Title: PYRAZINONES AS CRF1 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF CNS DISORDERS

Abstract: The present invention provides substituted pyrazinone derivatives of Formula (I) that are CRF\(_1\) receptor antagonists, including human CRF\(_1\) receptors. This invention also relates to use of compounds of the invention for treating a disorder or condition, the treatment of which can be effected or facilitated by antagonizing a CRF receptor, such as CNS disorders, particularly anxiety-related disorders and mood disorders.
PYRAZINONES AS CRF1 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF CNS DISORDERS

FIELD OF THE INVENTION

The present invention relates generally to compounds that bind to CRF receptors, and particularly to pyrazinone derivatives as CRF₁ receptor antagonists and to the use thereof as a treatment for disorders that are associated with CRF or CRF₁ receptors.

BACKGROUND OF THE INVENTION

Corticotropic releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland [J. Rivier et al., Proc. Natl. Acad. Sci (USA) 80:4851 (1983); W. Vale et al., Science 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, CRF is known to have a broad extrahypothalamic distribution in the CNS, contributing therein to a wide spectrum of autonomic behavioral and physiological effects consistent with a neurotransmitter or neuromodulator role in the brain [W. Vale et al., Rec. Prog. Horm. Res. 39:245 (1983); G.F. Koob, Persp. Behav. Med. 2:39 (1985); E.B. De Souza et al., J. Neurosci. 5:3189 (1985)]. There is evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors, in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders, and in the etiology and pathophysiology of Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, progressive supranuclear palsy and amyotrophic lateral sclerosis, as they relate to the dysfunction of CRF neurons in the central nervous system [J.E. Blalock, Physiological Reviews 69:1 (1989); J.E. Morley, Life Sci. 41:527 (1987); E.B. De Souza, Hosp. Practice 23:59 (1988)].

There is evidence that CRF plays a role in affective disorders. Affective disorders, also known as mood disorders, which are well recognized in the art, include, for example, depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; and cyclothymia. It was shown that in individuals afflicted with affective disorder, or major depression, the concentration of CRF in the cerebral spinal fluid (CSF) is significantly increased. [C.B. Nemeroff et al., Science 226:1342 (1984); C.M. Banki et al., Am. J. Psychiatry 144:873 (1987); R.D. France et al., Biol. Psychiatry 28:86 (1988); M. Arato et al., Biol. Psychiatry 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Memeroff et al., Arch. Gen. Psychiatry 45:577 (1988)]. In addition, there is a blunted adrenocorticotropic (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., Am. J. Psychiatry 141:619 (1984); F. Holsboer et al., Psychoneuroendocrinology 9:147 (1984); P.W. Gold et al., New Engl. J. Med. 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the
hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, Arch. Gen. Psychiatry 46:1047 (1989)]. There is also preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of receptors in the brain [Grigoriadis et al., Neuropsychopharmacology 2:53 (1989)].

CRF has also been implicated in the etiology of anxiety-related disorders. Anxiety-related disorders are a group of diseases, recognized in the art, that includes anxiety states, generalized anxiety disorder, phobic disorders, social anxiety disorder, anxiety with co-morbid depressive illness, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and atypical anxiety disorders. [The Merck Manual of Diagnosis and Therapy, 16th edition (1992)]. Emotional stress is often a precipitating factor in anxiety disorders, and such disorders generally respond to medications that lower response to stress. Excessive levels of CRF are known to produce anxiogenic effects in animal models [see, e.g., Britton et al., 1982; Berridge and Dunn, 1986 and 1987]. Interactions between benzodiazepine/non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., Life Sci. 31:363 (1982); C.W. Berridge and A.J. Dunn, Regul. Peptides 16:83 (1986)]. Studies using the putative CRF receptor antagonist α-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrates that the antagonist produces “anxiolytic-like” effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn, Horm. Behav. 21:393 (1987), Brain Research Reviews 15:71 (1990); G.F. Koob and K.T. Britton, In: Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, E.B. De Souza and C.B. Nemeroff eds., CRC Press p.221 (1990)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chloridiazepoxide attenuates the “anxiogenic” effects of CRF both in the conflict test [K.T. Britton et al., Psychopharmacology 86:170 (1985); K.T. Britton et al., Psychopharmacology 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., Psychopharmacology 88:147 (1986)] in rats. The benzodiazepine receptor antagonist Ro 15-1788, which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist FG 7142 enhanced the actions of CRF [K.T. Britton et al., Psychopharmacology 94:396 (1988)].


It has also been suggested that CRF₁ antagonists are useful for treating arthritis and inflammation disorders [Webster EL, et al.: J Rheumatol 2002 Jun; 29(6):1252-61; Murphy

It was disclosed recently that, in an animal model, stress-induced exacerbation of chronic contact dermatitis is blocked by a selective CRF₁ receptor antagonist, suggesting that that CRF₁ is involved in the stress-induced exacerbation of chronic contact dermatitis and that CRF₁ antagonist may be useful for treating this disorder. [Kaneko K, Kawana S, Arai K, Shibasaki T. *Exp Dermatol*, 12(1):47-52 (2003).

WO 0219975 discloses hair growth stimulants containing a corticotropin release factor CRF₁ receptor antagonist as the active ingredient. It was shown that CRF₁ receptor antagonist 2-[N-(2-methylythio-4-isopropylphenyl)-N-ethylamino]-4-[4-(3-fluorophenyl)-1,2,3,6-tetrahydropyridine-1-yl]-6-methylpyrimidine showed keratinocyte cell proliferation promoting effect in cultured human epidermal keratinocyte cells.

WO 0160806 discloses compounds as antagonists of CRF₁ receptors.

WO 0155115 discloses compounds as activators of caspases and inducers of apoptosis.

WO 0059902 discloses compounds as factor Xa inhibitors.

WO 9639374 discloses compounds having retinoid-like biological activity.

The following patents or patent applications disclose compounds as inhibitors of farnesyl-protein transferase: WO 9829119, WO 9736886, WO 9736898, and U.S. Patents Nos. 5872136, 5880140, and 5883105.

The following patent applications disclose compounds and their use in liquid crystal mixtures: W9827042, WO9827045, and WO9827179.

It is an object of the invention to provide novel pyrazinone derivatives, which are CRF₁ receptor antagonists.

It is another object of the invention to provide novel compounds as treatment of disorders or conditions that are associated with CRF or CRF₁ receptors, such as anxiety disorders, depression, and stress related disorders.

It is another object of the invention to provide a method of treating disorders or conditions that are associated with CRF or CRF₁ receptors, such as anxiety disorders, depression, and stress related disorders.

It is yet another object of the invention to provide a pharmaceutical composition useful for treating disorders or conditions that are associated with CRF or CRF₁ receptors, such as anxiety disorders, depression, and stress related disorders.

There are other objects of the invention which will be evident or apparent from the description of the invention in the specification of the application.
SUMMARY OF THE INVENTION

In one aspect, the present invention provides a compound of Formula I,

\[
\begin{array}{c}
\text{X} \quad \text{R}_2 \\
\text{R}_1 \quad \text{N} \quad \text{O} \\
\text{R}_3 \quad \text{N} \quad \text{Ar}
\end{array}
\]

Formula I

or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a prodrug thereof,

wherein in Formula I:

- \(X\) is selected from \(-\text{NR}_3\text{R}_4\), \(-\text{OR}_3\), \(-\text{CR}_3\text{R}_5\text{R}_6\), \(-\text{C(O)R}_5\), \(-\text{S(O)}_m\text{R}_5\), \(-\text{NR}_3\text{C(O)R}_4\), or \(-\text{NR}_3\text{S(O)}_m\text{R}_4\);

- \(\text{R}_3\) and \(\text{R}_4\) are selected from \(-\text{R}_6\), heterocycloalkyl, substituted heterocycloalkyl, aryl cycloalkyl, substituted aryl cycloalkyl, heteroaryl cycloalkyl, substituted heteroaryl cycloalkyl, aryl heterocycloalkyl, substituted aryl heterocycloalkyl, heteroaryl heterocycloalkyl, or substituted heteroaryl heterocycloalkyl;

- \(\text{R}_1\) and \(\text{R}_5\) are independently selected from \(-\text{H}, -\text{CN}, -\text{NO}_2, -\text{OR}_6, -\text{NR}_6\text{R}_7, -\text{C(O)R}_6, -\text{C(S)R}_6, -\text{C(O)OR}_6, -\text{C(S)OR}_6, -\text{C(O)NR}_6\text{R}_7, -\text{C(S)NR}_6\text{R}_7, -\text{NR}_6\text{C(O)R}_6, -\text{NR}_6\text{C(S)R}_6, -\text{NR}_6\text{C(O)NR}_6\text{R}_7, -\text{NR}_6\text{C(S)NR}_6\text{R}_7, -\text{OC(O)OR}_6, -\text{OC(S)OR}_6, -\text{OC(O)NR}_6\text{R}_7, -\text{OC(S)NR}_6\text{R}_7, -\text{S(O)}_m\text{NR}_6\text{R}_7, -\text{NR}_6\text{S(O)}_m\text{R}_7\), alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, cycloalkyl, and substituted cycloalkyl;

- \(\text{R}_2\) is independently selected from \(-\text{C(O)R}_6, -\text{C(S)R}_6, -\text{C(O)OR}_6, -\text{C(S)OR}_6, -\text{C(O)NR}_6\text{R}_7, -\text{C(S)NR}_6\text{R}_7, -\text{S(O)}_m\text{NR}_6\text{R}_7, -\text{NR}_6\text{S(O)}_m\text{R}_7\), alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, haloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl and substituted heterocycloalkyl;

- \(m\) is selected from 0, 1, or 2;

- \(\text{R}_6\) is independently selected from \(-\text{H}, \text{alkyl}, \text{cycloalkyl}, \text{haloalkyl}, \text{aryl}, \text{heteroaryl}, \text{or heterocycloalkyl}, \text{wherein alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, and heterocycloalkyl each is optionally substituted with 1-5 R}_7;

- \(\text{Ar}\) is independently selected from \(\text{aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl cycloalkyl, substituted aryl cycloalkyl, heteroaryl heterocycloalkyl, and substituted heteroaryl heterocycloalkyl}.

