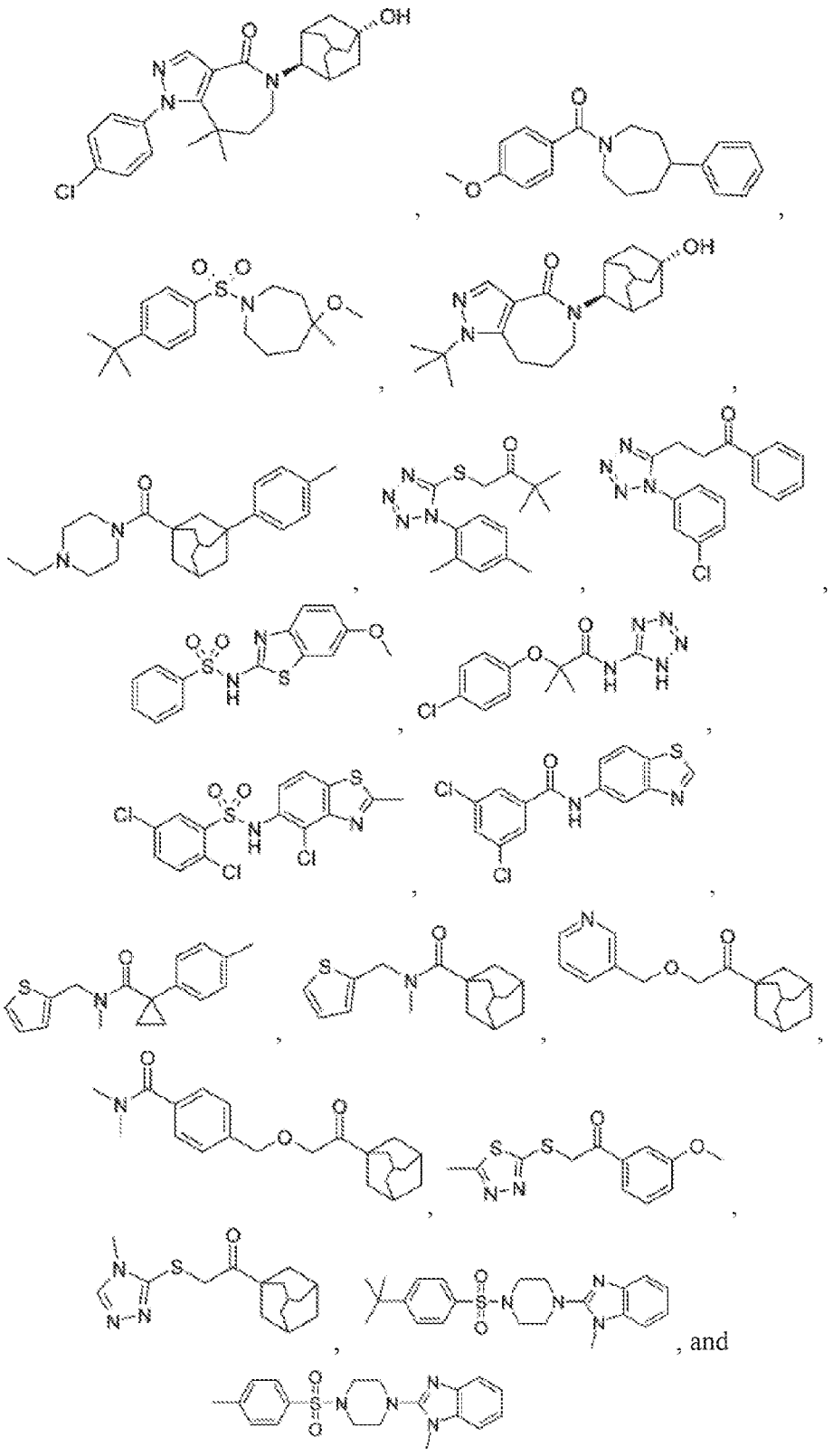
 ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,

 ,  ,



or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0049] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is a compound described in U.S. Patent Application Publication Nos. 20040048912, 20060079506, 20080096869, 20080108598, 20080108598, 20070066614, 20050009821, 20050227987, 20080153893, 20040138258, 20050227987, 20040106664, 20040133011, 20050239853, 20070244108, 20050245745, 20050245532, 20150183735, 20070287743, 20110082107, 20070281938, 20080318930, 20140179732, 20080064693, 20080214597, 20080064693, 20070259854, 2009010528, 20050245533, 20080275043, 20050154038, 20080214621, 20080207691, 20060149070, 20060258695, 20060281773, 20090042929, 20080255216, 20050228038, 20060223829, 20090264650, 20060235028, 20050261302, 20050277647, 20100197662, 20060281750, 20070072914, 20070207985, 20060205772, 20060159622, 20100184764, 20110312949, 20090124598, 20090170832, 20070197598, 20090227631, 20070179186, 20090036503, 20070167622, 20090082367, 20100168083, 20070225280, 20090131491, 20080076819, 20120004209, 20100292215, 20090306048, 20090170894, 20070049632, 20100009968, 20090325932, 20090186928, 20080234249, 20090258913, 20100069365, 20100022597, 20100004221, 20110003856, 20110003852, 20110039853, 20100331366, 20100076041, 20100113448, 20100113448, 20090111800, 20100137377, 20090088428, 20090156571, 20090111809, 20090069326, 20090239911, 20090099182, 20090099180, 20090275613, 20090088430, 20100240659, 20100009960, 20100022589, 20110034455, 20100234363, 20100267761, 20110190262, 20100267696, 20080221175, 20100022590, 20110028445, 20110071139, 20100197675, 20110015178, 20130012545, 20100056600, 20100144744, 20110060007, 2014/0179669, 20100280073, 20110105460, 20110124635, 20110269736, 20110015157, 20110009402, 20110059929, 20110237559, 20110129542, 20090054426, 20120115853, 20080312214, 20110172265, 20090093516, 20110275595, 20100324045, 20110263582, 20110098320, 20090131434, 20110112082, 20090181994, 20100324104, 20100041637, 20090192198, 20090192141, 20090176783, 20110136821, 20110105504, 20090203668, 20110112062, 20100331320, 20120071466, 20110160463, 20110269957, 20120108578, 20090306084, 20120165337, 20120135958, 20100144694, 20110136800, 20110224244, 20110237634, 20110312950, 20100222316, 20100204199, 20100256387,

20100267738, 20120172357, 20110053943, 20120208804, 20120095046, 20120190675, 20120232050, 20110218214, 20120157488, 20110159005, 20110077395, 20130123268, 20140024636, 20130244993, 20110288051, 20120004206, 20130310431, 2014/0249151, 20150141650, 20150158860, 20120289512, 20150210635, 20130045978, 20130059829, 20130244994, 20130338169, 20130245051, 20140128365, 20150065508, 20150080363, 20160257680, 20150265613, or 20160251346.

[0050] In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is a compound described in U.S. Patent Nos. US6849636, 7700583, 7179802, 7659408, 8138342, 7880001, 7915252, 7713979, 7834194, 7511175, 7759339, 7579360, 7572807, 7622492, 8541592, 7645773, 7932280, 7834178, 7528282, 7727978, 7932421, 7790711, RE041135, 8592410, 8329897, 7737137, 8598160, 8486964, 8575157, or 8907096. In some embodiments, the 11β-hydroxysteroid dehydrogenase type 1 inhibitor is a compound described in WO2010001946.

Antagonists of corticotropin releasing hormone receptor type 1 (CRHR1)

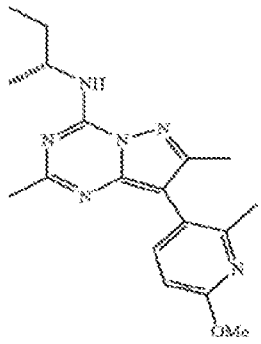
[0051] In some embodiments, the CRHR1 antagonist is a compound described in U.S. Patent Nos. 6191131, 7157578, and 7879862.

[0052] In some embodiments, the CRHR1 antagonist is selected from the group consisting of 4-((2-butyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; 4-((2-butyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; 4-((3-pentyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; 4-((3-pentyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; 4-(N-cyclopropylmethyl-N-propylamino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; 4-(N-cyclopropylmethyl-N-propylamino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; 4-(N-allyl-N-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; 4-(N-allyl-N-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; 4-(diallylamino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-

1,3,5-triazine; 4-(diallylamino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; 4-(N-ethyl-N-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine; and 4-(N-ethyl-N-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0053] In some embodiments, the CRHR1 antagonist is 4-(2-butylamino)-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)pyrazolo-[1,5-a]-1,3,5-triazine or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0054] In some embodiments, the CRHR1 antagonist is pexacerfont, which is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0055] In some embodiments, the CRHR1 antagonist is selected from [1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-propyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-propyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-phenyl-ethyl]-amine; [1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-propyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-butyl]-amine; [3-(4-Methoxy-2-methyl-

phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amine; (3-Cyclopropyl-[1,2,4]oxadiazol-5-ylmethyl)-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; (3-Isopropyl-[1,2,4]oxadiazol-5-ylmethyl)-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-(R)-1-methyl-ethyl]-[3-(4-methox- y-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(R)-1-methyl-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-trifluoromethyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-cyclopropyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-cyclopropyl]-amine; [1-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-cyclopropyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl-]-(3-propyl-[1,2,4]oxadiazol-5-ylmethyl)-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-trifluoromethyl-[1,2,4]oxadiazol-5-yl)-cyclopropyl]-amine; [2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-(R)-1-methyl-ethyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [3-(6-Dimethylamino-4-methyl-pyridin-3-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[3-methyl-(R)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-butyl]-amine; 3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-7-[(S)-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-pyrrolidin-1-yl]-pyrazolo[1,5-a]pyrimidine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-butyl]-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[3-methyl-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-butyl]-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-methyl-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amine; Benzyl-[3-(6-

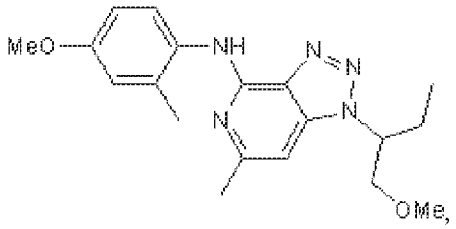
dimethylamino-4-methyl-pyridin-3-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-methyl-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amine; Benzyl-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[2,2,2-trifluoro-1-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-ethyl]-amine; [2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-1-methyl-ethyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [2-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-1-methyl-ethyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-(S)-1-methyl-ethyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [2-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-(S)-1-methyl-ethyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-methyl-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-propyl]-amine; [1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-ylmethyl)-propyl]-[3-(2,4-dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-propyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-butyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[2,2,2-trifluoro-(S)-1-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-ethyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-methyl-2-(3-trifluoromethyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amine; [3-(2-Chloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[2,2,2-trifluoro-(S)-1-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-ethyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(R)-1-methyl-2-(3-trifluoromethyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amine; [3-(2-Chloro-4-methoxy-

phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(R)-1-methyl-2-(3-trifluoromethyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(R)-1-methyl-2-(3-trifluoromethyl-[1,2,4]oxadiazol-5-yl)-ethyl]-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[2,2,2-trifluoro-(S)-1-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-ethyl]-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[2,2,2-trifluoro-(S)-1-(3-trifluoromethyl-[1,2,4]oxadiazol-5-ylmethyl)-ethyl]amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(R)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; 3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-7-[(S)-2-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-pyrrolidin-1-yl]-pyrazolo[1,5-a]pyrimidine; [3-(2-Chloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(2-methoxy-ethyl)-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amine; (5-{2,5-Dimethyl-7-[(S)-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-pyrrolidin-1-yl]-pyrazolo[1,5-a]pyrimidin-3-yl}-4-methyl-pyridin-2-yl)-dimethyl-amine; [3-(6-Dimethylamino-4-methyl-pyridin-3-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(2-methoxy-ethyl)-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amine; [3-(4-Ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(2-methoxy-ethyl)-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amine; [3-(2,4-Dimethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(2-methoxy-ethyl)-[3-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(R)-1-methyl-2-(5-methyl-[1,2,4]oxadiazol-3-yl)-ethyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(5-methyl-[1,2,4]oxadiazol-3-ylmethyl)-propyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(R)-1-(5-methyl-[1,2,4]oxadiazol-3-ylmethyl)-propyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-methyl-2-(5-methyl-[1,2,4]oxadiazol-3-yl)-ethyl]-amine; [(R)-2-(5-Cyclopropyl-[1,2,4]oxadiazol-3-yl)-1-methyl-ethyl]-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

