THERAPEUTIC COMBINATIONS OF ATYPICAL ANTIPSYCHOTICS WITH CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising combinations of an atypical antipsychotic, a prodrug thereof or a pharmaceutically acceptable salt of the atypical antipsychotic or prodrug thereof, and a corticotropin releasing factor antagonist, a prodrug thereof or a pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or prodrug thereof, kits containing such combinations and methods of using such combinations to treat mammals, including humans, suffering from treatment-resistant anxiety disorders, psychotic disorders or conditions, mood disorders or conditions, or a combination thereof. This invention also relates to additive and synergistic combinations of atypical antipsychotic, a prodrug thereof or a pharmaceutically acceptable salt of the atypical antipsychotic or prodrug thereof, and a corticotropin releasing factor antagonist, a prodrug thereof or a pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or prodrug thereof, whereby the additive and synergistic combinations are useful in treating mammals, including humans, suffering from treatment-resistant anxiety disorders, psychotic disorders or conditions, mood disorders or conditions, or a combination thereof.

BACKGROUND OF THE INVENTION

Atypical antipsychotics offer several clinical benefits over the conventional antipsychotics, which were the mainstays of care until the past decade. The principal mechanism underlying the many clinical benefits of the atypical antipsychotics is their ability to separate the antipsychotic effect from the extrapyramidal side effect (EPS). The distinct advantages over traditional antipsychotic medications include greater improvement in negative and cognitive symptoms, better antidepressant and mood stabilization effects, lower risk of parkinsonian side effects and tardive dyskinesia, and greater efficacy in otherwise refractory or treatment-resistant patients.

The differences in clinical profile between atypical and conventional antipsychotics can be understood in terms of their different pharmacological profiles. The conventional antipsychotics are antagonists of dopamine (D_2) receptors. The atypical antipsychotics also have D_2 antagonistic properties, but possess different binding kinetics to these receptors and activity at other receptors, particularly 5-HT_{2A}, 5-HT_{2C} and 5-HT_{1D} (Schmidt B et al, Soc. Neurosci. Abstr. 24:2177, 1998). For example, an atypical antipsychotic may have dual antagonism of serotonin 5-HT_{2A} and dopamine D2.

Examples of atypical antipsychotics for use in the present invention are the compounds generically and specifically disclosed in US 4,831,301, particularly ziprasidone (Geodon®), US 5,229,382, particularly olanzapine (Zyprexa®), US 3,539,573, particularly clozapine (Clozaril®), US 4,804,663, particularly risperidone (Risperdal®), US 4,710,500,

particularly sertindole, US 4,879,288, particularly quetiapine (Seroquel®), US 4,734,416, particularly aripiprazole (Abilify®), and US 4,401,822, particularly amisulpride, or pharmaceutically acceptable salts thereof.

Commonly assigned U.S. Pat. Nos. 4,831,031, 4,883,795, 5,229,382, and 6,245,766, which are hereby incorporated by reference, each disclose that ziprasidone has utility in the treatment of treatment-resistant anxiety disorders, psychotic disorders, and mood disorders.

Psychotic disorders or conditions, such as schizoaffective disorder, are serious mental disorders characterized by loss of contact with reality (psychosis), hallucinations (false perceptions), delusions (false beliefs), abnormal thinking, flattened affect, diminished motivation, and disturbed work and social functioning.

Mood disorders or conditions, also known as affective disorders, are a group of heterogeneous, typically recurrent illnesses including unipolar (depressive) and bipolar (manic-depressive) disorders, dysthymic disorder, and cyclothymic disorder that are characterized by pervasive mood disturbances, psychomotor dysfunction, and vegetative symptoms. Mood disorders may affect 20% of women and 12% of men during their lifetime. They are the most prevalent of psychiatric disorders, accounting for as many as 65% of psychiatric outpatients, and 10% of all patients seen in nonpsychiatric medical settings (The Merck Manual, 17th ed., Merck & Co. 1999, p. 1526). Lithium, the standard of care for mood disorder, has a response rate of only 50%, and is associated with side effects. Antipsychotic agents are also clinically used in this patient population.

Simplification of the regimen for the treatment of mood disorders or conditions, such as psychotic depression, or of psychotic disorders or conditions, such as schizoaffective disorders, may be achieved by combining two therapeutic agents. The combined treatment reduces the opportunity for patient noncompliance and occurs with a more rigorous schedule. Accordingly, there is a need for pharmaceutical combinations and pharmaceutical kits which employ atypical antipsychotics and another therapeutic agent efficacious for the treatment of conditions such as mood disorders or conditions, psychotic disorders or conditions, or a combination thereof.