- \(\text{R}_b\) is independently selected from \(-\text{NO}_2, -\text{NR}_b\text{R}_b, -\text{OR}_b, -\text{SR}_b, -\text{C(O)NR}_b\text{R}_b, -\text{OC(O)R}_b, -\text{NR}_b\text{C(O)NR}_b\text{R}_b, -\text{NR}_b\text{C(O)OR}_b, -\text{S(O)}_m\text{R}_b\text{R}_b, -\text{NR}_b\text{S(O)}_m\text{R}_b\text{R}_b, -\text{S(O)}_m\text{NR}_b\text{R}_b\text{R}_b, -\text{NR}_b\text{S(O)}_m\text{NR}_b\text{R}_b\text{R}_b, \text{halogen, alkyl,} \text{cycloalkyl,} \text{phenyl, benzyl, heteroaryl or heterocycloalkyl, wherein phenyl, benzyl, heteroaryl and heterocycloalkyl is optionally substituted with alkyl or halogen;
R₂ is independently selected from -H, -C(O)alkyl, -C(S)alkyl, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, or heterocycloalkyl, wherein -C(O)alkyl, -C(S)alkyl, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, and heterocycloalkyl each is optionally substituted with 1-5 R₃.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of Formula I, a stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a prodrug thereof, or a pharmaceutically acceptable salt of the prodrug thereof. The compositions can be prepared in any suitable forms such as tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, and ointments.

The compounds of the inventions are CRF₁ receptor antagonists and are useful for treating disorders or conditions associated with CRF or CRF₁ receptors, including human CRF₁ receptors.

Thus, in another aspect, the present invention provides a method of antagonizing CRF₁ receptors in a warm-blooded animal, comprising administering to the animal a compound of the invention at a amount effective to antagonize CRF₁ receptors.

In still another aspect, the present invention provides a method for screening for ligands for CRF₁ receptors, which method comprises: a) carrying out a competitive binding assay with CRF₁ receptors, a compound of Formula I which is labelled with a detectable label, and a candidate ligand; and b) determining the ability of said candidate ligand to displace said labelled compound.

In still another aspect, the present invention provides a method for detecting CRF₁ receptors in a tissue comprising: a) contacting a compound of Formula I, which is labelled with a detectable label, with a tissue, under conditions that permit binding of the compound to the tissue; and b) detecting the labelled compound bound to the tissue.

In yet another aspect, the present invention provides a method of inhibiting the binding of CRF to CRF₁ receptors in vitro, comprising contacting a compound of the invention with a solution comprising cells expressing the CRF₁ receptor, such as IMR32 cells, wherein the compound is present in the solution at a concentration sufficient to inhibit the binding of CRF to the CRF₁ receptor.

Compounds of the invention are useful for treating, in a warm-blooded animal, particularly a mammal, and more particularly a human, various disorders that are associated with CRF or CRF₁ receptors, or disorders the treatment of which can be effected or facilitated by antagonizing CRF₁ receptors. Examples of such disorders include anxiety-related disorders (such as anxiety states, generalized anxiety disorder, phobic disorders, social anxiety disorder, anxiety with co-morbid depressive illness, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and atypical anxiety disorders); mood disorders, also known as affective disorders (such as depression, including major depression,
single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; and cyclothymia); supranuclear palsy; immune suppression; inflammatory disorders (such as rheumatoid arthritis and osteoarthritis); fertility problems including infertility; pain; asthma; allergies; sleep disorders induced by stress; pain perception (such as fibromyalgia); chronic fatigue syndrome; stress-induced headache; cancer; human immunodeficiency virus (HIV) infections; neurodegenerative diseases (such as Alzheimer’s disease, Parkinson’s disease and Huntington’s disease); gastrointestinal diseases (such as ulcers, irritable bowel syndrome, Crohn’s disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress); eating disorders (such as anorexia and bulimia nervosa and other feeding disorders); hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone (ADH); obesity; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders (such as hypertension, tachycardia, congestive heart failure, and stroke); immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation; and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer’s type; multifarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependences on alcohol, cocaine, heroin, benzodiazepines, or other drugs); osteoporosis; psychosocial dwarfism, hypoglycemia, and skin disorders (such as acne, psoriasis, chronic contact dermatitis, and stress-exacerbated skin disorders). They are also useful for promoting smoking cessation and hair growth, or treating hair loss.

Thus, in yet a further aspect the present invention provides a method of treating a disorder, in warm-blooded animal, the treatment of which disorder can be effected or facilitated by antagonizing CRF₁ receptors, which method comprises administration to a patient in need thereof an effective amount of a compound of Formula I. In a particular embodiment the invention provides a method for the treatment of disorders that manifest hypersecretion of CRF. Examples of disorders that can be treated with the compounds of the invention include generalized anxiety disorder; social anxiety disorder; anxiety; obsessive-compulsive disorder; anxiety with co-morbid depressive illness; panic disorder; and mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, postpartum depression, hair loss, and contact dermatitis. It is preferred that the warm-blooded animal is a mammal, and more preferred that the animal is a human.
DETAILED DESCRIPTION OF THE INVENTION

In the first aspect, the invention provides a compound of Formula I as described above.

Following are examples of particular compounds of the invention, with each compound being identified both by a chemical name and a structural formula immediately below the chemical name:

3-(2,4-dichlorophenyl)-6-[[1R,2S]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one

(1R,2S)-1-[[5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2,4-dichlorophenyl)-6-[[1R,2S]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-dieethylpyrazin-2(1H)-one
(1R,2S)-1-[[5-(2,4-dichlorophenyl)-1,3-diethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2,4-dichlorophenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-dimethylpyrazin-2(1H)-one

(1R,2S)-1-[[5-(2,4-dichlorophenyl)-1,3-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2,4-dichlorophenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1-ethyl-5-methylpyrazin-2(1H)-one
(1R,2S)-1-([5-(2,4-dichlorophenyl)-1-ethyl-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate

3-(2,4-dichlorophenyl)-6-[[[1S,2S]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one

3-(2,4-dichlorophenyl)-6-[[[1R,2R]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one

3-(2-chloro-4-methoxyphenyl)-6-[[[1R,2S]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one
(1R,2S)-1-[[5-(2-chloro-4-methoxyphenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2-chloro-4-methoxyphenyl)-6-[[1R,2S]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethylpyrazin-2(1H)-one

(1R,2S)-1-[[5-(2-chloro-4-methoxyphenyl)-1,3-diethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2-chloro-4-methoxyphenyl)-6-[[1R,2S]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-dimethylpyrazin-2(1H)-one
(1R,2S)-1-[[5-(2-chloro-4-methoxyphenyl)-1,3-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2-chloro-4-methoxyphenyl)-6-(((1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl)amino)-1-ethyl-5-methylpyrazin-2(1H)-one

(1R,2S)-1-[[5-(2-chloro-4-methoxyphenyl)-1-ethyl-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-[2-chloro-4-(dimethylamino)phenyl]-6-(((1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl)amino)-5-ethyl-1-methylpyrazin-2(1H)-one
(1R,2S)-1-((5-[2-chloro-4-(dimethylamino)phenyl]-3-ethyl-1-methyl-6-oxo-1,6-
dihydropyrazin-2-yl)amino)-2,3-dihydro-1H-inden-2-yl acetate

3-[2-chloro-4-(dimethylamino)phenyl]-6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-
yl]amino)-1,5-diethylpyrazin-2(1H)-one

(1R,2S)-1-((5-[2-chloro-4-(dimethylamino)phenyl]-1,3-diethyl-6-oxo-1,6-
dihydropyrazin-2-yl)amino)-2,3-dihydro-1H-inden-2-yl acetate

3-[2-chloro-4-(dimethylamino)phenyl]-6-([(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-
yl]amino)-1,5-dimethylpyrazin-2(1H)-one
(1R,2S)-1-((5-[2-chloro-4-(dimethylamino)phenyl]-1,3-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate

3-[2-chloro-4-(dimethylamino)phenyl]-6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1-ethyl-5-methylpyrazin-2(1H)-one

(1R,2S)-1-((5-[2-chloro-4-(dimethylamino)phenyl]-1-ethyl-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate

3-[6-(dimethylamino)-4-methylpyridin-3-yl]-6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one
(1R,2S)-1-((5-[(6-(dimethylamino)-4-methylpyridin-3-yl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl)acetate

3-[(6-(dimethylamino)-4-methylpyridin-3-yl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethylpyrazin-2(1H)-one]

(1R,2S)-1-((5-[(6-(dimethylamino)-4-methylpyridin-3-yl)-1,3-diethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl)acetate

3-[(6-(dimethylamino)-4-methylpyridin-3-yl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-dimethylpyrazin-2(1H)-one]
(1R,2S)-1-[(5-[6-(dimethylamino)-4-methylpyridin-3-yl]-1,3-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl)amino]-2,3-dihydro-1H-inden-2-yl acetate

3-[6-(dimethylamino)-4-methylpyridin-3-yl]-6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl)amino]-1-ethyl-5-methylpyrazin-2(1H)-one

(1R,2S)-1-[(5-[6-(dimethylamino)-4-methylpyridin-3-yl]-1-ethyl-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl)amino]-2,3-dihydro-1H-inden-2-yl acetate

6-[[1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl)amino]-5-ethyl-3-(4-methoxy-2-methylphenyl)-1-methylpyrazin-2(1H)-one
(1R,2S)-1-[[3-ethyl-5-(4-methoxy-2-methylphenyl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2,4-dimethoxyphenyl)-6-[[1R,2S]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one

(1R,2S)-1-[[5-(2,4-dimethoxyphenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2,6-dimethoxypyridin-3-yl)-6-[[1R,2S]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one
(1R,2S)-1-[[5-(2,6-dimethoxyypyridin-3-yl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2,6-dimethoxyppyridin-3-yl)-6-[[1(R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethylpyrazin-2(1H)-one

(1R,2S)-1-[[5-(2,6-dimethoxyppyridin-3-yl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2,6-dimethoxyppyridin-3-yl)-6-[[1(R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-dimethylpyrazin-2(1H)-one
(1R,2S)-1-[[5-(2,6-dimethoxypyridin-3-yl)-1,3-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

3-(2,6-dimethoxypyridin-3-yl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1-ethyl-5-methylpyrazin-2(1H)-one

(1R,2S)-1-[[5-(2,6-dimethoxypyridin-3-yl)-1-ethyl-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-3-(6-methoxy-2-methylpyridin-3-yl)-1-methylpyrazin-2(1H)-one
(1R,2S)-1-[(3-ethyl-5-(6-methoxy-2-methylpyridin-3-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)amino]-2,3-dihydro-1H-inden-2-yl acetate