[3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(R)-1-methyl-2-(5-trifluoromethyl-[1,2,4]oxadiazol-3-yl)-ethyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-2,2,2-trifluoro-1-(5-methyl-[1,2,4]oxadiazol-3-ylmethyl)-ethyl]-amine; Ethyl-[3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-amine; 3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-7-[2-(3-methyl-[1,2,4]oxadiazol-5-ylmethyl)-piperidin-1-yl]-pyrazolo[1,5-a]pyrimidine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl-(1-[1,3,4]oxadiazol-2-yl-propyl)-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(5-methyl-[1,3,4]oxadiazol-2-yl)-propyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-methyl-2-(5-methyl-[1,3,4]oxadiazol-2-yl)-ethyl]-amine; [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-methyl-2-(5-trifluoromethyl-[1,3,4]oxadiazol-2-yl)-ethyl]-amine; [3-(2-Chloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [3-(4-Chloro-2-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [3-(3-Chloro-4-fluoro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [3-(4-Chloro-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; [3-(2-Chloro-4-trifluoromethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine; and [3-(2-Chloro-4-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

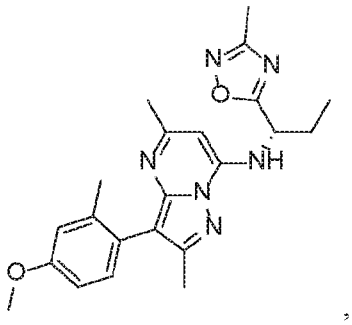
[0056] In some embodiments, the CRHR1 antagonist is a compound described in Progress in corticotropin-releasing factor-1 antagonist development, Zorrilla and Koob, Drug Discov. Today, 2010, 15(9-10):371-83.

[0057] In some embodiments, the CRHR1 antagonist is SN 003 of the formula:



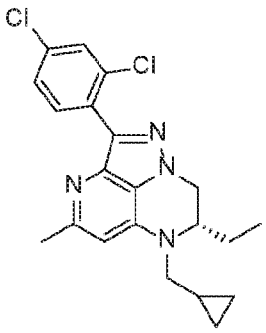
or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0058] In some embodiments, the CRHR1 antagonist is verucerfont (GSK561679), which is of the formula:

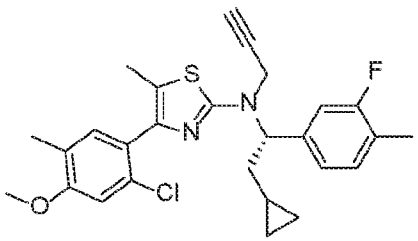


or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

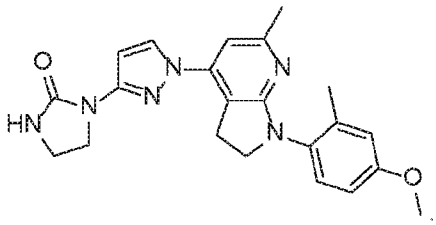
[0059] In some embodiments, the CRHR1 antagonist is selected from the group consisting of antalarmin, emicerfont, LY2371712, NBI-35965, NBI-30775, NBI-34101, NBI-30545, NBI-27914, NBI-34101, CP-316,311, CRA 5626, CP-154,526, CP-376,396, ONO-2333Ms, pexacerfont, SSR125543, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, R121919, PF-572778, GSK561579, and GSK586529. An exemplary CRHR1 antagonist is NBI-35965, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof, and which has the following structure:



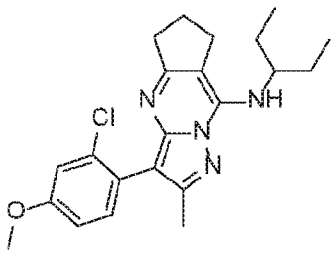
[0060] Another exemplary CRHR1 antagonist is SSR125543, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof, and which has the following structure:



[0061] Still another exemplary CRHR1 antagonist is emicerfont, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof, and which has the following structure:

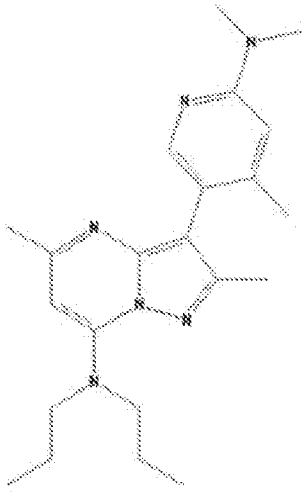


[0062] Another exemplary CRHR1 antagonist is ONO-2333Ms, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof, and which has the following structure



[0063] In some embodiments, the CRHR1 antagonist is selected from the group consisting of LWH-234, CP-154,526, NBI-27914 and R121919.

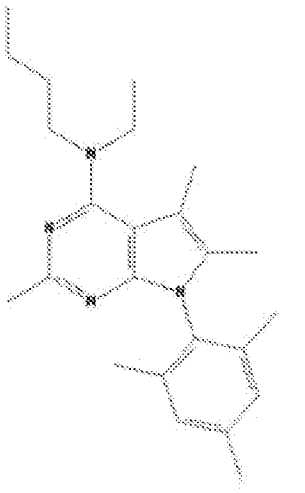
[0064] In some embodiments, the CRHR1 antagonist is R121919, which is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

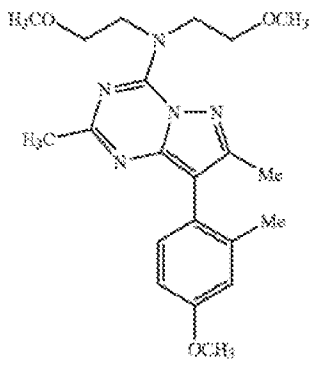
[0065] In some embodiments, the CRHR1 antagonist is antalarmin, which is of the formula:



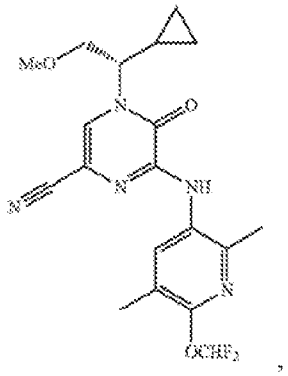
,

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0066] In some embodiments, the CRHR1 antagonist is



or



or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, tautomer, N-oxide or prodrug thereof.

[0067] In some embodiments, the CRHR1 antagonist is a compound described in U.S. Patent Application Publication Nos. 20110301087, 20030220333, 20030149059, 20030064993, 20020022632, 20020049227, 20020022632, 20020058668, 20020111490, 20020042422, 20040254382, 20030229091, 20030055059, 20030119831, 20040225130, 20030055059, 20100029684, 20040014760, 20110124662, 20020161019, 20020065290, 20020016328, 20040235924, 20040209917, 20040235871, 20040176400, 2010/0029684, 20110124662, 20110190360, 20110201629, 20010036945, 20020183375, 20020019525, 20020019525, 20020016333, 20040014760, 20010025042, 20030008885, 20030114468, 20030220333, 20030114502, 20030125330, 20030171380, 20030105117, 20030195222, 20060252756, 20040082781, 20040229891, 20040204414, 20040242623, 20050038040, 20030208068, 20070155740, 20070219232, 20070054913, 20070021429, 20070066640, 20040171829, 20040082784, 20040209917, 20040224974, 20050113375, 20050020601, 20080139567, 2008/0076943, 20080153828, 20080113978, 20080306092, 20080194589, 20080015196, 20080312444, 20080194589, 20010036945, 20020049208, 20020049227, 20030114468, 20030045514, 20030152520, 20030114468, 20080139567, 20070004708, 20070155740, 20030149059, 20030119844, 20020022632, 20100222339, 20100022560, 20100035874, 20100249138, 20100298287, 20030078277, 20140179919, 20090023757, 20090023757, 20090137604, 20060199823, 20020019406, 20020058668, 20050038055, 20050054661, 20050020601, 20050038040, 2011/0190360, 20120295942, 20120316185, 20080194589, 20140088105, 20070281919, 20070021429, 20150094310, or 20150094310.

[0068] In some embodiments, the CRHR1 antagonist is a compound described in U.S. Patent Nos. 5861398, 5861398, 6200979, 7094782, 7297708, 7112585, 6103737, 6399609, 6136809, 6218391, 6358950, 6174912, 6521636, 6518271, 6448261, 6107300, 6083948, 6124289, 6159980, 6143743, 6245769, 6107294, 6509338, 6271380, 7297708, 6365589, 6350750, 6630476, 7612067, 5795905, 6133276, 6133282, 6194574, 6995161, 5955613, 5644057, 6281220, 5973152, 6114530, 5723608, 6127399, 6353103, 6147085, 6436932, 6355651, 6300360, 6469041, 6291473, 6310063, 6362186, 6194574, 6284766, 5063245, 7807688, 7947697, 5712303, 6103900, 6765008, 5646152, 5668145, 6492520, 6844351, 5968944, 5962479, 6833378, 6956047, 5958948, 6992188, 6005109, 5705646, 5109111, 4605642 or 5880135.

[0069] In some embodiments, the CRHR1 antagonist is a compound described in International Patent Application Publication Nos. WO02072101, WO9533727, WO9735539, WO9803510, WO9413676, WO9413644, WO9413677, WO9413661, WO9533750, WO9534563, WO9808846, WO9938868, WO9901439, WO2004062665, WO2008083070, WO2007133756, WO2010053546, WO2011095450, WO2011092293, WO2017035528, or WO2018048953.

Pharmaceutical Compositions and Administration

[0070] The HSD11β1 inhibitors or the CRHR1 antagonists are administered using any suitable methods known in the art. For example, the HSD11β1 inhibitors or the CRHR1 antagonists are administered orally, bucally, ophthalmically, osmotically, parenterally (intramuscularly, intraperitoneally intrasternally, intravenously, subcutaneously), rectally, topically, transdermally, or vaginally.

[0071] In accordance with various embodiments, the HSD11β1 inhibitors or the CRHR1 antagonists are administered in the form of pharmaceutical compositions. Thus, provided herein are also pharmaceutical compositions that contain one or more of the compounds of any of the formulae disclosed herein or a pharmaceutically acceptable salt, isomers, prodrug, or solvate thereof, and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants and excipients. Suitable pharmaceutically acceptable vehicles may include, for

example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. See, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0072] The pharmaceutical composition is administered in either single or multiple doses. The pharmaceutical composition is administered by various methods including, for example, oral, intravenous, intraperitoneal, parenteral, intramuscular, subcutaneous, topical, rectal, buccal, intranasal and transdermal routes, or as an inhalant. In some embodiments, the pharmaceutical composition is administered orally.

[0073] In some embodiments, the pharmaceutical composition administered is parenterally, for example, by injection. The pharmaceutical compositions used for administration by injection include, for example, aqueous or oil solutions, suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0074] Oral administration may be another route of administration. The pharmaceutical compositions may in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders. In certain embodiments, the pharmaceutical composition is in the form of tablets. Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

The tablets or pills may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach.

[0075] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions can contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[0076] The specific dose level of a HSD11β1 inhibitor or a CRHR1 antagonist for any particular subject depends upon a variety of factors including, for example, 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 in the subject undergoing therapy. For example, a dosage is expressed as a number of milligrams of a compound per kilogram of the subject's body weight (mg/kg). Illustrative dosages include those between about 0.01 and 200 mg/kg. In some embodiments, about 0.01 and 150 mg/kg may be administered. In other embodiments a dosage of between 0.05 and 100 mg/kg may be administered. Normalizing according to the subject's body weight can be useful, for example, when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

[0077] The daily dosage may also be described as a total amount of a HSD11β1 inhibitor or a CRHR1 antagonist administered per dose or per day. Daily dosage

of a compound may be between about 0.1 mg and 2,000 mg/day, between about 1 to 2,000 mg/day, between about 1 to 1,000 mg/day, between about 1 to 500 mg/day, between about 10 to 150 mg/day, between about 1 to 100 mg/day, between about between about 1 to 50 mg/day, between about 5 to 100 mg/day, between about 10 to 125 mg/day, between about 10 to 100 mg/day, or between about 5 to 200 mg/day.