6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethyl-3-(6-methoxy-2-methylpyridin-3-yl)pyrazin-2(1H)-one

(1R,2S)-1-[(1,3-diethyl-5-(6-methoxy-2-methylpyridin-3-yl)-6-oxo-1,6-dihydropyrazin-2-yl)amino]-2,3-dihydro-1H-inden-2-yl acetate

6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-3-(6-methoxy-2-methylpyridin-3-yl)-1,5-dimethylpyrazin-2(1H)-one
(1R,2S)-1-[[5-(6-methoxy-2-methylpyridin-3-yl)-1,3-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

6-[[1R,2S]-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1-ethyl-3-(6-methoxy-2-methylpyridin-3-yl)-5-methylpyrazin-2(1H)-one

(1R,2S)-1-[[1-ethyl-5-(6-methoxy-2-methylpyridin-3-yl)-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate

benzyl (3R,4S)-3-[[5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxyprrolidine-1-carboxylate
3-((2,4-dichlorophenyl)-6-(((3R,4S)-4-ethoxy pyrrolidin-3-yl)amino)-5-ethyl-1-methylpyrazin-2(1H)-one

methyl (3R,4S)-3-((5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)amino)-4-ethoxy pyrrolidine-1-carboxyla

O-methyl (3R,4S)-3-((5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)amino)-4-ethoxy pyrrolidine-1-carbothioate

6-(((3R,4S)-1-acetyl-4-ethoxy pyrrolidin-3-yl)amino)-3-(2,4-dichlorophenyl)-5-ethyl-1-methylpyrazin-2(1H)-one
ethyl (3R,4S)-3-[[5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxypyrrolidine-1-carboxylate

isopropyl (3R,4S)-3-[[5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxypyrrolidine-1-carboxylate

(3R,4S)-3-[[5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxy-N-methylpyrrolidine-1-carboxamide

(3R,4S)-3-[[5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxy-N-methylpyrrolidine-1-carbothioamide

benzyl (3R,4S)-3-[[5-(2-chloro-4-methoxyphenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxypyrrolidine-1-carboxylate
methyl (3R,4S)-3-[[5-(2-chloro-4-methoxyphenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxypyrrolidine-1-carboxylate

benzyl (3R,4S)-3-[[5-[2-chloro-4-(dimethylamino)phenyl]-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxypyrrolidine-1-carboxylate

methyl (3R,4S)-3-[[5-[2-chloro-4-(dimethylamino)phenyl]-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxypyrrolidine-1-carboxylate

benzyl (3R,4S)-3-[[5-[6-(dimethylamino)-4-methylpyridin-3-yl]-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxypyrrolidine-1-carboxylate
methyl (3R,4S)-3-[[5-[(6-dimethylamino)-4-methylpyridin-3-yl]-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl] amino]-4-ethoxypyrrolidine-1-carboxylate

benzyl (3R,4S)-3-[[5-(2,6-dimethoxypyridin-3-yl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl] amino]-4-ethoxypyrrolidine-1-carboxylate

methyl (3R,4S)-3-[[5-(2,6-dimethoxypyridin-3-yl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl] amino]-4-ethoxypyrrolidine-1-carboxylate

benzyl (3S,4R)-3-ethoxy-4-[[3-ethyl-5-(6-methoxy-2-methylpyridin-3-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl] amino]pyrrolidine-1-carboxylate
methyl (3S,4R)-3-ethoxy-4-[[3-ethyl-5-((6-methoxy-2-methylpyridin-3-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)amino]pyrrolidine-1-carboxylate

3-(2,4-dichlorophenyl)-6-[[3R,4S]-4-ethoxy-1-pyrindin-2-yl]pyrrolidin-3-yl]amino)-5-ethyl-1-methylpyrazin-2(1H)-one

3-(2-chloro-4-methoxyphenyl)-6-[[3R,4S]-4-ethoxy-1-pyrindin-2-yl]pyrrolidin-3-yl]amino)-5-ethyl-1-methylpyrazin-2(1H)-one

3-(2,4-dichlorophenyl)-6-[[3R,4S]-4-ethoxy-1-pyrimidin-2-yl]pyrrolidin-3-yl]amino)-5-ethyl-1-methylpyrazin-2(1H)-one
3-(2-chloro-4-methoxyphenyl)-6-[[[3R,4S]-4-ethoxy-1-pyrimidin-2-ylpyrrolidin-3-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one

3-(2,4-dichlorophenyl)-6-[[[3R,4S]-4-ethoxy-1-{(1,3-thiazol-2-yl)pyrrolidin-3-yl}amino]-5-ethyl-1-methylpyrazin-2(1H)-one

Compounds of the present invention can be prepared using the reactions depicted in Chart A, B, C and D indicated below. Starting materials can be prepared by procedures described in these charts or by procedures that would be well known to one of ordinary skill in organic chemistry.

According to the general Chart A, wherein \( R_1 \) is as defined for Formula I, compound A-II can be prepared from A-I and an amine in the presence of a suitable transition metal catalyst such as, but not limited to, palladium(II) acetate or tris(dibenzylideneacetone)dipalladium(0), a ligand such as, but not limited to, 1,1'-bis(diphenylphosphino)ferrocene, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, dicyclohexyl(2-biphenyl)phosphine, tricyclohexylphosphine, or tri-tert-butylphosphine, and a base such as sodium or potassium tert-butoxide in inert solvents such as, but not limited to, toluene, ethyleneglycol dimethyl ether, diglyme, DMF, or N-methylpyrrolidinone at temperatures ranging from ambient to 100 °C. (Thio)alkoxy pyrazines can be prepared by
treating A-I with a sodium or potassium salt of an alcohol or thiol in an inert solvent such as THF, DMF, N-methylpyrrolidinone, or methyl sulfoxide at ambient temperature or at elevated temperature up to the boiling point of the solvent employed. Halogenation of A-II to afford A-III may be accomplished by a variety of methods known in the art, including treatment with N-chlorosuccinimide, bromine, N-bromosuccinimide, pyridinium tribromide, triphenylphosphine dibromide, iodine, and N-iodosuccinimide in solvents such as but not limited to dichloromethane, acetic acid, or methyl sulfoxide. The halopyrazine A-III can be converted to arylpyrazine A-IV by a transition metal-catalyzed coupling reaction with a metalloaryl reagent (G-[M]). More commonly employed reagent/catalyst pairs include aryl boronic acid/palladium(0) (Suzuki reaction; N. Miyaura and A. Suzuki, Chemical Review 1995, 95, 2457), aryl trialkylstannane/palladium(0) (Stille reaction; T. N. Mitchell, Synthesis 1992, 803), arylzinc/palladium(0) and aryl Grignard/nickel(II). Palladium(0) represents a catalytic system made of a various combination of metal/ligand pair which includes, but not limited to, tetrakis(triphenylphosphine)palladium(0), palladium(II) acetate/tri(o-tolyl)phosphine, tris(dibenzylideneacetone)dipalladium(0)/tri-tert-butylphosphine and dichloro[1,1’-bis(diphenylphosphino)ferrocene]palladium(0). Nickel(II) represents a nickel-containing catalyst such as [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) and [1,3-bis(diphenylphosphino)propane]dichloronickel(II). The arylpyrazine A-IV, when X is NH, may be further transformed to V by N-alkylation. The N-H group is deprotonated by a strong base such as, but not limited to, alkali metal hydride, alkali metal amide, or alkali metal alkoxide in inert solvents such as, but not limited to, THF, DMF, or methyl sulfoxide. Alkylation may be conducted using alkyl halide, suitably bromide or iodide, at temperatures ranging from 0 °C to 100 °C. Oxidation of the sterically less hindered nitrogen of A-IV can be effected by using a variety of oxidizing agents known in the art, which includes m-chloroperoxybenzoic acid, trifluoroperacetic acid, hydrogen peroxide and monoperoxyphthalic acid to provide A-V. The N-oxide can undergo rearrangement to give pyrazinone A-VI upon treatment with an acid anhydride such as acetic anhydride (N. Bashir and D. G. I. Kingston, Heterocycles 1989, 29, 1127). Alkylation of pyrazinone A-VI may be accomplished by a variety of methods known in the art, including treatment with a suitable electrophiles, such as alkyl halide, alkyl mesylate or alkyl triflate, in the presence of a suitable base, such as, but not limited to, sodium hydroxide, potassium hydroxide, sodium methoxide, or sodium hydride in a suitable solvent such as, but not limited to, methanol, diethyl ether, or dimethylformamide. Alternatively, diazomethane can be used to accomplish the aforementioned transformation wherein R₂ would be a methyl group (Dutcher, J. Biol. Chem. 1947, 171, 321).
Chart A illustrates an alternative synthesis whereby A-V, prepared as described in Chart A, undergoes rearrangement to give chloropyrazine B-I upon treatment with phosphorus oxychloride at temperatures ranging from ambient to 100 °C. Displacement of the chloride to afford B-II with can be accomplished upon by a variety of methods known in the art, including treatment with a suitable alcohol such as, but not limited to, methanol or benzyl alcohol in the presence of a suitable base, such as, but not limited to, sodium hydroxide, potassium hydroxide, sodium methoxide, N-methylpyrrolidinone or sodium hydride in a suitable solvent such as, but not limited to, methanol, diethyl ether, or dimethylformamide. Transformation of B-II into pyrazinone B-III may be accomplished by a variety of methods known in the art, including treatment with a suitable Lewis acid such as, but not limited to, boron tribromide or trimethylsilyl iodide, treatment with a suitable base such as trimethylsiloxyate, or by hydrogenolysis. Alkylation of B-III to afford B-IV proceeds as described in Chart A.
An alternate route to the target molecules is shown in Chart C. Treating C-I with an amine base in an inert solvent such as THF, DMF, N-methylpyrrolidinone, or methyl sulfoxide at ambient temperature or at elevated temperature up to the boiling point of the solvent employed. (Thio)alkoxypyrazines can be prepared by treating C-I with a sodium or potassium salt of an alcohol or thiol in an inert solvent such as THF, DMF, N-methylpyrrolidinone, or methyl sulfoxide at ambient temperature or at elevated temperature up to the boiling point of the solvent employed. Displacement of the remaining chloride from C-II can be accomplished upon by a variety of methods known in the art, including treatment with a suitable alcohol such as, but not limited to, methanol or benzyl alcohol in the presence of a suitable base, such as, but not limited to, sodium hydroxide, potassium hydroxide, sodium methoxide, N-methylpyrrolidinone or sodium hydride in a suitable solvent such as, but not limited to, methanol, diethyl ether, or dimethylformamide. Halogenation of C-III to afford C-IV may be accomplished by a variety of methods known in the art, including treatment with N-chlorosuccinimide, bromine, N-bromosuccinimide, pyridinium tribromide, triphenylphosphine dibromide, iodine, and N-iodosuccinimide in solvents such as but not limited to dichloromethane, acetic acid, or methyl sulfoxide. The halopyrazine C-IV can be converted to arylpyrazine C-V by a transition metal-catalyzed coupling reaction with a metalloaryl reagent (G-[M]). More commonly employed reagent[catalyst] pairs include aryl boronic acid/palladium(0) (Suzuki reaction; N. Miyaura and A. Suzuki, Chemical Review 1995, 95, 2457), aryl trialkylstannane/palladium(0) (Stille reaction; T. N. Mitchell, Synthesis 1992, 803), arylzinc/palladium(0) and aryGrignard/nickel(II). Palladium(0) represents a catalytic system made of a various combination of metal/ligand pair which includes, but not limited to, tetrakis(triphenylphosphine)palladium(0), palladium(II) acetate/tri(o-toly)phosphine, tris(dibenzylideneacetone)dipalladium(0)/tri-tert-butyolphosphine and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(0). Nickel(II) represents a nickel-containing catalyst such as [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) and [1,3-bis(diphenylphosphino)propane]dichloronickel(II). The arylpyrazine C-V, when X is NH,
may be further transformed by N-alkylation. The N-H group is deprotonated by a strong base such as, but not limited to, alkali metal hydride, alkali metal amide, or alkali metal alkoxide in inert solvents such as, but not limited to, THF, DMF, or methyl sulfoxide. Alkylation may be conducted using alkyl halide, suitably bromide or iodide, at temperatures ranging from 0 °C to 100 °C. C-V can be halogenated again as described previously. Stille coupling or Suzuki coupling is used to prepare C-VII. Transformation of C-VII into pyrazinone C-VIII may be accomplished by a variety of methods known in the art, including treatment with a suitable Lewis acid such as, but not limited to, boron tribromide or trimethylisilyl iodide, treatment with trimethylsilanoate, or hydrogenolysis. Alkylation of C-VIII to afford C-IX proceeds as described in Chart A.