[0078] The daily dosage of a HSD11β1 inhibitor or a CRHR1 antagonist may be administered all in one time (once a day) or in several times, such as two times, three times, four times, five times or more throughout the day.

Example

[0079] As illustrated below, we offer a new view of the neurobiological origins of chronic anxiety and related emotional symptoms in FXS, one that highlights novel and clinically proximal ways for mechanism-based pharmaceutical intervention, and disclose and claim use of therapeutic agents that can be suitable for treatment of these conditions.

[0080] Efforts to understand the neurobiological basis of emotional symptoms in FXS have been focused (for good reasons) on the amygdala [80,90,91], a limbic structure implicated in the expression of cued anxiety and fear [92,93,94], the encoding of explicit fear memories [95], and memory consolidation [96]. In simplified terms, the basolateral amygdala (BLA) is a locus for association of stimuli predicting and eliciting fear, and the central nucleus (CeA) orchestrates behavioral, autonomic and hormonal responses to these cues [97]. However, the unusually persistent nature of anxiety and social avoidance in FXS, which can be thought of as a form of "trait anxiety", suggest that its neurobiological underpinnings relate more directly to a different structure. Long-term anxiety and fear states are mediated by the *bed nucleus of the stria terminalis* (BNST), a region of the extended amygdala [98,99] that serves as a hub for corticolimibic modulation of anxiety and stress responses [100,101,102,103,104,105,106]. In contrast to the amygdala "proper", which mediates *acute* fear responses to transient or phasic cues, the BNST acts to set the *long-term* gain of emotional and physiological responses to stressful or fear-evoking stimuli [14,94,107,108,109,110]. Indeed, the BNST has been implicated in chronic anxiety states, social

avoidance, obsessive compulsive disorders, PTSD and other persistent negative emotional traits that align well with emotional symptoms of FXS [111,112,113,114,115]. This key functional distinction of the BNST [101,114,115] appears much better suited (than the amygdala proper [115]) to explain the remarkably persistent anxiety and other emotional phenotypes of FXS. While there is considerable evidence in FXS for alterations in amygdala structure, activation (reviewed in [90,91]), and synaptic excitatory / inhibitory (E/I) balance [80,83] that may lead to increased expression of acute conditioned fear, some studies indicate that amygdalar activity is actually deficient in FXS in some of the contexts that elicit debilitating forms of anxiety / fear in FXS subjects (*e.g.* social anxiety) [116,117,118]. In contrast, several features of BNST anatomy and function provide a compelling basis on which to consider this region as a key locus of pathophysiology underlying chronic anxiety, social avoidance, and other emotional symptoms in FXS.

[0081] It was observed that neurons in the BNST have altered intrinsic and synaptic properties, and elevated cortisol signaling, in the *Fmr1*$^{-/y}$ (KO) mouse model of FXS. As developed below and supported by data, these alterations underlie chronic anxiety states and attendant social symptoms in FXS. Further, the data demonstrate that these changes result from pathologically high local production of cortisol that ensues from synaptic upregulation of a cortisol biosynthesis enzyme, HSD11β1.

[0082] The BNST is an anatomically complex, multinucleated, and highly interconnected region of the extended amygdala [98,99] that acts as a hub for corticolimbic modulation of stress responses [94,101,102,105,108]. A simplified diagram of anterior BNST (aBNST) anatomy as appears in a typical slice recording experiment is shown in **Fig. 1**. The aBNST integrates cortical and limbic inputs that set expectant fear and modulate anxiety responses, including glutamatergic inputs from the insular cortex ("*insula*"), medial prefrontal cortex (mPFC), BLA, and ventral hippocampus (vHip) [100,101,102,103,104,105,119,120,121]. Under normal conditions, these inputs are thought to provide anxiolytic tone and, in the case of BLA afferents, to limit the duration and magnitude of anxiety responses mediated by the amygdala. Projections of the aBNST include a GABAergic output to the paraventricular nucleus of the hypothalamus (PVN) –

which blunts activity of the HPA axis – as well as the BLA, CeA, insula and mPFC, and other regions mediating emotional, autonomic and visceromotor responses to stress [101,122].

[0083] Importantly, while acute activation of the aBNST by cortico-limbic inputs normally attenuates anxiety & physiological stress responses, chronic stress-induced activation of these networks results in long-term anxiogenic output of the BNST, and to changes in the volume and activity of structures innervating it [94,107,108,119,123]. Some of these changes, including reduced volume and enhanced activation of insula by social stimuli, are robust neural correlates of FXS severity and are suggested to mediate social anxiety symptoms [11,124,125]. It is notable in this regard that activity within the insula and BNST tracks the degree of anticipatory fear to social stimuli [14], a function of particular relevance to social anxiety symptoms of FXS. Further, structural and functional changes in BNST inputs such as the insula correlate with IQ in FXS subjects [124,125], which suggests that normalizing the function of these networks may improve cognitive function as it helps resolve the most disruptive comorbid features of FXS.

[0084] Several distinct types of neurons can be identified in the aBNST – namely type I, II and III – which differ in their relative expression of specific voltage-gated channels regulating spike threshold and rate [119,126]; each type is readily identifiable by its distinct electrophysiological characteristics during patch clamp recording. Type III neurons, which are medium-sized spiny GABAergic projection neurons, are highly concentrated in a vertically oriented strip bordering the internal capsule called the "juxtacapsular" region or jcBNST (**Fig. 1**). Using viral vectors, it was observed that Type III jcBNST neurons project strongly to the lateral hypothalamus (LH). This complements existing data showing that jcBNST sends GABAergic projections to many areas, including the anterior BLA, medial CeA, and PVN to suppress physiological and behavioral responses to stress [101,103,119,122,127]. Importantly, the jcBNST is a major target of the corticolimbic inputs noted above (BLA, insula, mPFC) that negatively modulate stress and long-term anxiety by stimulating jcBNST GABAergic neurons. The special role of jcBNST in anxiolytic drive is underscored by the fact that a massive BLA glutamatergic projection to aBNST

terminates almost exclusively in the jcBNST, forming an anxiolytic circuit limiting amygdalar activation through jcBNST GABAergic projections to CeA [128,129].

[0085] In contrast, neighboring nuclei within the anterolateral group of the aBNST (BNST-AL; **Fig. 1**) [103,130] harbor distinct cell types with different connectivity and functions. Adjacent to the jcBNST is the so-called "oval" nucleus (ovBNST, **Fig. 1**), in which preliminary studies and prior work by others [131] find mostly Type I and II neurons that are sparsely distributed in the broader anterodorsal BNST. Unlike Type III GABAergic projection neurons of the jcBNST, Type I and II GABAergic neurons in the ovBNST send intra-BNST afferents to other nuclei and the parabrachial nucleus (a hedonic center), inhibiting their output. An example of this is the GABA-GABA pathway from ovBNST to ventral BNST, to the VPN, which disinhibits the HPA axis. Additionally, while most of the BNST-AL (including ovBNST and the fusiform BNST) receives dense inputs from the lateral portion of the CeA, the jcBNST is devoid of these connections [132], suggesting that inhibitory (anxiolytic) tone from the jcBNST to CeA is not subject to direct reciprocal modulation by CeA. Recent optogenetic studies indicate that activation of the ovBNST is anxio*genic*, whereas the rest of the BNST-AL has an anxio*lytic* influence [133]. Long-term anxiety states appear to be mediated by a weakening of anxiolytic pathways to BNST, particularly the jcBNST [94,101,107,108,119,123,126,127,129]. Anxiolytic functions of jcBNST are supported most recently by elegant optogenetic studies of BLA-jcBNST [129] circuits and human deep brain stimulation studies [111]. jcBNST and ovBNST are thus morphologically [134,135,136] and functionally distinct, differentially regulating chronic anxiety and related behaviors [114].

[0086] In studies of BNST function in the *Fmr1* KO mouse, we focused on the jcBNST due to its heavy innervation by the insula (implicated in social anxiety in FXS) and the fact that it is composed primarily of GABAergic Type III projection neurons that monosynaptically inhibit the BLA, CeA, PVN, LH and other structures mediating psychological, autonomic, endocrine, and visceromotor responses to stress [101,119,122,127,137]. We discovered that jcBNST Type III neurons are intrinsically less excitable and receive less spontaneous excitatory synaptic input in the *Fmr1* KO model of FXS (**Fig. 2**). Such changes

are reminiscent of reduced excitability and plasticity of jcBNST that we observed in previous work in models of chronic stress [119,127]. These changes result in chronically reduced anxiolytic drive of BNST by insula, and other corticolimbic inputs, and to cortisol axis dysregulation.

[0087] Anxio*genic* shifts in BNST function are promoted by corticotropin releasing hormone (CRH) released within the BNST during chronic stress [127,138,139,140,141]. CRH infusion into the BNST is strongly anxiogenic and it preferentially causes social anxiety [142,143,144]. Accordingly, infusion of CRH antagonists into the BNST blocks the ability of chronic stress to induce long-term anxiety [94,145,146]. In prior work, we demonstrated that long-term potentiation of intrinsic excitability (LTP-IE) of Type III neurons in the jcBNST is blocked by CRH. LTP-IE is an enhancement of spiking responses to excitatory inputs that requires NMDA and mGluR5 receptors, as well as dopamine signaling, for its induction [101]. The ability of CRH to block LTP-IE indicates that excessive CRH signaling during chronic stress can reduce the ability of jcBNST inputs (*e.g.* insula) to activate this structure and trigger anxiolytic GABAergic output [127]. Afferents from the BLA are a major source of CRH in the jcBNST, and it is thought that recurrent stress-induced activation of the amygdala leads to CRH release in BNST [101,127,142,143,144,145,147,148]. Thus, chronic amygdalar activation can blunt anxiolytic tone from areas such as insula involved in interoception and threat monitoring of social stimuli.

[0088] Glucocorticoid signaling increases CRH expression in the jcBNST [101,127,138,149]. In recent studies of synaptic protein expression in *Fmr1* KO brain [29], we observed large increases in the cortisol synthetic enzyme HSD11β1, suggesting that synaptic cortisol levels in FXS are exceedingly high. As illustrated in **Fig. 3**, we validated upregulation of HSD11β1 in the jcBNST of *Fmr1* KO mice by immunofluorescence deconvolution microscopy (in collaboration with Dr. Lauterborn, UC Irvine) and by Western blot analyses of isolated jcBNST samples. Additionally, we obtained evidence of exaggerated cortisol signaling in *Fmr1* KO brain as detected by phosphorylated glucocorticoid receptor (p-GR; **Fig. 3**). These observations and data indicate that the set point of BNST function in FXS is biased towards anxiety by tonic increases in cortisol-driven CRH production. Further, these data show that

inhibiting HSD11β1 activity or antagonizing CRH receptors reduces the anxiety, social avoidance and other emotional symptoms of FXS. These data additionally show that clinically tested inhibitors of HSD11β1 and CRHR1 (the CRH receptor variant implicated in CRH-induced anxiogenesis [127]) can be repurposed for use in FXS, providing therapeutic agents for treatment of these conditions in human patients.

[0089] The rationale and data disclosed herein demonstrate that increased HSD11β1-mediated cortisol synthesis in FXS resulted in CRH-dependent changes in jcBNST that are chronically anxio*genic*, creating a state at baseline that is analogous to the effects of long-term stress on BNST function in normal individuals (**Fig. 6**). The changes entail insula-BNST pathways that mediate social anxiety and social aversion.