Chart C

Pyrrolidinyl substituted pyrazinones can be prepared as described in Chart D. D-II can be prepared from D-I and a pyrrolidinyl amine in the presence of a suitable transition metal catalyst such as, but not limited to, palladium(II) acetate or tris(dibenzylideneacetone)dipalladium(0), a ligand such as, but not limited to, 1,1'-bis(diphenylphosphine)ferrocene, 2,2'-bis(diphenylphosphine)-1,1'-binaphthyl, dicyclohexyl(2-biphenyl)phosphine, tricyclohexylphosphine, or tri-tert-butylphosphine, and a base such as sodium or potassium tert-butoxide in inert solvents such as, but not limited to, toluene, ethyleneglycol dimethyl ether, diglyme, DMF, or N-methylpyrrolidinone at temperatures ranging from ambient to 100 °C. Halogenation of D-II to afford D-III may be accomplished as previously described. Halopyrazine D-III can be converted to arylpyrazine D-IV by a transition metal-catalyzed coupling reaction as previously described. Alcohol D-IV can be converted to D-V by deprotonation with a base such as, but not limited to, alkali metal hydride, alkali metal amide, or alkali metal alkoxide in inert solvents such as, but not limited to, THF, DMF, or methyl sulfoxide. Alkylation may be conducted using alkyl halide, suitably
bromide or iodide, at temperatures ranging from 0 °C to 100 °C. Oxidation of the sterically less hindered nitrogen of D-V can be effected by using a variety of oxidizing agents known in the art, which includes m-chloroperoxybenzoic acid, trifluoroperacetic acid, hydrogen peroxide and monoperoxyphthalic acid to provide D-VI. The N-oxide can undergo rearrangement upon treatment with an acid anhydride as previously described to give pyrazinone D-VII. Hydrolysis of the acetamide from D-VII provides D-VIII. Alkylation of pyrazinone D-VIII may be accomplished by a variety of methods known in the art, including treatment with a suitable electrophiles, such as alkyl halide, alkyl mesylate or alkyl triflate, in the presence of a suitable base, such as, but not limited to, sodium hydroxide, potassium hydroxide, sodium methoxide, or sodium hydride in a suitable solvent such as, but not limited to, methanol, diethyl ether, or dimethylformamide. Alternatively, diazomethane can be used to accomplish the aforementioned transformation wherein R₂ would be a methyl group (Dutcher, J. Biol. Chem. 1947, 171, 321). Removal of the CBZ-protecting group from D-IX may be accomplished by a variety of reductive methods, including but not limited to hydrogenolysis or treatment with triethylsilane. Acylation of D-X proceeds in the presence of a suitable acyl halide and base in a non-reactive solvent such as, but not limited to, tetrahydrofuran, diethyl ether, dimethylformamide or methylene chloride at temperatures ranging from 0 °C to 100 °C. Alternatively, D-X may be derivatized by reaction with an aryl boronic acid in the presence of a suitable transition metal catalyst such as, but not limited to, palladium(II) acetate or tris(dibenzylideneacetone)dipalladium(0), a ligand such as, but not limited to, 1,1'-bis(diphenylphosphino)ferrocene, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, dicyclohexyl(2-biphenyl)phosphine, tricyclohexylphosphine, or tri-tert-butylphosphine, and a base such as sodium or potassium tert-butoxide in inert solvents such as, but not limited to, toluene, ethylene glycol dimethyl ether, diglyme, DMF, or N-methylpyrrolidinone at temperatures ranging from ambient to 100 °C.
The present invention also encompasses pharmaceutically acceptable salts of compounds of Formula I. Examples of pharmaceutically acceptable salts are salts prepared from inorganic acids or organic acids, such as inorganic and organic acids of basic residues.
such as amines, for example, acetic, benzenesulfonic, benzoic, amorphsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, barbatic acid, p-toluenesulfonic and the like; and alkali or organic salts of acidic residues such as carboxylic acids, for example, alkali and alkaline earth metal salts derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, trimethylammonia, triethylammonia, ethylendiamin, lysine, arginine, ornithine, choline, N,N-dibenzylethlenediamine, chlorprocaine, diethanolamine, procaine, n-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington’s Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

In another aspect, the present invention provides a prodrug of a compound of Formula I. The prodrug is prepared with the objective(s) of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity (including improved brain penetration), improved formulation (e.g., increased hydrophilicity), and/or decreased side effects (e.g., toxicity). See e.g. T. Higuchi and V. Stella, "Prodrugs as Novel Delivery Systems", Vol. 14 of the A.C.S. Symposium Series; Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, (1987). Prodrugs include, but are not limited to, compounds derived from compounds of Formula I wherein hydroxy, amine or sulfhydryl groups, if present, are bonded to any group that, when administered to the subject, cleaves to form the free hydroxy, amino or sulfhydryl group, respectively. Selected examples include, but are not limited to, biohydrolyzable amides and biohydrolyzable esters and biohydrolyzable carbamates, carbonates, acetate, formate and benzoate derivatives of alcohol and amine functional groups.

Prodrugs: Bioreversible-Derivatives for Various Functional Groups and Chemical Entities,* in Design of Prodrugs (H. Bundgaard, ed.), Elsevier, N.Y. (1985); Burger's Medicinal Chemistry and Drug Chemistry, Fifth Ed., Vol. 1, pp. 172-178, 949-982 (1995). For example, the compounds of Formula I can be transformed into prodrugs by converting one or more of the hydroxy or carboxy groups into esters.

The invention also includes isotopically-labeled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as $^3$H, $^{11}$C, $^{14}$C, $^{18}$F, $^{123}$I, and $^{125}$I. Compounds of Formula I that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as $^3$H and $^{14}$C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., $^3$H, and carbon-14, i.e., $^{14}$C, isotopes are particularly useful in PET (positron emission tomography), and $^{125}$I isotopes are particularly useful in SPECT (single photon emission computed tomography); all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., $^2$H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, maybe preferred in some circumstances. Isotopically labeled compounds of Formula I of this invention can generally be prepared by carrying out the synthetic procedures by substituting a isotopically labeled reagent for a non-isotopically labeled reagent.

The compounds of Formula I are antagonists at the CRF$_1$ receptor, capable of inhibiting the specific binding of CRF to CRF$_1$ receptor and antagonizing activities associated with CRF$_1$ receptor. The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. A compound of Formula I may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (J. Neuroscience 7:88, 1987) and Battaglia et al. (Synapse 1:572, 1987). CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (e.g., $^3$H]tyrosine-CRF) to its receptor (e.g., receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (supra, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC$_{50}$ as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "Ki" value. IC$_{50}$ and Ki values are calculated using standard methods known in the art, such as with the non-linear
curve-fitting program GraphPad Prism (GraphPad Software, San Diego, CA). A compound is considered to be active if it has an Ki of less than about 10 micromolar (\(\mu M\)) for the inhibition of CRF\(_1\) receptors. The binding affinity of the compounds of Formula I expressed as Ki values generally ranges from about 0.5 nanomolar to about 10 micromolar. It is preferred that compounds of Formula I exhibit Ki value of 1 micromolar or less, more preferred that compounds of Formula I exhibit Ki values of less than 100 nanomolar, and still more preferred that compounds of Formula I exhibit Ki values of less than 10 nanomolar.

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylyl cyclase activity. Therefore, compounds may be evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylyl cyclase activity by, for example, measuring cAMP levels. The CRF-stimulated adenylyl cyclase activity assay described by Battaglia et al. (supra, 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Alternatively, adenylyl cyclase activity or cAMP production can be assessed in a 96/384-well format utilizing the cAMP competitive ELISA system from Applied Biosystems (Bedford, MA) according to the protocols provided. Briefly, a fixed amount of diluted cAMP-alkaline phosphatase conjugate (cAMP-AP) is added to 96 or 386-well plates containing samples from cells that were stimulated with CRF in the presence or absence of inhibitors. Anti-cAMP antibody is added to the mixture and incubated for 1 hr. Following successive wash steps, the chemiluminescent substrate/enhancer solution is added which then produces a light signal that can be detected using a microplate scintillation counter such as the Packard TopCount. cAMP produced by the cells will displace the cAMP-AP conjugate from the antibody yielding a decrease of detectable signal. An example of the CRF-stimulated adenylyl cyclase activity assay is provided in Example C below.