[0090] Chronic intense anxiety in many forms is a highly debilitating, disruptive, and costly aspect of FXS symptomology, one that plays a major role in other emotional symptoms of FXS and perhaps even some aspects of cognitive dysfunction. The present disclosure offers a significant new inroad into the etiology of anxiety in FXS.

[0091] Our data demonstrated reduced spontaneous excitatory input to Type III jcBNST neurons in the *Fmr1* KO and a reduction in the intrinsic excitability of these neurons (**Fig. 2**). A strong prediction of reduced mEPSC frequency without changes in mEPSC amplitude in *Fmr1* KO Type III neurons is that the probability of glutamate release is reduced [150], thus reducing evoked release onto Type III neurons. This would result in weaker drive of *Fmr1* KO Type III neurons by inputs that normally exert anxiolytic effects through jcBNST. Reductions in intrinsic excitability of *Fmr1* KO Type III neurons may compound this effect, resulting in dramatically reduced anxiolytic drive of jcBNST. Such changes may be expressed by subsets of inputs to Type III jcBNST neurons, or they may be manifest across all glutamatergic inputs as postulated for stress/CRF-induced impairments in LTP-IE [101,119,127]. Indeed, it is possible that reduced intrinsic excitability reflects from mechanisms similar to those that impair LTP-IE during chronic stress.

[0092] We used optogenetic approaches to define the origin of synaptic connections to jcBNST Type III neurons that exhibit altered release properties in the *Fmr1* KO, and whether these inputs are affected by alterations in baseline intrinsic excitability and, potentially, LTP-IE. Type III jcBNST neurons receive excitatory input from many cortical and limbic areas, including: the dysgranular insular cortex, the prelimbic and infralimbic divisions of the mPFC, the posterior BLA, the amygdalo-hippocampal transition area (AHTA), the transitional postpyriform cortex (TRPC), and the amygdalo-piriform transition area (APir) [100,122,128,151,152]. This presents a functionally intriguing, but complex picture. However, observations in FXS and recent work on jcBNST circuitry place a strong emphasis on three regions, which are prioritized here as follows: (1) the insula, because an insula-to-BNST circuit sets the level of expectant fear to social cues, and robust changes in insula activity and volume are observed in FXS brain that correlate with gaze aversion; (2) the BLA because it sends a massive CRH-expressing projection to jcBNST, and recent data show that reductions in glutamate release at BLA-to-BNST synapses triggered by dynorphin are anxiogenic [129]; and (3) the mPFC because it provides a tonic inhibitory tone on stress by activating jcBNST, and hypoactivation of mPFC in FXS contributes to social anxiety [153]. Taken with our data, these and other observations suggest that inputs from insula, BLA, and mPFC to the jcBNST can be disrupted in FXS to create a chronically anxiogenic state.

[0093] To identify the specific inputs to Type III neurons that exhibit reduced release probability in the *Fmr1* KO jcBNST, and which inputs are affected by reduced Type III neuron excitability, we used optogenetic tools to identify and stimulate specific inputs to this region. We used viral vectors that encode for the blue light-sensitive cation-pump *Chlamydomonas reinhardtii* channelrhodopsin-2 (ChR2) fused with eYFP [157,158] to activate either insula, BLA, and mPFC inputs to Type III neurons in jcBNST [129,154]. Microinjections (0.5-1 ul) of AAV_5-CaMKIIα-ChR2(H134R)-eYFP ($2\text{-}5 \times 10^{12}$ viral particles / mL) were stereotaxically placed unilaterally into one of the target fields in WT and *Fmr1* KO mice; stereotaxic coordinates were based on the mouse brain atlas by Paxinos and Franklin, with additional reference to recent work by Crowley et al [129], and verified prior to AAV injection. Following a 4-5 week post-operative

period, to allow sufficient AAV expression and transport of ChR2 to distal terminals [158], mice were used for physiological studies of jcBNST Type III neurons. All injection sites were verified at the time of sacrifice. For optogenetic stimulation, a blue light (473nm) are flashed at projections visualized under eYFP fluorescence. Presynaptic fibers were identified initially using 5x and 20x objectives, after which we shifted to 60x objective for optogenetic stimulation.

[0094] Following conventions established in the field and utilized extensively in our prior work [101,119,126,127,130], jcBNST Type III neurons in slices that were prepared from WT and *Fmr1* KO mice were electrophysiologically identified according to their voltage responses to hyperpolarizing and depolarizing current injections (**Fig. 1**). Whole-cell patch recordings were performed in BNST slices that were perfused at 2ml/min with oxygenated artificial cerebrospinal fluid consisting of (in mM): 130 NaCl, 2 KCl, 2 $CaCl_2$, 1.25 KH_2PO_4, 2 $MgSO_4$, $7H_2O$, 26 $NaHCO_3$, 10 d-glucose, pH 7.4 at 32°C. Patch recording electrodes were filled with a solution consisting of (in mM): 120 K-Gluconate, 10 KCl, 10 HEPES, 10 EGTA, 2 Mg-ATP, 0.3 Na-GTP, and osmolarity of 300 ± 10 mOsm. In some variations, electrodes also contained 0.1% biocytin to label neurons *post hoc* for morphological analyses. After achieving whole-cell configuration with an access resistance <30 <MΩ, cells were allowed to equilibrate for a minimum of 5 min before assessing baseline physiological properties. For each recorded neuron, intrinsic membrane properties – resting membrane potential, input resistance, rheobase, input-output curve (I/O), and voltage threshold – were determined in current clamp mode by analyzing the voltage of responses evoked with intracellular injections of a series of hyperpolarizing and depolarizing current steps of 350 ms, starting from -200 pA and increasing in steps of 5 pA until firing. Identification of Type III neurons exploited their characteristic high rheobase and prominent inward rectification (**Fig. 1B**), which was indicative of an inwardly rectifying K^+ current (I_{Kir}) [126]. Type III neurons were also characterized both by the presence of depolarizing voltage ramp and by delayed spiking when depolarizing threshold current pulses were applied (**Fig. 1B**). As shown in **Fig. 1A**, neurons with these electrophysiological characteristics were

recorded in the anterodorsal aspect of BNST adjacent to the internal capsule, corresponding to the jcBNST (see also [131]).

[0095] Optically evoked excitatory postsynaptic currents (oEPSCs) are were recorded in whole-cell patch voltage clamp mode from jcBNST type III neurons in response to specific inputs (BLAp, Insula and mPFC). Recording is was performed at a holding potential of -70 mV and in the presence of picrotoxin (25 μM) to isolate mainly AMPA-R-mediated responses. For optogenetic stimulation of specific afferent fibers, we followed the same technical approach used in our recent paper [154]. Briefly, a 473-nm blue laser 50 μm diameter spot (Crystalaser, Reno, NV) of 30 mW power and 1-2 ms duration will bewas flashed every 10–20 s. Each stimulation will consisted of three repeated laser flashes with an inter-trial interval of 1.2 s. Light intensity, measured in mW/mm2, will bewas increased to generate a calibration curve. We will maintain cConstant pulse duration (1-2 ms) was maintained while gently increasing laser intensity until an oEPSC of 70-100 pA is was obtained. For every cell recoded, and for every specific input (BLAp, Insula and mPFC), in slices from WT and *Fmr1* KO mice, we generated I/O curves plotting the amplitude of the oEPSCs as a function of light power [159]. This tuning is was obtained using neutral density filters and microscope apertures. As Because levels of viral expression may can vary across experiments, we adjusted the amplitude at the beginning of each experiment of the first oEPSCs between 70 to 100 pA. Postsynaptic parameters are were monitored continuously throughout the duration of the experiments.

[0096] To assess changes in release probability at specific inputs to jcBNST, we use two methods. In the first, we compared the degree of paired-pulse facilitation (PPF) resulting from optogenetic stimulation of specific inputs (BLAp, insula, mPFC) to jcBNST Type III neurons in WT and *Fmr1* KO slices. PPF is a widely used protocol to evaluate release probability wherein a greater degree of facilitation of EPSCs elicited by the second of two closely paired (~50ms) pulses indicates a lower baseline probability of transmitter release [150]. To elicit PPF, pairs of blue light flashes are were applied at a 50 msec inter-pulse interval using blue light intensities that evoke a subsaturative oEPSC (30% of max). A PPF ratio (PPR) is was calculated as the peak amplitude of the second oAMPA-EPSC

divided by the first (PPR=oAMPA-EPSC2/oAMPA-EPSC1). In a parallel approach, we compared the CV of oAMPA-EPSCs in WT and *Fmr1* KO Type III neurons measured as the ratio of the standard deviation (δ) to the mean (μ) of the peak oAMPA-EPSC amplitude. A change of CV is was associated with either a change of release probability (Pr) or the number of release sites (n) [160].

[0097] The data described herein revealed a decrease in the intrinsic excitability of Type III jcBNST neurons in the *Fmr1* KO, and a reduction in spontaneous, action potential-independent release onto these neurons (**Fig. 2**). The former is highly suggestive of altered K^+ channel activity in the *Fmr1* KO. The latter is indicative of changes in presynaptic release probability, and it is notable that reduced excitatory drive of several GABAergic cell types has been reported in the *Fmr1* KO mouse [156]. Accordingly, we investigated the mechanistic basis of both aspects of altered jcBNST physiology.

[0098] Type III neurons responded to supra-threshold depolarization with a delayed spike superimposed on a depolarizing ramp (**Fig.1**). The delay in spike generation reflected the activation of the α-dendrotoxin (α-DTX)-sensitive, slowly inactivating D-type K^+ current (I_D) first identified in hippocampus [163]. The I_D current controls spike threshold in various neuronal types [163,164,165,166], with the common effect of reducing intrinsic excitability. Previously, we demonstrated that the I_D current blocks LTP-IE of Type III neurons in jcBNST during protracted withdrawal from drugs of abuse (a model of chronic anxiety/stress) [127]. Reduction of intrinsic excitability by stress-related increases in the I_D current diminishes the anxiolytic drive of the jcBNST circuit.

[0099] Three features of the I_D current are of particular interest in the context of FXS and our data. First, the I_D current is mediated primarily by Kv1.2 (Kcna2) K^+ channels [167] that regulate excitability in many neuron types [168], and the mRNA for Kcna2 is a putative FMRP target [24]. Second, we demonstrated that impairments in LTP-IE during chronic stress – equivalent to reduced excitability – are induced by CRH [127]. Third, the I_D current is inactivated by mGluRs [101,169], potentially by a mechanism involving phosphorylation-dependent endocytosis [170]. These factors raise the possibility that decreased intrinsic excitability of *Fmr1* KO Type III neurons is due to upregulation of Kv1.2 K^+ channels,

potentially by elevated CRH signaling or deficient mGluR-induced Kv1.2 inactivation.

[00100] Several presynaptic mechanisms may be responsible for our observation that sEPSCs onto *Fmr1* KO jcBNST Type III neurons exhibit reduced frequency without a change in amplitude. Two specific pathways are of particular interest: endocannabinoid (eCB) signaling and the opioid dynorphin. eCB signaling is enhanced at some synapses in the *Fmr1* KO [85], and can trigger a reduction in the frequency of mEPSCs and mIPSCs [171,172,173,174]. It has been shown that the eCB receptor CB1R is present at high levels on excitatory presynaptic boutons contacting anterolateral BNST (alBNST [175]), and that application of a CB1R agonist results in decreases in the frequency, but not amplitude, of mEPSCs. In addition, it was shown that synthesis of the eCB 2-arachidonoylglycerol (2-AG) in alBNST is triggered by dendritic L-type Ca^{++} channels, leading to CB1R-mediated presynaptic depression [176]. In our recent studies of the *Fmr1* KO cortical synaptic proteome [177], we observed that a β regulatory subunit of L-type Ca^{++} channels that increases their unitary conductance [178], CACNB4, is upregulated > 2 fold in the KO. Together, these observations suggest that elevated 2-AG synthesis and signaling through CB1R in *Fmr1* KO jcBNST can result in the changes in release we observed.

[00101] Another mechanism of interest is dynorphin signaling. In elegant optogenetic studies, Crowley et al [129] demonstrated that dynorphin released from BLA afferents into a region corresponding to jcBNST triggers a Kappa Opioid Receptor (KOR)-dependent reduction in the frequency of mEPSCs, but not the amplitude. The BLA-jcBNST pathway contributes anxiolytic tone, and dynorhpin-KOR-induced reduction of glutamate release reduces this tone (*i.e.* is anxiogenic). It is notable that the anxiogenic effects of CRH are blocked by KOR antagonists. Interestingly, dynorphin did not affect glutamate release from mPFC afferents.

[00102] We compared the amplitude and kinetics of I_D currents in WT and *Fmr1* KO Type III neurons using protocols that we employed in our previous work [101,127]. Specifically, Type III neurons were voltage-clamped at Vh = -70 mV, and a 2000 ms pulse to –100 mV was applied to increase the amount of I_D

available for activation during subsequent voltage steps. Voltage steps from - 50 to -40 mV was then applied for 500 ms, and these responses were used for the analysis of I_D current. Since these voltage steps also co-activate the A-current, we inactivated the A-current applying a 100 ms pulse to - 40 mV just before application of the 500 ms voltage steps. The I_D current was isolated by subtracting recordings made in the presence of α-DTX (1 μM) from control recordings (see also [164]), and then compared in WT and *Fmr1* KO Type III neurons.

[00103] Using Western blot and qRT-PCR approaches, we quantified the relative levels of Kcna2 (Kv1.2, I_D current) in samples of jcBNST subdissected from WT and *Fmr1* KO, as well as K^+ channels we observed to have altered expression in recent proteomic studies of P17 cortical synapse [29] – these include Kcnma1α, Kcnj10, Kcnb2 (Kv2.2) and HCN1. Some of these channels were implicated in FXS and / or autism [26,72,77,179,180], and could under some conditions contribute to altered intrinsic excitability in the KO jcBNST.

[00104] As noted earlier, CRH is highly anxiogenic in the BNST, and we demonstrated that CRH plays a specific role in regulating jcBNST Type III neuron excitability, blocking LTP-IE by enhancing the I_D current [127]. These effects are mediated by the CRH receptor 1 (CRHR1) [101,127,146,190]. Our recent proteomic work [29] identified the cortisol synthetic enzyme HSD11β1 as being greatly upregulated in cortical synapses of the *Fmr1* KO, and our data showed that this occurs in BNST as well, along with elevated cortisol signaling (**Fig. 3**). This raises the prospect of exceedingly high synaptic cortisol levels in FXS brain. Importantly, cortisol actually increases CRH production in the BNST [138,149]. Thus, a pathway emerges in which reductions in the intrinsic excitability of Type III neurons in *Fmr1* KO jcBNST are due to excessive HSD11β1 → cortisol → CRH signaling. In accordance with methods disclosed herein, this pathway is therapeutically targeted with HSD11β1 inhibitors and CRHR1 antagonists.

[00105] We quantified levels of CRH protein in jcBNST by immunofluorescence microscopy. Anesthetized WT and *Fmr1* KO mice (PND17 and 45) were perfused with 4% paraformaldehyde in 0.1 M phosphate

buffer, pH=7. Brains were sectioned in the coronal plane through the forebrain. Tissue was processed for dual immunofluorescence localization of CRH and the inhibitory marker GAD65/67 in the jcBNST using standard procedures [191,192]. Tissue sections were incubated overnight at 4°C in a cocktail of anti-CRF purified goat polyclonal antibody (1:200; sc-1761, Santa Cruz Biotech.) and anti-GAD65/67 rabbit polyclonal antibody (1;1000; ab11070, Abcam) in PBS, 0.5% Tween-20 and 5% normal donkey serum. Control sections were incubated in antibody diluent. Anti-goat AlexaFluor-488 and Anti-rabbit AlexaFluor-594 (1:1000) were used as secondary antibodies to visualize co-labeling. Slide-mounted sections were coverslipped with Vectashield containing DAPI to stain nuclei. Z-stack images were acquired on a Zeiss 780 laser scanning confocal microscope at the TSRI Microscopy Core, then reconstructed and analyzed using IMARIS, and differences between WT and *Fmr1* KO in jcBNST CRH expression were quantified in somata and neuropil.

[00106] Pharmacological inhibition of HSD11β1 normalized CRH signaling in the *Fmr1* KO BNST downstream of elevated HSD11β1 expression ([29] and **Fig. 3**). Another option, albeit potentially less specific, is the naturally occurring compound curcumin, which is a potent blood-brain barrier penetrant HSD11β1 inhibitor [197]. Either compound can be repurposed for use in treating symptoms of FXS.

[00107] **Pharmacological Treatment of Trait Anxiety**. *Fmr1* KO mice exhibit exaggerated hyponeophagia, a form of trait anxiety in which rodents are hesitant to eat new food. This form of anxiety involves the BNST and mPFC. The level of apprehension to eat new food is quantified in terms of the latency (in seconds) to try a new food when it is presented.

[00108] Performances of wild type (WT) and *Fmr1* KO (KO) mice in the hyponeophagia paradigm under control (vehicle treated) conditions and during treatment were tested with three structurally distinct inhibitors of HSD11β1: AMG-221 (30mg/kg) dosed p.o. for 10 days; PF 915275 (10mg/kg) dosed p.o. for 3 days; and BVT2733 (30mg/kg) dosed i.p. for 3 days (**Fig. 5**, panels A – C, respectively). *Fmr1* KO mice exhibit much greater apprehension to eat new

food, manifested as a longer latency to sample the food, whereas mice treated with HSD11b1 inhibitors exhibited greatly reduced anxiety.

[00109] In addition, we demonstrated that administration of CRHR1 antagonists also greatly reduces this form of anxiety, reducing the latency to eat new food to a level not different from vehicle-treated controls. Performance of wild type and *Fmr1* KO mice in the hyponeophagia paradigm under control conditions and during treatment were evaluated with three structurally distinct antagonists of CRHR1: NBI 35965 (10mg/kg) dosed p.o. for 3 days; Antalarmin (30mg/kg) dosed i.p. for 3 days; and SSR125543A (30mg/kg) dosed i.p. for 3 days (**Fig. 5**, panels D – F, respectively). As with the HSD11b1 inhibitors, the CRHR1 antagonists greatly reduced anxiety.

[00110] Data was analyzed using statistical functions present in GraphPad Prism software (La Jolla, CA) and under direct consultation with our biostatistician, Dr. Chunlei Wu at TSRI. All studies were designed such that the experimenter and data analyst were blinded to the genotypes and treatments examined. In general, "outliers" were not discarded unless there was an independent observation (*e.g.* health of the slice preparation or animal) that indicates inadequate control of conditions.

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[00112] All patents and publications referred to herein are incorporated by reference herein to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

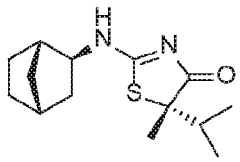
WE CLAIM:

1. A method of treatment of an emotional or psychological symptom of Fragile X Syndrome (FXS), comprising administering to a patient afflicted therewith an effective amount of an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) or an effective amount of an antagonist of corticotropin releasing hormone type 1 receptor (CRHR1).

2. The method of claim 1 wherein the emotional or psychological symptom of FXS is selected from chronic anxiety, social aversion, self-injurious behavior, aggression, obsessive compulsive behaviors, perseverative behavior, and any combination thereof.

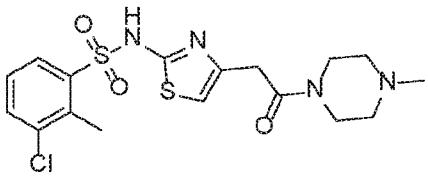
3. The method of claim 2, wherein the emotional or psychological symptom is a chronic anxiety selected from generalized anxiety, social anxiety, specific phobias, novelty anxiety, and combinations thereof.

4. The method of any one of claims 1 to 3, wherein the 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) inhibitor is AMG-221:


(AMG-221)

or a pharmaceutically acceptable salt thereof.

5. The method of any one of claims 1 to 3, wherein the 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) inhibitor is selected from: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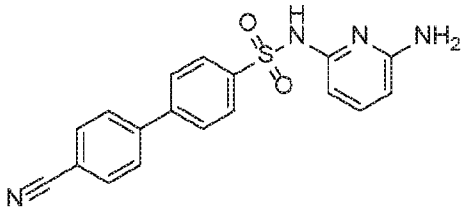

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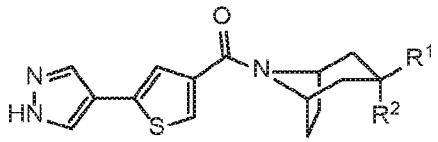

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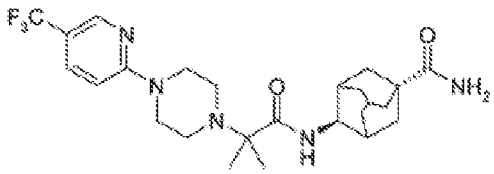
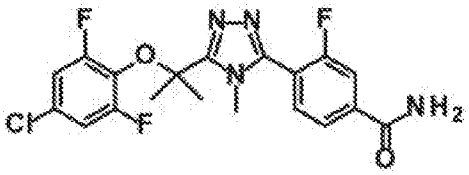


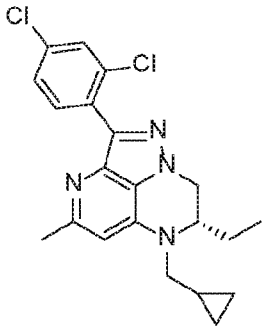
(ABT-384),



(ASP3662), and

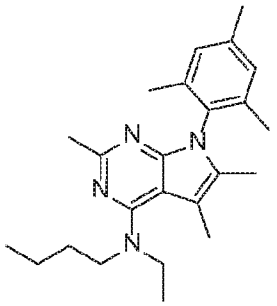
pharmaceutically acceptable salts thereof.

6. The method of any one of claims 1 to 3, wherein the corticotropin releasing hormone receptor type 1 (CRHR1) antagonist is NBI-35965:



or a pharmaceutically acceptable salt thereof.

7. The method of any one of claims 1 to 3, wherein the corticotropin releasing hormone receptor type 1 (CRHR1) antagonist is selected from:



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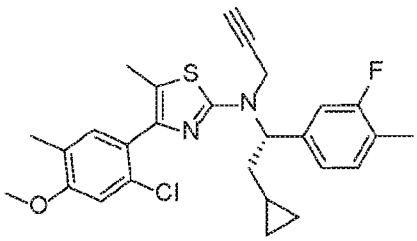

(SSR125543)

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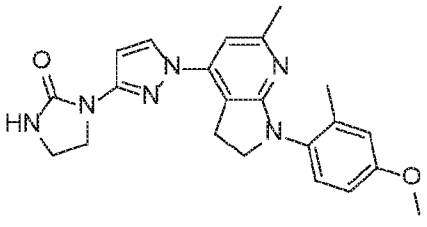

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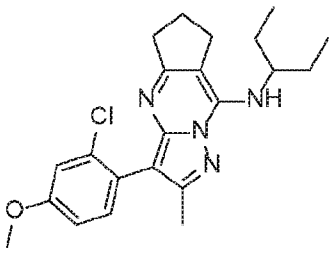

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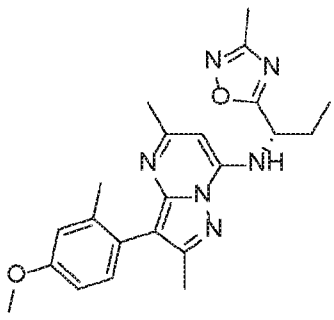


(verucerfont),

and pharmaceutically acceptable salts thereof.

8. A compound that is an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) or an antagonist of corticotropin releasing hormone type 1

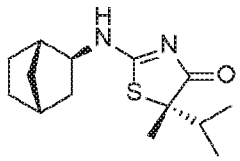
receptor (CRHR1) for use in treating an emotional or psychological symptom of Fragile X Syndrome (FXS).

9. Use of an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) or an antagonist of corticotropin releasing hormone type 1 receptor (CRHR1) for the manufacture of a medicament for treating an emotional or psychological symptom of Fragile X Syndrome (FXS).