Thus, in another aspect, the present invention provides a method of antagonizing CRF\(_1\) receptors in a warm-blooded animal, comprising administering to the animal a compound of the invention at amount effective to antagonize CRF\(_1\) receptors. The warm-blooded animal is preferably a mammal, and more preferably a human.

In another aspect, the present invention provides a method of treating a disorder in a warm-blooded animal, which disorder manifests hypersecretion of CRF, or the treatment of which disorder can be effected or facilitated by antagonizing CRF\(_1\) receptors, comprising administering to the animal a therapeutically effective amount of a compound of the invention. The warm-blooded animal is preferably a mammal, and more preferably a human.

In another aspect, the present invention provides a method for screening for ligands for CRF\(_1\) receptors, which method comprises: a) carrying out a competitive binding assay with CRF\(_1\) receptors, a compound of Formula I which is labelled with a detectable label, and a
candidate ligand; and b) determining the ability of said candidate ligand to displace said labelled compound. Assay procedure for competitive binding assay is well known in the art, and is exemplified in Example A.

In another aspect, the present invention provides a method for detecting CRF₁ receptors in tissue comprising: a) contacting a compound of Formula I, which is labeled with a detectable label, with a tissue, under conditions that permit binding of the compound to the tissue; and b) detecting the labeled compound bound to the tissue. Assay procedure for detecting receptors in tissues is well known in the art.

In another aspect, the present invention provides a method of inhibiting the binding of CRF to CRF₁ receptors, comprising contacting a compound of the invention with a solution comprising cells expressing the CRF₁ receptor, wherein the compound is present in the solution at a concentration sufficient to inhibit the binding of CRF to the CRF₁ receptor. An example of the cell line that expresses the CRF₁ receptor and can be used in the *in vitro* assay is IMR32 cells known in the art.

Compounds of formula (I), or a stereoisomer, a pharmaceutically acceptable salt, or a prodrug thereof, are useful for the treatment of a disorder in a warm-blooded animal, which disorder manifests hypersecretion of CRF, or the treatment of which disorder can be effected or facilitated by antagonizing CRF₁ receptors. Examples of such disorders are described herein above. They are also useful for promoting smoking cessation or promoting hair growth.

Thus, in still another aspect, the present invention provides a method of treating a disorder described herein above, comprising administering to a warm-blooded animal a therapeutically effective amount of a compound of the invention. The warm-blooded animal is preferably a mammal, particularly a human.

Particular disorders that can be treated by the method of the invention preferably include the following: anxiety-related disorders (such as generalized anxiety disorder; social anxiety disorder; anxiety; anxiety with co-morbid depressive illness, obsessive-compulsive disorder, and panic disorder); mood disorders (such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression); bipolar disorders; post-traumatic stress disorder; substance abuse disorder (e.g., nicotine, cocaine, ethanol, opiates, or other drugs); inflammatory disorders (such as rheumatoid arthritis and osteoarthritis); gastrointestinal diseases (such as irritable bowel syndrome, ulcers, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress); inflammatory disorder; and skin disorders (such as acne, psoriasis, and chronic contact dematitis).
Particular disorders that can be treated by the method of the invention more preferably include the following: anxiety-related disorders; mood disorders; inflammation disorders; and chronic contact dermatitis.

Particular disorders that can be treated by the method of the invention even more preferably include anxiety-related disorders, particularly generalized anxiety, and mood disorders, particularly depression.

The therapeutically effective amounts of the compounds of the invention for treating the diseases or disorders described above in a warm-blooded animal can be determined in a variety of ways known to those of ordinary skill in the art, e.g., by administering various amounts of a particular agent to an animal afflicted with a particular condition and then determining the effect on the animal. Typically, therapeutically effective amounts of a compound of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect. It will be understood, however, that the specific dose levels for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease. Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most CNS disorders, a dosage regimen of four-times daily or less is preferred. For the treatment of stress and depression, a dosage regimen of one or two-times daily is particularly preferred.

A compound of this invention can be administered to treat the above disorders by means that produce contact of the active agent with the agent's site of action in the body of a mammal, such as by oral, topical, dermal, parenteral, or rectal administration, or by inhalation or spray using appropriate dosage forms. The term "parenteral" as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. The compound can be administered alone, but will generally be administered with a pharmaceutically acceptable carrier, diluent, or excipient.

In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of Formula I, a stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a prodrug thereof, or a pharmaceutically acceptable salt of the prodrug thereof. In one embodiment, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, diluent, or excipient therefore. A "pharmaceutically acceptable carrier, diluent, or excipient" is a medium generally accepted in the art for the delivery of biologically active agents to mammals, e.g., humans. Such carriers are generally formulated according to a number of factors well within the purview of those of ordinary skill in the art to determine
and account for. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers and excipients include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources, e.g., Remington’s Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, the contents of which are incorporated herein by reference.

Compositions intended for oral use may be in the form of tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs, and can be prepared according to methods known to the art. Such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and a delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example
polyoxyethylene stearate, or condensation products of ethylene oxide with long aliphatic alcohols, for example heptadecaethyleneoxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexital such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, soybean oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occuring gums, for example gum acacia or gum tragacanth, naturally-occuring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

Suppositories for rectal administration of a compound of the invention can be prepared by mixing the compound with a suitable non-irritating excipient, which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Examples of such materials are cocoa butter and polyethylene glycols.

Pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents, which have been
mentioned above. The sterile injectable solution or suspension may be formulated in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Dosage forms suitable for administration generally contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition. Examples of dosage forms for administration of compounds of the invention includes the following: (1) Capsules. A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate; (2) Soft Gelatin Capsules. A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried; (3) Tablets. A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

In still another aspect, the present invention provides an article of manufacture comprising: a) a packaging material; b) a pharmaceutical agent comprising a compound of the invention contained within said packaging material; and c) a label or package insert which indicates that said pharmaceutical agent can be used for treating a disorder described above.

**DEFINITIONS AND CONVENTIONS**

The following definitions are used throughout the application, unless otherwise described.

The term "alkyl" means both straight and branched chain moieties having from 1-10 carbon atoms optionally containing one or more double or triple bonds;

The term "substituted alkyl" means an alkyl group having 1-5 substituents independently selected from halogen, -NO₂, -CN, -Rₐ, -ORₐ, -S(O)ₙRₐ, -NRₐRₐ, -C(O)NRₐRₐ, -C(S)NRₐRₐ, -S(O)ₙRₐ, -NRₐS(O)ₙRₐ, -NRₐC(O)ORₐ, -OC(O)NRₐRₐ, -NRₐC(O)NRₐRₐ, -NRₐC(S)NRₐRₐ, -C(O)ORₐ, -C(S)ORₐ, and -OC(O)ORₐ;

The term "haloalkyl" means an alkyl moiety having 1 to (2v+1) independently selected halogen substituent(s) where v is the number of carbon atoms in the moiety.
The term "cycloalkyl" means a monocyclic, non-aromatic hydrocarbon moiety, having from 3 to 10 carbon atoms or a bicyclic non-aromatic alkyl moiety, having from 4 to 10 carbon atoms, optionally containing 1 to 2 double bonds;

The term "substituted cycloalkyl" means a cycloalkyl group having 1-5 substituents independently selected from halogen, -NO₂, -CN, -R₉, -OR₉, -S(O)mR₉, -NR₉R₉, -C(O)NR₉R₉, -C(S)NR₉R₉, -S(O)mNR₉R₉, -NR₉S(O)mR₉, -NR₉C(O)OR₉, -NR₉C(S)OR₉, -NR₉C(O)NR₉R₉, -NR₉C(S)NR₉R₉, -C(O)OR₉, -C(S)OR₉, and -OC(O)OR₉;

The term "aryl" is independently selected from phenyl and naphthyl;

The term "substituted aryl" means an aryl group substituted with 1-5 substituents independently selected from halogen, oxo (=O), thione (=S), -NO₂, -CN, -R₉, -OR₉, -S(O)mR₉, -NR₉R₉, -C(O)NR₉R₉, -C(S)NR₉R₉, -S(O)mNR₉R₉, -NR₉S(O)mR₉, -NR₉C(O)OR₉, -OC(O)NR₉R₉, -NR₉C(S)NR₉R₉, -C(O)OR₉, -C(S)OR₉, and -OC(O)OR₉;

The term "aryl cycloalkyl" means a bicyclic ring system containing 8 to 14 carbon atoms wherein one ring is aryl and the other ring is fused to the aryl ring and may be fully or partially saturated in the portion of the ring fused to the aryl ring, wherein either ring may act as a point of attachment;

The term "substituted aryl cycloalkyl" means an aryl cycloalkyl group having 1-5 substituents independently selected from halogen, oxo (=O), thione (=S), -NO₂, -CN, -R₉, -OR₉, -S(O)mR₉, -NR₉R₉, -C(O)NR₉R₉, -C(S)NR₉R₉, -S(O)mNR₉R₉, -NR₉S(O)mR₉, -NR₉C(O)OR₉, -OC(O)NR₉R₉, -NR₉C(S)NR₉R₉, -C(O)OR₉, -C(S)OR₉, and -OC(O)OR₉;

The term "heteroaryl cycloalkyl" means a bicyclic ring system containing 8 to 14 atoms wherein one ring is heteroaryl and the other ring is fused to the heteroaryl ring and may be fully or partially saturated in the portion of the ring fused to the heteroaryl ring, provided that either ring may act as a point of attachment;

The term "substituted heteroaryl cycloalkyl" means a heteroaryl cycloalkyl group having 1-5 substituents independently selected from halogen, oxo (=O), thione (=S), -NO₂, -CN, -R₉, -OR₉, -S(O)mR₉, -NR₉R₉, -C(O)NR₉R₉, -C(S)NR₉R₉, -S(O)mNR₉R₉, -NR₉S(O)mR₉, -NR₉C(O)OR₉, -OC(O)NR₉R₉, -NR₉C(S)NR₉R₉, -C(O)OR₉, -C(S)OR₉, and -OC(O)OR₉;

The term "aryl heterocycloalkyl" means a bicyclic ring system containing 8 to 14 atoms wherein one ring is aryl and the other ring is heterocycloalkyl, and wherein either ring may act as a point of attachment;

The term "substituted aryl heterocycloalkyl" means an aryl heterocycloalkyl group having 1-5 substituents independently selected from halogen, oxo (=O), thione (=S), -NO₂, -CN, -R₉, -OR₉, -S(O)mR₉, -NR₉R₉, -C(O)NR₉R₉, -C(S)NR₉R₉, -S(O)mNR₉R₉, -NR₉S(O)mR₉, -NR₉C(O)OR₉, -OC(O)NR₉R₉, -NR₉C(S)NR₉R₉, -C(O)OR₉, -C(S)OR₉, and -OC(O)OR₉;
NR\textsubscript{a}C(O)OR\textsubscript{a}, -OC(O)NR\textsubscript{a}R\textsubscript{a}, -NR\textsubscript{a}C(O)NR\textsubscript{a}R\textsubscript{a}, -NR\textsubscript{a}C(S)NR\textsubscript{a}R\textsubscript{a}, -C(O)OR\textsubscript{a}, -C(S)OR\textsubscript{a}, and -OC(O)OR\textsubscript{a};

The term "heteroaryl heterocycloalkyl" means a bicyclic ring system containing 8 to 14 atoms, wherein one ring is heteroaryl and the other ring is heterocycloalkyl, and wherein that either ring may act as a point of attachment;

The term "substituted heteroaryl heterocycloalkyl" means an heteroaryl heterocycloalkyl group having 1-5 substituents independently selected from halogen, oxo (=O), thione (=S), -NO\textsubscript{2}, -CN, -R\textsubscript{a}, -OR\textsubscript{a}, -S(O)\textsubscript{m}R\textsubscript{a}, -NR\textsubscript{a}R\textsubscript{b}, -C(O)NR\textsubscript{a}R\textsubscript{a}, -C(S)NR\textsubscript{a}R\textsubscript{a}, -S(O)\textsubscript{m}NR\textsubscript{a}R\textsubscript{a}, -NR\textsubscript{a}S(O)\textsubscript{m}R\textsubscript{a}, -NR\textsubscript{a}C(O)OR\textsubscript{a}, -OC(O)NR\textsubscript{a}R\textsubscript{a}, -NR\textsubscript{a}C(S)NR\textsubscript{a}R\textsubscript{a}, -C(O)OR\textsubscript{a}, -C(S)OR\textsubscript{a}, and -OC(O)OR\textsubscript{a};

The term "heteroaryl" means a radical of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and 1 to 4 heteroatoms each selected from the group consisting of non-peroxide O, S, N, with appropriate bonding to satisfy valence requirements, wherein the attachment may be via a ring carbon or ring nitrogen where a nitrogen is present.

The term "heteroaryl" also includes a radical of a fused bicyclic heteroaromatic ring having eight to ten ring atoms consisting of carbon and 1 to 6 heteroatoms each selected from non-peroxide O, S, N, with appropriate bonding to satisfy valence requirements, wherein the attachment may be via a ring carbon or ring nitrogen where a nitrogen is present. Examples of heteroaryl include thienyl, benzothienyl, pyridyl, thiazolyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzimidazolyl, indolyl, and benzoxazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, pyrrolyl, isquinolinyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthridinyl, and furylpyridinyl;

The term "substituted heteroaryl" means a heteroaryl group having 1-5 substituents independently selected from halogen, oxo (=O), thione (=S), -NO\textsubscript{2}, -CN, -R\textsubscript{a}, -OR\textsubscript{a}, -S(O)\textsubscript{m}R\textsubscript{a}, -NR\textsubscript{a}R\textsubscript{b}, -C(O)NR\textsubscript{a}R\textsubscript{a}, -C(S)NR\textsubscript{a}R\textsubscript{a}, -S(O)\textsubscript{m}NR\textsubscript{a}R\textsubscript{a}, -NR\textsubscript{a}S(O)\textsubscript{m}R\textsubscript{a}, -NR\textsubscript{a}C(O)OR\textsubscript{a}, -OC(O)NR\textsubscript{a}R\textsubscript{a}, -NR\textsubscript{a}C(S)NR\textsubscript{a}R\textsubscript{a}, -C(O)OR\textsubscript{a}, -C(S)OR\textsubscript{a}, and -OC(O)OR\textsubscript{a};

The term "heterocycloalkyl" means a 3 to 8 membered monocyclic non-aromatic ring or a 4 to 8 membered bicyclic non-aromatic ring, wherein at least one carbon atom is replaced with a heteroatom selected from oxygen, nitrogen, -NH-, or -S(O)\textsubscript{m} wherein m is zero, 1, or 2, optionally containing from one to three double bonds, and wherein the ring attachment can occur at either a ring carbon or ring nitrogen atom. Examples of heterocycloalkyl includes tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, [2.2.1]-azabicyclic rings, [2.2.2]-azabicyclic rings, [3.3.1]-azabicyclic rings, quinuclidinyl, azetidinyl, azetidinonyl, oxindolyl, dihydroimidazolyl, and pyrrolidinonyl;
The term "substituted heterocycloalkyl" means a heterocycloalkyl group having 1-5 substituents independently selected from halogen, oxo (=O), thione (=S), -NO₂, -CN, -R₉, -OR₉, -S(O)ₓR₁₀, -NR₉R₁₀, -C(O)NR₉R₁₀, -C(S)NR₉R₁₀, -S(O)ₓNR₉R₁₀, -NR₉S(O)ₓR₁₀, -NR₉C(O)OR₉, -OC(O)NR₉R₁₀, -NR₉C(O)NR₉R₁₀, -NR₉C(S)NR₉R₁₀, -C(O)OR₉, -C(S)OR₉, and -OC(O)OR₉.

The term "halogen" means a group selected from -F, -Cl, -Br, -I;

m is selected from 0, 1, or 2;

R₉ is selected from -H, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, or heterocycloalkyl each optionally substituted with 1-5 R₉;

R₉ is selected from R₉, halogen, -NO₂, -NR₉R₁₀, -OR₉, -SR₉, -CN, -C(O)NR₉R₁₀, -C(O)NR₉R₁₀, -OC(O)NR₉R₁₀, -OC(O)OR₉, -NR₉C(O)R₁₀, -NR₉C(O)NR₉R₁₀, -NR₉C(O)OR₉, -S(O)ₓR₁₀, -NR₉S(O)ₓR₁₀, and -NR₉S(O)ₓR₁₀;

R₉ is independently selected from -H, alkyl, cycloalkyl, phenyl, benzyl, heteroaryl or heterocycloalkyl where phenyl, benzyl, heteroaryl and heterocycloalkyl may be optionally substituted with alkyl or halogen; and

m is 0, 1, or 2.

The term "pharmaceutically acceptable," unless otherwise described, refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

The term "pharmaceutically acceptable salt" refers to a salt which retains the biological effectiveness and properties of the compounds of this invention and which is not biologically or otherwise undesirable.

The term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

The term "prodrug" means compounds that are transformed in vivo to yield a compound of Formula I. The transformation may occur by various mechanisms, such as through hydrolysis in blood.
The term "therapeutically effective amount," "effective amount," "therapeutic amount," or "effective dose" is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the disease.

The phrases "a compound of the invention," "a compound of the present invention," "compounds of the present invention," or "a compound in accordance with Formula I" and the like, refer to compounds of Formula I, or stereoisomers thereof, pharmaceutically acceptable salts thereof, or prodrugs thereof, or pharmaceutically acceptable salts of a prodrug of compounds of Formula I.

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

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. Examples A-D are provided to illustrate biological assays that can be used for determining the biological properties of the compounds of the inventions. These examples are provided to illustrate the invention and are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those skilled in the art will promptly recognize appropriate variations from the procedures described in the examples.

Example A:

**In vivo CRF₁ Receptor Binding Assay for the Evaluation of Biological Activity**

The following is a description of a standard *in vitro* binding assay for the evaluation of biological activity of a test compound on CRF₁ receptors. It is based on a modified protocol described by De Souza (De Souza, 1987).

The binding assay utilizes brain membranes, commonly from rats. To prepare brain membranes for binding assays, rat frontal cortex is homogenized in 10 mL of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM MgCl₂, 2 mM EGTA, 1 µg/mL aprotinin, 1 µg/mL leupeptin and 1 µg/mL pepstatin). The homogenate is centrifuged at 48,000 x g for 10 min. and the resulting pellet rehomogenized in 10 mL of tissue buffer. Following an additional centrifugation at 48,000 x g for 10 min., the pellet is resuspended to a protein concentration of 300 µg/mL.
Binding assays are performed in 96 well plates at a final volume of 300 μL. The assays are initiated by the addition of 150 μL membrane suspension to 150 μL of assay buffer containing $^{125}$I-ovine-CRF (final concentration 150 pM) and various concentrations of inhibitors. The assay buffer is the same as described above for membrane preparation with the addition of 0.1% ovalbumin and 0.15 mM bacitracin. Radioligand binding is terminated after 2 hours at room temperature by filtration through Packard GF/C unifilter plates (presoaked with 0.3% polyethyleneimine) using a Packard cell harvester. Filters are washed three times with ice cold phosphate buffered saline pH 7.0 containing 0.01% Triton X-100. Filters are assessed for radioactivity in a Packard TopCount.

Alternatively, tissues and cells that naturally express CRF receptors, such as IMR-32 human neuroblastoma cells (ATCC; Hogg et al., 1996), can be employed in binding assays analogous to those described above.

A compound is considered to be active if it has an IC$_{50}$ value of less than about 10 μM for the inhibition of CRF. Nonspecific binding is determined in the presence of excess (10 μM) α-helical CRF.

Example B:

**Ex vivo CRF$_1$ Receptor Binding Assay for the Evaluation of Biological Activity**

The following is a description of a typical *ex vivo* CRF$_1$ receptor binding assay for assessing the biological activity of a test compound on CRF$_1$ receptors.

Fasted, male, Harlem-bred, Sprague-Dawley rats (170-210 g) were orally dosed with test compound or vehicle, via gastric lavage between 12:30 and 2:00 PM. Compounds were prepared in vehicle (usually 10 % soybean oil, 5% polysorbate 80, in dH2O). Two hours after drug administration, rats were sacrificed by decapitation, frontal cortices were quickly dissected and placed on dry ice, then frozen at $-80$ °C until assayed; trunk blood was collected in heparinized tubes, plasma separated by centrifugation (2500 RPM's for 20 minutes), and frozen at $-20$ °C.