10. The compound or use according to claim 8 or 9, wherein the emotional or psychological symptom of FXS is selected from chronic anxiety, social aversion, obsessive compulsive behavior, self-injurious behavior, aggression, perseverative behavior, and any combination thereof.

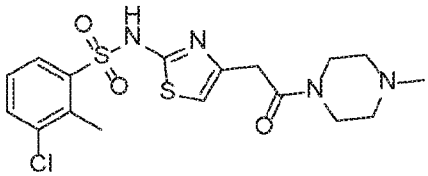
11. The compound or use according to claim 10, wherein the emotional or psychological symptom is a chronic anxiety selected from generalized anxiety, social anxiety, specific phobias, novelty anxiety, and combinations thereof.

12. The compound or use according to any one of claims 8 – 11, wherein the 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) inhibitor is AMG-221:


(AMG-221)

or a pharmaceutically acceptable salt thereof.

13. The compound or use according to any one of claims 8 – 11, wherein the 11β-hydroxysteroid dehydrogenase type 1 (HSD11β1) inhibitor is selected from: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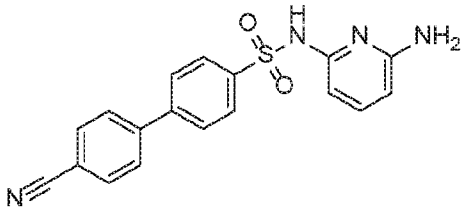

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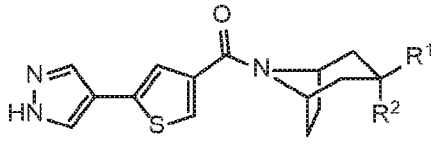

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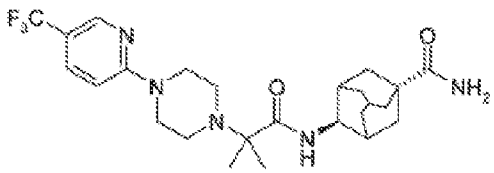

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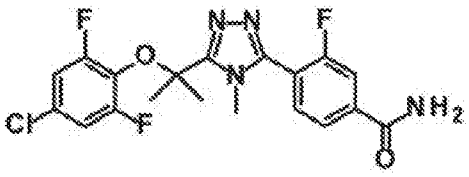
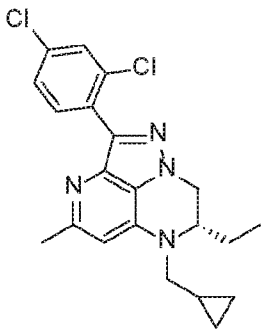


(ASP3662), and

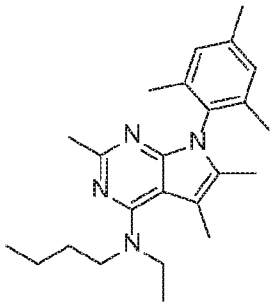
pharmaceutically acceptable salts thereof.

14. The compound or use according to any one of claims 8 – 11, wherein the corticotropin releasing hormone receptor type 1 (CRHR1) antagonist is NBI-35965:



or a pharmaceutically acceptable salt thereof.

15. The compound or use according to any one of claims 8 – 11, wherein the corticotropin releasing hormone receptor type 1 (CRHR1) antagonist is



(antalarmin)

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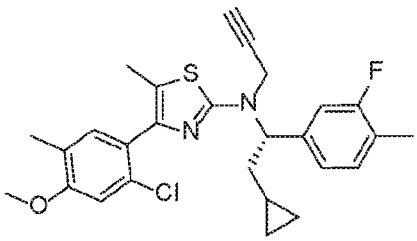

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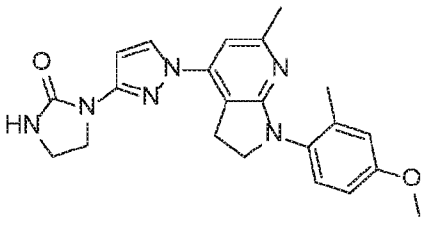

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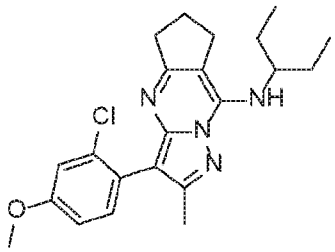

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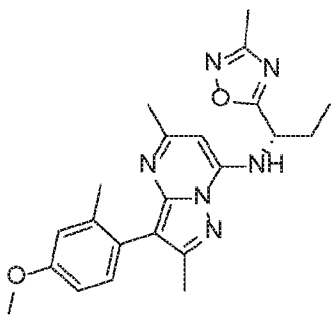


(verucerfont),

and pharmaceutically acceptable salts thereof.

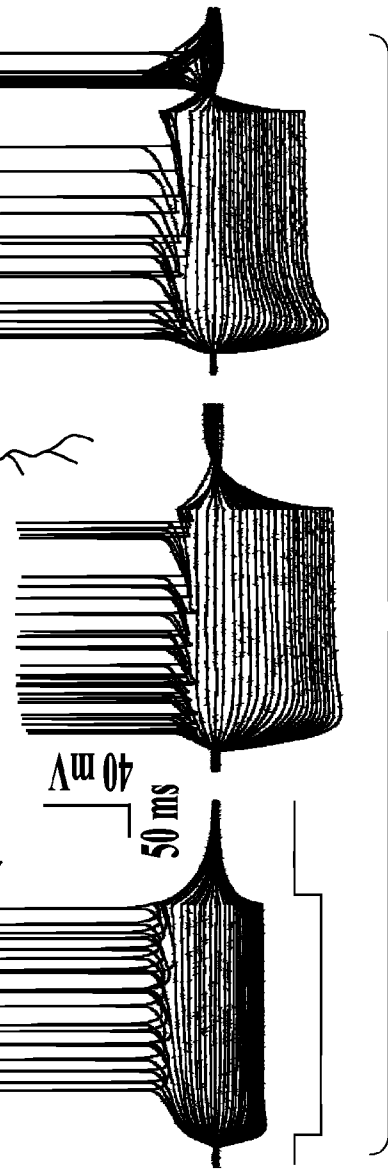


Fig. 1B

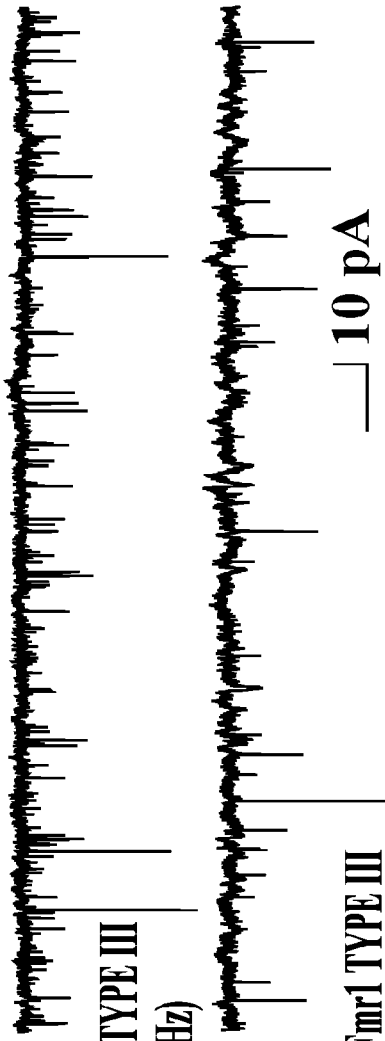


Fig. 1C

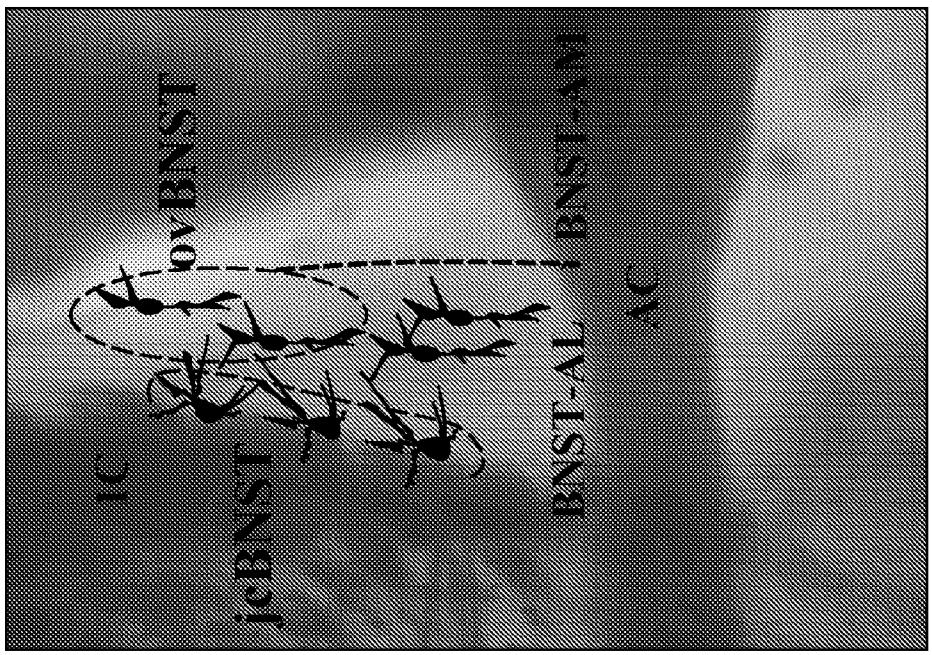


Fig. 1A

	WT	KO	2-TAIL T
RIN	293.5±41.9	196.1±36.9	0.10
I/O	78.1±14.3	45.2±5.8	0.03
RHEO	0.08±0.02	0.17±0.03	0.03
RMP	−64.1±3.7	−69.0±3.3	0.33
VTH	−33.8±1.4	−34.0±1.0	0.89
SPW	1.7±0.15	1.4±0.09	0.14

Fig.2A

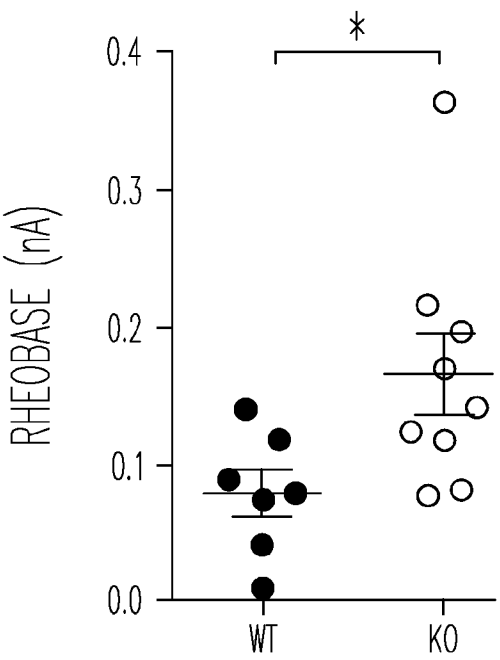


Fig.2B

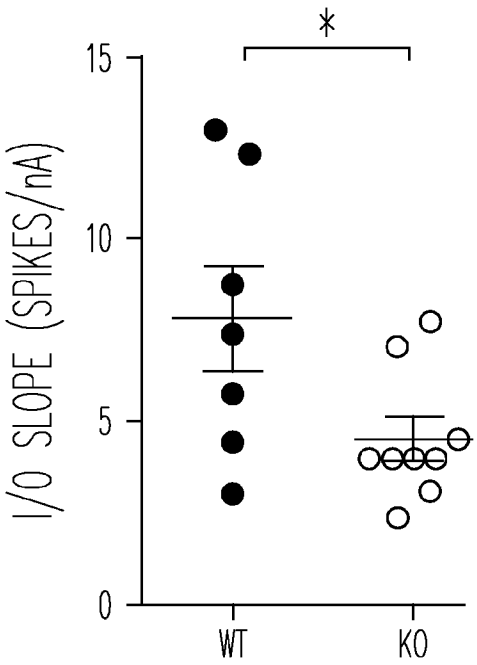


Fig.2C

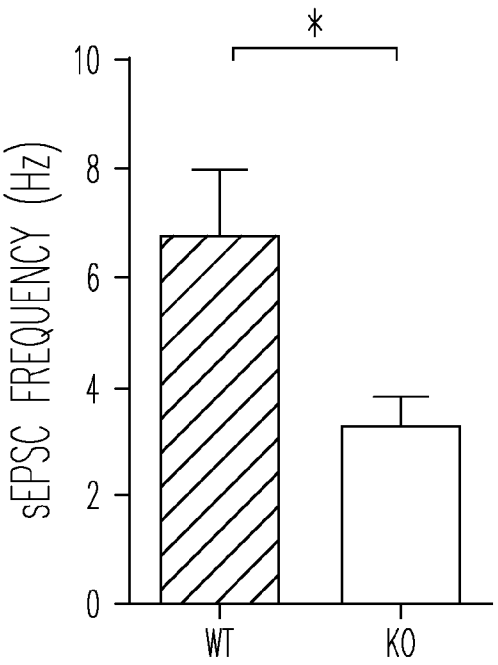

*
10
8
6
4
2
0
sEPSC FREQUENCY (Hz)
WT
KO

Fig.2D

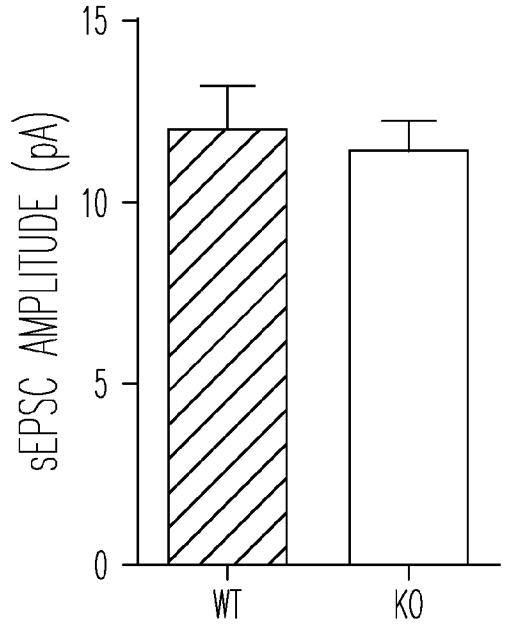

15
10
5
0
sEPSC AMPLITUDE (pA)
WT
KO

Fig.2E

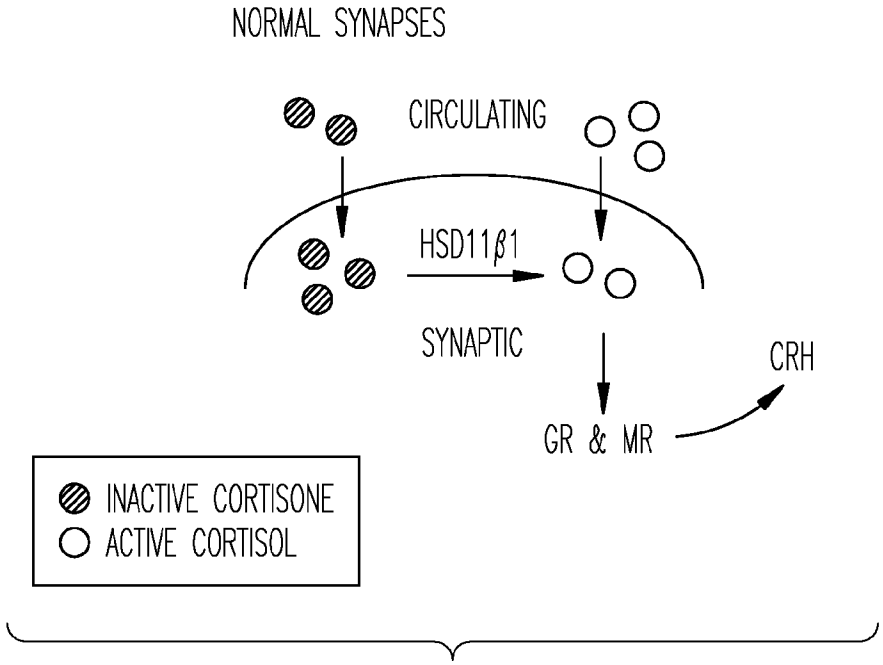

NORMAL SYNAPSES
CIRCULATING
HSD11β1
SYNAPTIC
CRH
GR & MR
INACTIVE CORTISONE
ACTIVE CORTISOL

Fig. 3A

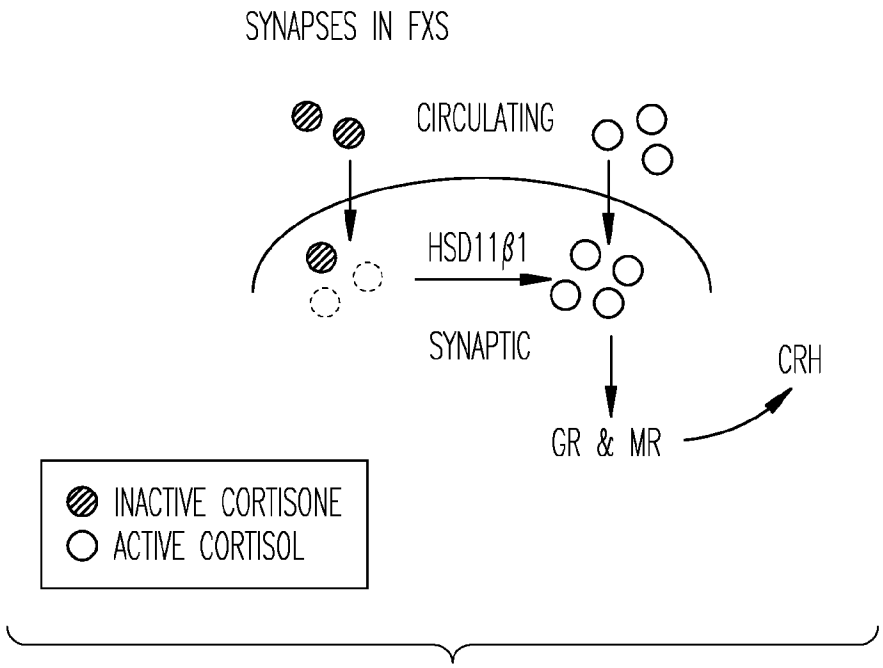

SYNAPSES IN FXS
CIRCULATING
HSD11β1
SYNAPTIC
CRH
GR & MR
INACTIVE CORTISONE
ACTIVE CORTISOL

Fig. 3B

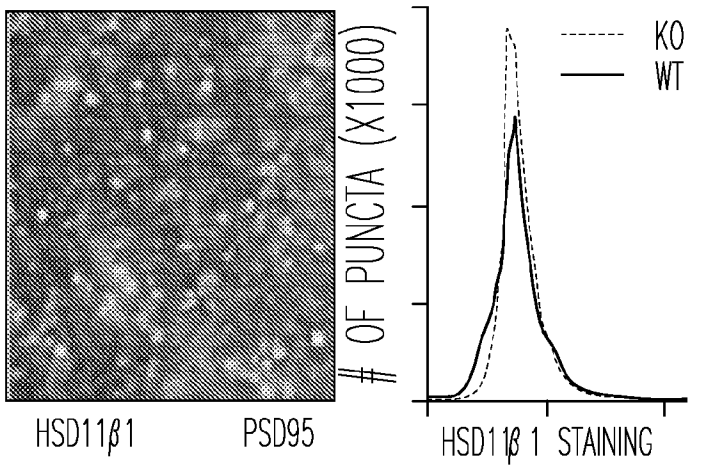


Fig. 3C

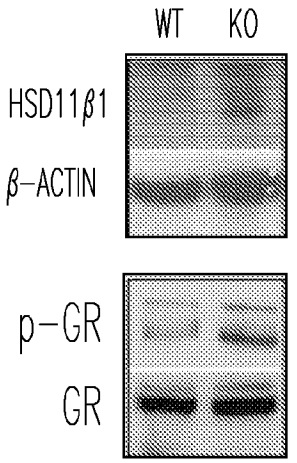


Fig. 3D

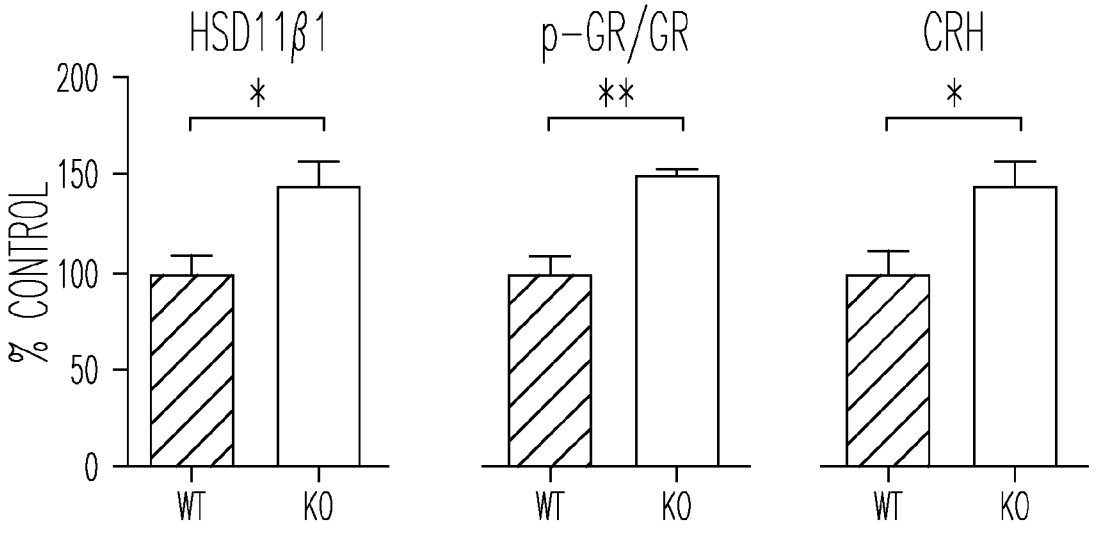


Fig. 3E

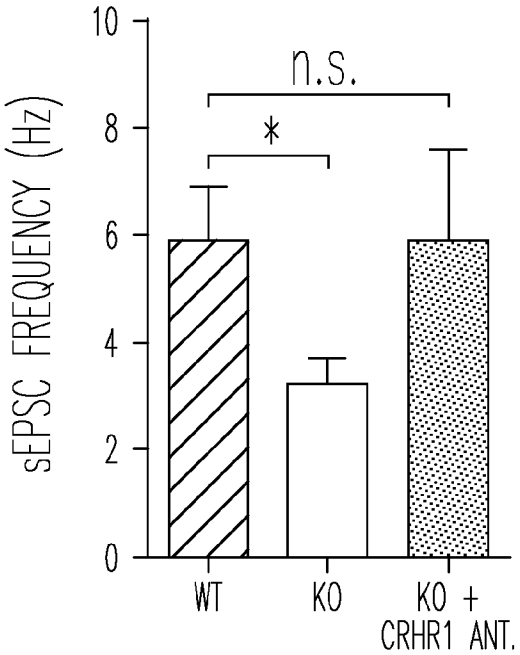


Fig. 4

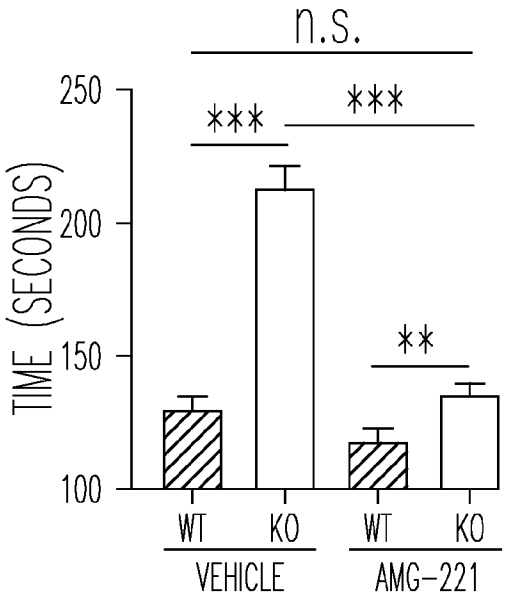


Fig. 5A

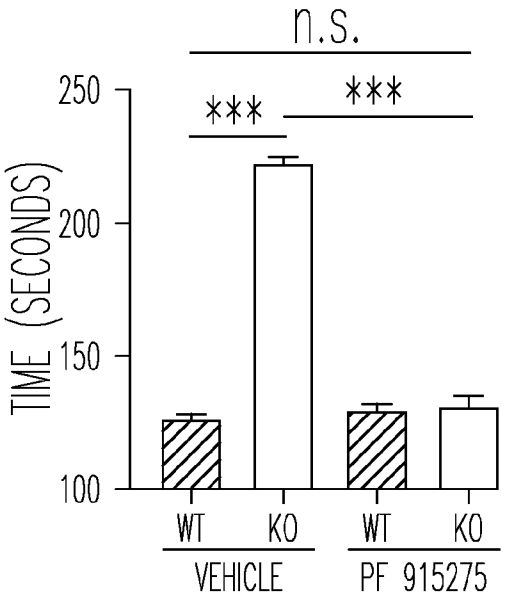


Fig. 5B

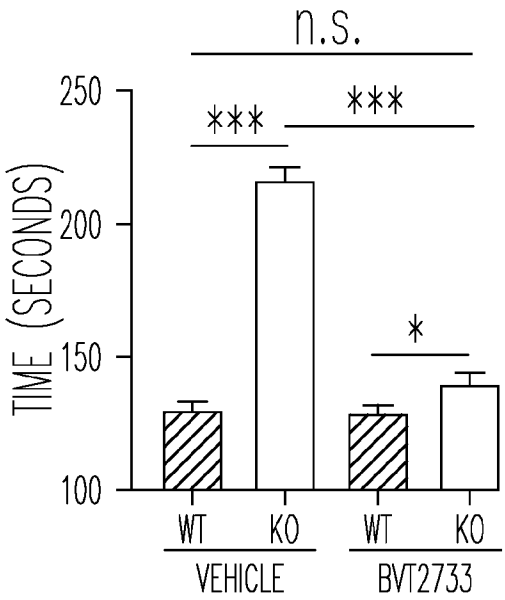


Fig. 5C

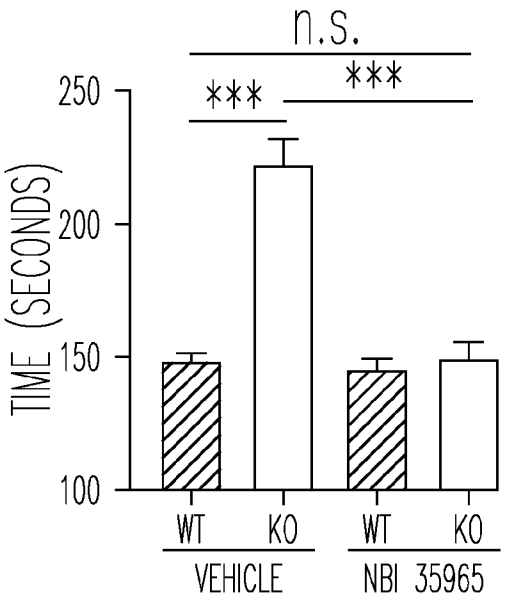


Fig. 5D

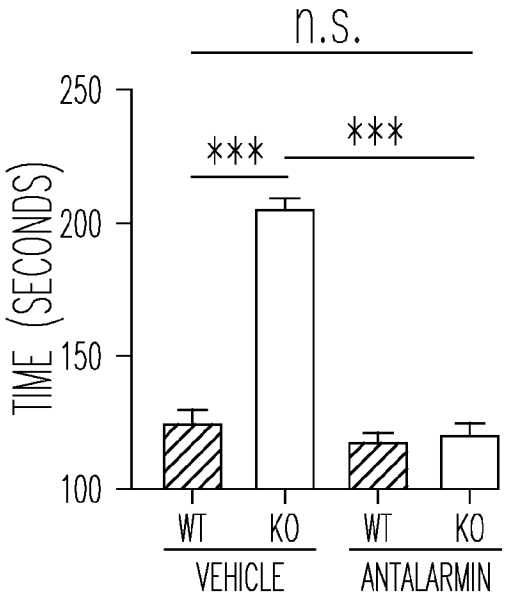
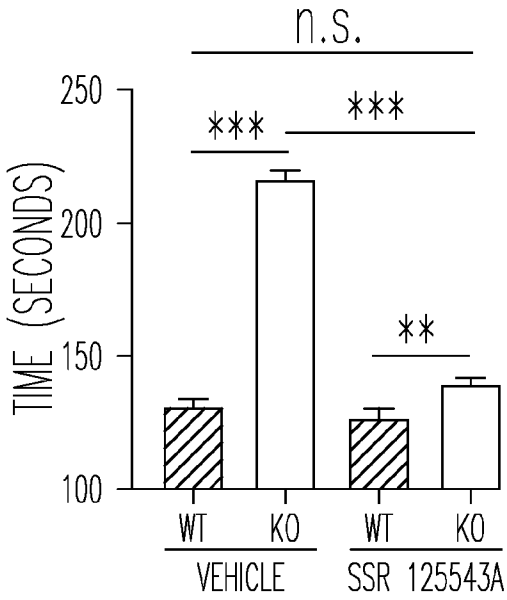

n.s.
***
***
250
200
150
100
TIME (SECONDS)
WT
KO
WT
KO
VEHICLE
ANTALARMIN

Fig. 5E


n.s.
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TIME (SECONDS)
WT
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KO
VEHICLE
SSR 125543A

Fig. 5F

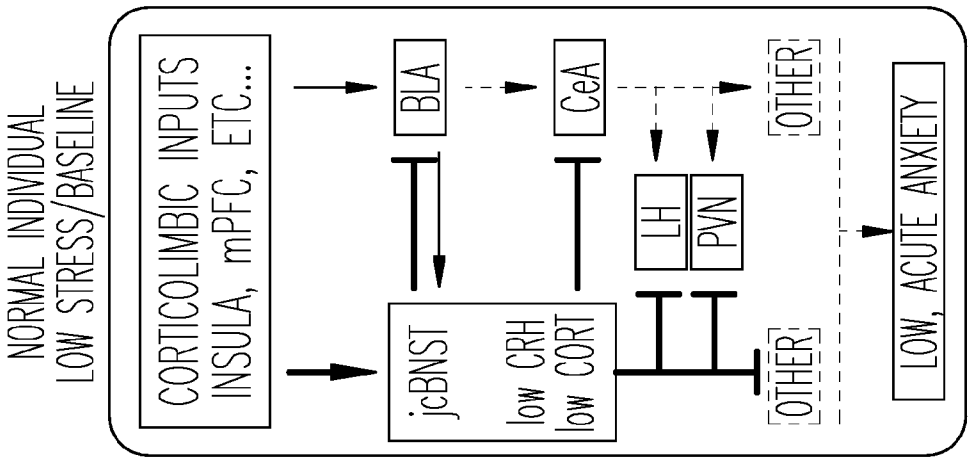

Fig. 6A

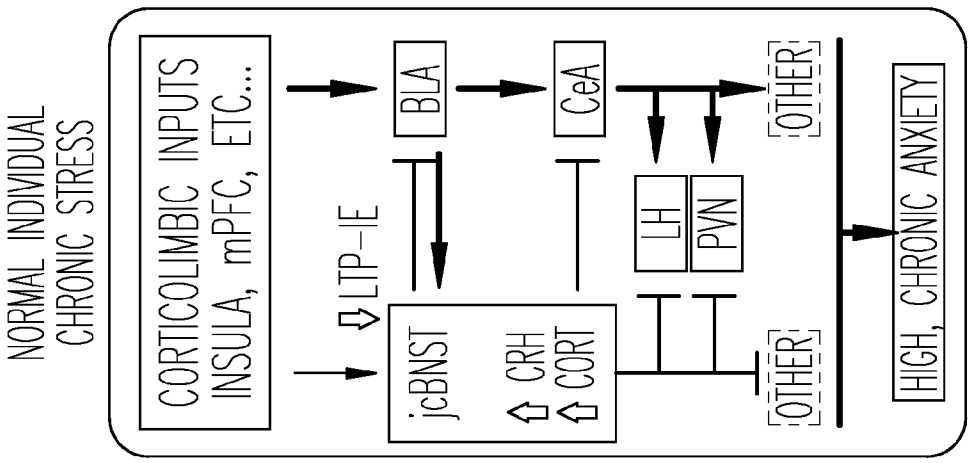

Fig. 6B

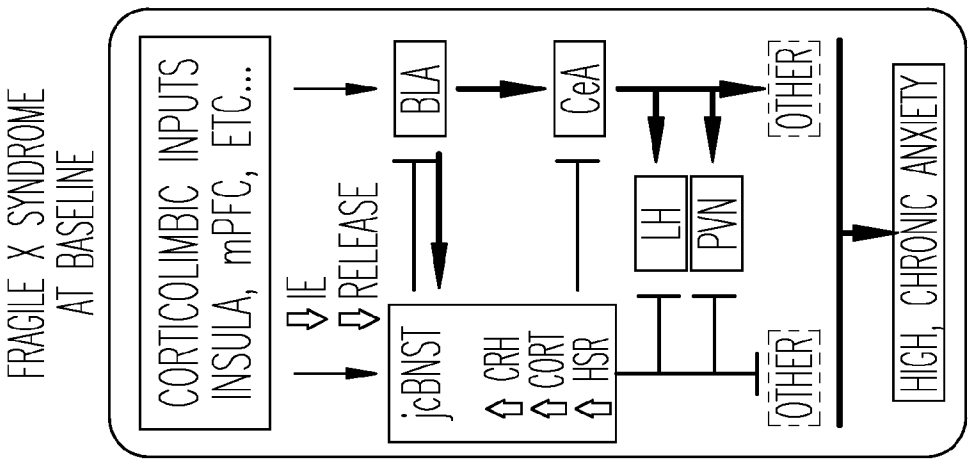

Fig. 6C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/055703

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4155 A61K31/4196 A61K31/426 A61K31/437 A61K31/44