On the day of the binding assay, tissue samples were weighed and allowed to thaw in ice cold 50 mM Hepes buffer (containing 10 mM MgCl$_2$, 2 mM EGTA, 1 μg/mL aprotinin, 1 μg/mL leupeptin hemisulfate, and 1 μg/mL pepstatin A, 0.15 mM bacitracin, and 0.1% ovalbumin, pH = 7.0 at 23 °C) and then homogenized for 30 sec at setting 5 (Polytron by Kinematica). Homogenates were incubated (two hours, 23 °C, in the dark) with $[^{125}I]$ CRF (0.15 nM, NEN) in the presence of assay buffer (as described above) or DMP-904 (10 nM). The assay was terminated by filtration (Packard FilterMate, GF/C filter plates); plates were counted in Packard TopCount LSC; total and non-specific fmoles calculated from DPM's. Data are expressed as % of vehicle controls (specific fmoles bound). Statistical significance was determined using student's t-test.
Example C:

Inhibition of CRF Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as previously described [G. Battaglia et al., Synapse 1:572 (1987)]. Briefly, assays are carried out at 37 °C for 10 min in 200 mL of buffer containing 100 mM Tris-HCl (pH 7.4 at 37 °C), 10 mM MgCl₂, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/mL phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5’-triphosphate, 100 nM o-CRF, antagonist peptides (various concentrations) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/[³²P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 mL of 50 mM Tris-HCl, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 mL of [³H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [³²P]cAMP from [³²P]ATP is performed by sequential elution over Dowex and alumina columns.

Alternatively, adenylate cyclase activity can be assessed in a 96-well format utilizing the Adenyllyl Cyclase Activation FlashPlate Assay from NEN Life Sciences according to the protocols provided. Briefly, a fixed amount of radiolabeled cAMP is added to 96-well plates that are precoated with anti-cyclic AMP antibody. Cells or tissues are added and stimulated in the presence or absence of inhibitors. Unlabeled cAMP produced by the cells will displace the radiolabeled cAMP from the antibody. The bound radiolabeled cAMP produces a light signal that can be detected using a microplate scintillation counter such as the Packard TopCount. Increasing amounts of unlabeled cAMP results in a decrease of detectable signal over a set incubation time (2-24 hours).

Example D:

in vivo Biological Assay

The in vivo activity of a compound of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn Brain Research Reviews 15:71 (1990). A compound may be tested in any species of rodent or small mammal.
CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula I,

```
   R2
 /   \
N   O
 /   \
R1
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Formula I

or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a prodrug thereof, wherein in Formula I:

- \( X \) is selected from -NR\(_3\)R\(_4\), -OR\(_3\), -CR\(_3\)R\(_5\), -C(O)R\(_3\), -S(O)\(_m\)R\(_3\), -NR\(_3\)C(O)R\(_4\), or -NR\(_3\)S(O)\(_m\)R\(_4\);

- R\(_3\) and R\(_4\) are selected from -R\(_5\), heterocycloalkyl, substituted heterocycloalkyl, aryl cycloalkyl, substituted aryl cycloalkyl, heteroaryl cycloalkyl, substituted heteroaryl cycloalkyl, aryl heterocycloalkyl, substituted aryl heterocycloalkyl, heteroaryl heterocycloalkyl, or substituted heteroaryl heterocycloalkyl;

- R\(_1\) and R\(_5\) are independently selected from -H, -CN, -NO\(_2\), -OR\(_3\), -NR\(_3\)R\(_5\), -C(O)R\(_3\), -C(S)R\(_5\), -C(O)NR\(_3\)R\(_5\), -C(S)NR\(_3\)R\(_5\), -NR\(_3\)C(O)R\(_5\), -NR\(_3\)C(S)R\(_5\), -NR\(_3\)C(O)NR\(_3\)R\(_5\), -NR\(_3\)C(S)NR\(_3\)R\(_5\), -OC(O)NR\(_3\)R\(_5\), -OC(S)NR\(_3\)R\(_5\), -S(O)\(_m\)NR\(_3\)R\(_5\), -NR\(_3\)S(O)\(_m\)R\(_5\), alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, cycloalkyl, and substituted cycloalkyl;

- R\(_2\) is independently selected from -C(O)R\(_3\), -C(S)R\(_5\), -C(O)NR\(_3\), -C(S)OR\(_3\), -C(O)NR\(_3\)R\(_5\), -C(S)OR\(_3\), -C(O)NR\(_3\)R\(_5\), -C(S)OR\(_3\), -S(O)\(_m\)NR\(_3\)R\(_5\), alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, haloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl and substituted heterocycloalkyl;

- m is selected from 0, 1, or 2;

- R\(_6\) is independently selected from -H, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, or heterocycloalkyl each optionally substituted with 1-5 R\(_5\);

- Ar is independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl cycloalkyl, substituted aryl cycloalkyl, heteroaryl heterocycloalkyl, and substituted heteroaryl heterocycloalkyl;

- R\(_7\) is independently selected from R\(_6\), halogen, -NO\(_2\), -NR\(_3\)R\(_6\), -OR\(_3\), -SR\(_3\), -CN, -C(O)NR\(_3\)R\(_6\), -C(O)R\(_3\), -OC(O)NR\(_3\)R\(_6\), -OC(O)R\(_3\), -NR\(_3\)C(O)NR\(_3\)R\(_6\), -NR\(_3\)C(O)OR\(_3\), -S(O)\(_m\)NR\(_3\)R\(_6\), -NR\(_3\)S(O)\(_m\)R\(_6\), -S(O)\(_2\)NR\(_3\)R\(_6\), and -NR\(_3\)S(O)\(_2\)NR\(_3\)R\(_6\);

- R\(_8\) is independently selected from -H, alkyl, cycloalkyl, phenyl, benzyl, heteroaryl or heterocycloalkyl where phenyl, benzyl, heteroaryl and heterocycloalkyl may be optionally substituted with alkyl or halogen; and
Rₖ is independently selected from -H, -C(O)alkyl, -C(S)alkyl, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, or heterocycloalkyl each optionally substituted with 1-5 Rₖ.

2. A compound according to claim 1, which is selected from the group consisting of:

3-(2,4-dichlorophenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-(2,4-dichlorophenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-(2,4-dichlorophenyl)-1,3-diethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-(2,4-dichlorophenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-dimethylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-(2,4-dichlorophenyl)-1,3-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-(2,4-dichlorophenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1-ethyl-5-methylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-(2,4-dichlorophenyl)-1-ethyl-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-(2,4-dichlorophenyl)-6-[[[(1S,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
3-(2,4-dichlorophenyl)-6-[[[(1R,2R)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
3-(2-chloro-4-methoxyphenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-(2-chloro-4-methoxyphenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-(2-chloro-4-methoxyphenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-(2-chloro-4-methoxyphenyl)-1,3-diethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-(2-chloro-4-methoxyphenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-dimethylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-(2-chloro-4-methoxyphenyl)-1,3-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-(2-chloro-4-methoxyphenyl)-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1-ethyl-5-methylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-(2-chloro-4-methoxyphenyl)-1-ethyl-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-[2-chloro-4-(dimethylamino)phenyl]-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-[2-chloro-4-(dimethylamino)phenyl]-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-[2-chloro-4-(dimethylamino)phenyl]-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-[2-chloro-4-(dimethylamino)phenyl]-1,3-diethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-[2-chloro-4-(dimethylamino)phenyl]-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-[2-chloro-4-(dimethylamino)phenyl]-1,3-diethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-[2-chloro-4-(dimethylamino)phenyl]-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1-ethyl-5-methylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-[2-chloro-4-(dimethylamino)phenyl]-1-ethyl-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-[6-(dimethylamino)-4-methylpyridin-3-yl]-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-[6-(dimethylamino)-4-methylpyridin-3-yl]-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-[6-(dimethylamino)-4-methylpyridin-3-yl]-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-[6-(dimethylamino)-4-methylpyridin-3-yl]-1,3-diethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-[6-(dimethylamino)-4-methylpyridin-3-yl]-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1,5-diethylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-[6-(dimethylamino)-4-methylpyridin-3-yl]-1,3-diethyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
3-[6-(dimethylamino)-4-methylpyridin-3-yl]-6-[[[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino]-1-ethyl-5-methylpyrazin-2(1H)-one;
(1R,2S)-1-[[5-[6-(dimethylamino)-4-methylpyridin-3-yl]-1-ethyl-3-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-2,3-dihydro-1H-inden-2-yl acetate;
6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-5-ethyl-3-(4-methoxy-2-methylphenyl)-1-methylpyrazin-2(1H)-one;
(1R,2S)-1-[(3-ethyl-5-(4-methoxy-2-methylphenyl)-1-methyl-6-oxo-1,6-dihdropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
3-(2,4-dimethoxyphenyl)-6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-5-ethyl-1-methylpyrazin-2(1H)-one;
(1R,2S)-1-[(5-(2,4-dimethoxyphenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihdropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
3-(2,6-dimethoxypyridin-3-yl)-6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-5-ethyl-1-methylpyrazin-2(1H)-one;
(1R,2S)-1-[(5-(2,6-dimethoxypyridin-3-yl)-3-ethyl-1-methyl-6-oxo-1,6-dihdropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
3-(2,6-dimethoxypyridin-3-yl)-6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-1,5-diethylpyrazin-2(1H)-one;
(1R,2S)-1-[(5-(2,6-dimethoxypyridin-3-yl)-3-ethyl-1-methyl-6-oxo-1,6-dihdropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
3-(2,6-dimethoxypyridin-3-yl)-6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-1,5-diethylpyrazin-2(1H)-one;
(1R,2S)-1-[(5-(2,6-dimethoxypyridin-3-yl)-1,3-dimethyl-6-oxo-1,6-dihdropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
3-(2,6-dimethoxypyridin-3-yl)-6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-1-ethyl-5-methylpyrazin-2(1H)-one;
(1R,2S)-1-[(5-(2,6-dimethoxypyridin-3-yl)-1-ethyl-3-methyl-6-oxo-1,6-dihdropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-5-ethyl-3-(6-methoxy-2-methylpyridin-3-yl)-1-methylpyrazin-2(1H)-one;
(1R,2S)-1-[(3-ethyl-5-(6-methoxy-2-methylpyridin-3-yl)-1-methyl-6-oxo-1,6-dihdropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-1,5-diethyl-3-(6-methoxy-2-methylpyridin-3-yl)pyrazin-2(1H)-one;
(1R,2S)-1-[(3-ethyl-5-(6-methoxy-2-methylpyridin-3-yl)-6-oxo-1,6-dihdropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-3-(6-methoxy-2-methylpyridin-3-yl)-1,5-diethylpyrazin-2(1H)-one;
(1R,2S)-1-[(5-(6-methoxy-2-methylpyridin-3-yl)-1,3-dimethyl-6-oxo-1,6-dihdropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
6-[(1R,2S)-2-ethoxy-2,3-dihydro-1H-inden-1-yl]amino)-1-ethyl-3-(6-methoxy-2-
 methylpyridin-3-yl)-5-methylpyrazin-2(1H)-one;
(1R,2S)-1-[(1-ethyl-5-[(6-methoxy-2-methylpyridin-3-yl)-3-methyl-6-oxo-1,6-
dihydropyrazin-2-yl]amino)-2,3-dihydro-1H-inden-2-yl acetate;
benzyl (3R,4S)-3-[(5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-
2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
3-(2,4-dichlorophenyl)-6-[(3R,4S)-4-ethoxypyrrolidin-3-yl]amino)-5-ethyl-1-
methylpyrazin-2(1H)-one;
methyl (3R,4S)-3-[(5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-
2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
O-methyl (3R,4S)-3-[(5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-
dihydropyrazin-2-yl]amino)-4-ethoxypyrrolidine-1-carbothioate;
6-[(3R,4S)-1-acetyl-4-ethoxypyrrolidin-3-yl]amino)-3-(2,4-dichlorophenyl)-5-ethyl-1-
methylpyrazin-2(1H)-one;
ethyl (3R,4S)-3-[(5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-
yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
isopropyl (3R,4S)-3-[(5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-
dihydropyrazin-2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
(3R,4S)-3-[(5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-
yl]amino)-4-ethoxy-N-methylpyrrolidine-1-carboxamide;
(3R,4S)-3-[(5-(2,4-dichlorophenyl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-
yl]amino)-4-ethoxy-N-methylpyrrolidine-1-carbothioamide;
benzyl (3R,4S)-3-[(5-(2-chloro-4-methoxyphenyl)-3-ethyl-1-methyl-6-oxo-1,6-
dihydropyrazin-2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
methyl (3R,4S)-3-[(5-(2-chloro-4-methoxyphenyl)-3-ethyl-1-methyl-6-oxo-1,6-
dihydropyrazin-2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
benzyl (3R,4S)-3-[(5-[2-chloro-4-(dimethylamino)phenyl]-3-ethyl-1-methyl-6-oxo-1,6-
dihydropyrazin-2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
methyl (3R,4S)-3-[(5-[2-chloro-4-(dimethylamino)phenyl]-3-ethyl-1-methyl-6-oxo-1,6-
dihydropyrazin-2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
benzyl (3R,4S)-3-[(5-[6-(dimethylamino)-4-methylpyridin-3-yl]-3-ethyl-1-methyl-6-oxo-
1,6-dihydropyrazin-2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
methyl (3R,4S)-3-[(5-[6-(dimethylamino)-4-methylpyridin-3-yl]-3-ethyl-1-methyl-6-oxo-
1,6-dihydropyrazin-2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
benzyl (3R,4S)-3-[(5-(2,6-dimethoxyphenyl)-3-yl)-3-ethyl-1-methyl-6-oxo-1,6-
dihydropyrazin-2-yl]amino)-4-ethoxypyrrolidine-1-carboxylate;
methyl (3R,4S)-3-[[5-(2,6-dimethoxypyridin-3-yl)-3-ethyl-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]-4-ethoxypyrrolidine-1-carboxylate;
benzyl (3S,4R)-3-ethoxy-4-[[3-ethyl-5-(6-methoxy-2-methylpyridin-3-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]pyrrolidine-1-carboxylate;
methyl (3S,4R)-3-ethoxy-4-[[3-ethyl-5-(6-methoxy-2-methylpyridin-3-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl]amino]pyrrolidine-1-carboxylate;
3-(2,4-dichlorophenyl)-6-[[3R,4S]-4-ethoxy-1-pyridin-2-ylpyrrolidin-3-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
3-(2-chloro-4-methoxyphenyl)-6-[[3R,4S]-4-ethoxy-1-pyridin-2-ylpyrrolidin-3-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
3-(2,4-dichlorophenyl)-6-[[3R,4S]-4-ethoxy-1-pyrimidin-2-ylpyrrolidin-3-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
3-(2-chloro-4-methoxyphenyl)-6-[[3R,4S]-4-ethoxy-1-pyrimidin-2-ylpyrrolidin-3-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
3-(2,4-dichlorophenyl)-6-[[3R,4S]-4-ethoxy-1-(1,3-thiazol-2-yl)pyrrolidin-3-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one;
3-(2-chloro-4-methoxyphenyl)-6-[[3R,4S]-4-ethoxy-1-(1,3-thiazol-2-yl)pyrrolidin-3-yl]amino]-5-ethyl-1-methylpyrazin-2(1H)-one; and a pharmaceutically acceptable salt of any of said compounds.

3. A pharmaceutical composition comprising a compound of claim 1 or claim 2.

4. A method of inhibiting the binding of CRF to the CRF₁ receptor in vitro, the method comprising contacting, in the presence of CRF, a solution comprising a compound of claim 1 with cells expressing the CRF₁ receptor, wherein the compound is present in the solution at a concentration sufficient to reduce levels of CRF binding to the cells in vitro.

5. A method of antagonizing a CRF₁ receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound of claim 1.

6. A method for screening for ligands for CRF₁ receptors, which method comprises: a) carrying out a competitive binding assay with a CRF₁ receptor, a compound of claim 1, which is labeled with a detectable label, and a candidate ligand; and b) determining the ability of said candidate ligand to displace said labeled compound.

7. A method of treating a disorder the treatment of which can be effected or facilitated by antagonizing CRF, in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

8. The method according to claim 7 wherein the disorder manifests hypersecretion of CRF.

9. A method of treating a disorder in a human, comprising administering to the human a therapeutically effective amount of a compound of claim 1, wherein the disorder is
selected the group consisting of anxiety-related disorders; mood disorders; post-traumatic stress disorder; supranuclear palsy; immune suppression; drug or alcohol withdrawal symptoms; inflammatory disorders; pain; asthma; psoriasis and allergies; phobias; sleep disorders induced by stress; fibromyalgia; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; human immunodeficiency virus infections; neurodegenerative diseases; gastrointestinal diseases; eating disorders; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions; psychosocial dwarfism, hypoglycemia, and skin disorders; and hair loss.

10. A method according to claim 9 wherein the disorder is selected the group consisting of anxiety-related disorders; mood disorders; bipolar disorders; post-traumatic stress disorder; inflammatory disorders; chemical dependencies and addictions; gastrointestinal disorders; and skin disorders.

11. A method according to claim 10 wherein the disorder is selected from anxiety-related disorders and mood disorders and wherein the anxiety-related disorder is generalized anxiety and the mood disorder is depression.

12. A method of promoting hair growth in a human, comprising administering to the human in need thereof an effective amount of a compound of claim 1.

13. A method of promoting smoking cessation in a human, comprising administering to the human in need thereof an effective amount of a compound of claim 1.

14. A compound of claim 1 wherein, in a standard in vitro CRF receptor-binding assay, the compound exhibits a Ki value of 1 micromolar or less.

15. A compound of claim 14 wherein the compound exhibits a Ki value of 100 nanomolar or less.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D241/20 C07D401/04 C07D403/12 C07D401/14 C07D403/14
C07D417/14 A61K31/50 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D 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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>WO 02/092090 A (BRISTOL MYERS SQUIBB PHARMA CO) 21 November 2002 (2002-11-21) claims 1,22-24</td>
<td>1,3,12, 14,15</td>
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<td>X</td>
<td>US 6 200 982 B1 (COLLINS IAN JAMES ET AL) 13 March 2001 (2001-03-13) column 2, line 23 - column 3, line 61</td>
<td>1-3, 9-11,14, 15</td>
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<td>15</td>
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<td>X</td>
<td>EP 0 242 957 A (TOYO Jozo KK) 28 October 1987 (1987-10-28) examples 14-17, p. 52; claim 1</td>
<td>1,3,14, 15</td>
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<tr>
<td>X</td>
<td>EP 0 411 150 A (OTSUKA PHARMA CO LTD) 6 February 1991 (1991-02-06) Formula (1c), claim 47; examples A-3,A-8,A-9</td>
<td>1,3,14, 15</td>
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Further documents are listed in the continuation of box C.

Date of the actual completion of the international search

29 July 2004

Date of mailing of the international search report

12/08/2004

Name and mailing address of the EPO

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Authorized officer

Johnson, C
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>CHEESEMAN ET AL: &quot;Pyrazines. IV. 2,6-Dihydroxy-3,5-diphenylpyrazine and related compounds&quot; JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL SOCIETY, LONDON, GB, vol. 18, 1971, pages 2977-2979, XP002077515 ISSN: 0368-1769 6-hydroxy-1-methyl-3,5-diphenylpyrazin-2-one; page 2979, right-hand column</td>
<td>1,14,15</td>
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<td>X</td>
<td>BUYSENS K J ET AL: &quot;Synthesis of New Pyrrolo'3,4-b!'- and '3,4-c!pyridin(on)es and Related 1,7-Naphthyridinones and 2,7-Naphthyridines via Intramolecular Diels-Alder Reactions of 2(1H)-Pyrazinones&quot; TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 52, no. 27, 1 July 1996 (1996-07-01), pages 9161-9178, XP004104003 ISSN: 0040-4020 examples 3c,3d,5c,5d</td>
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<td>NISHIO, T: &quot;4+2!Cycloaddition of 2(1H)-pyrazinones and 1,2,4-triazoline-3,5-diones&quot; J. HETEROCYCLIC CHEM., vol. 35, 1998, pages 655-658, XP002290218 example 1h</td>
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<td>BUYSENS, K.J. ET AL.: &quot;Generation of 6-alkylidene/benzylidene-3,6-2(1H)-ones with methoxide and further conversion into specific piperazine-2,5-diones and pyrazin-2(1H)-ones.&quot; J. CHEM. SOC., PERKIN TRANS. 1, vol. 3, 1996, pages 231-237, XP009034546 p. 234, left-hand column, last 4 lines; examples 6g,17b</td>
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INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 5, 7-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. □ Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
## INTERNATIONAL SEARCH REPORT

### Information on patent family members

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