A61K31/4427 A61K31/4985 A61K31/505 A61P25/22 A61P43/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JESSICA EZZELL HUNTER ET AL: "Depression and anxiety symptoms among women who carry the FMR1 premutation: Impact of raising a child with fragile X syndrome is moderated by CRHR1 polymorphisms", AMERICAN JOURNAL OF MEDICAL GENETICS PART B: NEUROPSYCHIATRIC GENETICS, vol. 159B, no. 5, 9 May 2012 (2012-05-09), pages 549-559, XP055540727, ISSN: 1552-4841, DOI: 10.1002/ajmg.b.32061 abstract ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C.

[ ] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2019	25/01/2019

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, Fax: (+31-70) 340-3016	Strack, Eberhard

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/055703

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NOLAN S O ET AL: "The effects of dietary supplementation with n-3 fatty acids on the behavioral and neuroinflammatory phenotype of the Fmr1 knockout mouse (24th Annual PsychoNeuroImmunology Scientific Meeting)", BRAIN, BEHAVIOR AND IMMUNITY, vol. 66, 7 June 2017 (2017-06-07), - 10 June 2017 (2017-06-10), XP085238977, ISSN: 0889-1591, DOI: 10.1016/J.BBI.2017.07.114 the whole document --- Carlo Paribello ET AL: "Open-label add-on treatment trial of minocycline in fragile X syndrome", BMC neurology, 11 October 2010 (2010-10-11), pages 91-91, XP055541472, England DOI: 10.1186/1471-2377-10-91 Retrieved from the Internet: URL:https://bmcneurol.biomedcentral.com/track/pdf/10.1186/1471-2377-10-91 abstract ---	1-15 1-15