Corticotropin releasing factor (CRF) antagonists are another class of therapeutic agents that have been described as effective in the treatment of certain disorders or conditions. CRF antagonists are disclosed in U.S. Pat. Nos. 4,605,642 and 5,063,245. Other CRF antagonists are disclosed in International patent publications WO 95/33750; WO 95/34563; WO 94/13661; WO 94/13644; WO 94/13643; WO 94/13676; WO 94/13677; WO 95/33727; WO 98/05661; WO 98/08847; WO 98/08846; and European patent publications EP 778277 and EP 773023. Yet other CRF antagonists are disclosed in the following patent publications: EP 576350; EP 659747; EP 812831; WO 95/10506; WO 96/35689; WO 96/39400; WO 97/00868; WO 97/14684; WO 97/29109; WO 97/29110; WO 97/35539; WO

97/35580; WO 97/35846; WO 97/44038; WO 97/45421; WO 98/03510; WO 98/08821; WO 98/11075; WO 98/15543; WO 98/21200; WO 98/27066; WO 98/29397; WO 98/29413; WO 98/42699; WO 98/35967; WO 98/42706; WO 98/45295; WO 98/47874; WO 98/47903; WO 98/51312; WO 99/01454; WO 99/01439; WO 99/10350; WO 99/12908; WO 99/00373; WO 99/38868; WO 99/51597; WO 99/51599; WO 99/40089; WO 99/51598; and WO 99/51600. Still more CRF antagonists are disclosed in U.S. Pat. Nos. 5,109,111; 5,132,111; 5,245,009; 5,464,847; 5,493,006; 5,510,458; 5,644,057; 5,663,292; 5,668,145; 5,705,646; 5,712,303; and 5,723,608. An overview of the patent literature on CRF antagonists is provided in T. E. Christos and A. Arvanitis, Exp. Opin. Ther. Patents (1998) 8(2):143-152. Many of the above cited publications include information on how to make the CRF antagonists described therein. The importance of CRF antagonists is also set out in, e.g., P. Black, Scientific American: "Science & Medicine," 1995, 2:16-25; T. Lovenberg, et al., Current Pharmaceutical Design, 1995, 1: 305-316; D. T. Chalmers et al., Trends in Pharmacological Sciences, April 1996, pages 166-172; and U.S. Pat. No. 5,063,245. An outline of the activities possessed by CRF antagonists is found in M. J. Owens et al., 1991, Pharm. Rev., 43:425-473.

In particular, CRF antagonists have been described as effective in the treatment of, for example, stress-related illnesses; mood disorders such as depression, including, for example, depression in cancer patients, depression in Parkinson's patients, Postmyocardial Infarction depression, depression in patients with human immunodeficiency virus (HIV), Subsyndromal Symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, DSM-IV major depression, treatment-refractory major depression, severe depression, psychotic depression, post-stroke depression, neuropathic pain, manic depressive illness, including manic depressive illness with mixed episodes and manic depressive illness with depressive episodes, seasonal affective disorder, bipolar depression BP I, bipolar depression BP II, or major depression with dysthymia; chronic fatigue syndrome; dysthymia; pain perception, such as fibromyalgia; gastrointestinal diseases; hemorrhagic stress; ulcers; stress-induced psychotic episodes; fever; diarrhoea; post-operative ileus; colonic hypersensitivity; irritable bowel syndrome; Chron's disease; spastic colon; inflammatory disorders such as rheumatoid arthritis and osteoarthritis; pain; asthma; psoriasis; allergies; osteoporosis; premature birth; hypertension; congestive heart failure; sleep disorders; neurogenerative diseases such as Alzheimer's disease, senile dementia of the Alzheimer's type, multiinfarct dementia, and Huntington's disease; head trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; spinal cord trauma; psychosocial dwarfism; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; cancer; muscular spams; urinary incontinence; hypoglycemia and immune dysfunctions, including stress-induced immune dysfunctions, immune suppressions,

and human immunodeficiency virus infections; stress-induced infections; anxiety disorders, including, for example, generalized anxiety disorder, panic disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder; phobias, including, for example, agoraphobia, social phobia or simple phobias; eating disorders, including, for example, anorexia nervosa or bulimia nervosa; chemical dependencies and addictions, including, for example, addictions to alcohol, cocaine, amphetamine and other psychostimulants, morphine, heroin and other opioid agonists, phenobarbital and other barbiturates, nicotine, and diazepam and other benzodiazepines; drug and alcohol withdrawal symptoms; Parkinson's diseases, including, for example, dementia in Parkinson's disease, neuroleptic-induced parkinsonism or tardive dyskinesias; and headache, including, for example, headache associated with vascular disorders. See, for example, P. Black, Scientific American, 1995, 2:16-25; T. Lovenberg, et al., Current Pharmaceutical Design, 1995, 1:305-316; D. T. Chalmers et al., Trends in Pharmacological Sciences, April 1996, pages 166-172; M. J. Owens et al., Pharm. Rev., 1991, 43:425-473; and U.S. Patent No. 5,063,245.

The present invention is directed to compositions, methods and kits which fulfill the need for simplification of treatment of mood disorders or conditions, psychotic disorders or conditions, or a combination thereof by combining two therapeutic agents. In particular, the compositions contain atypical antipsychotics and corticotropin releasing factor antagonists for the treatment of mood disorders or conditions, psychotic disorders or conditions, or a combination thereof.

SUMMARY OF THE INVENTION

The present invention is directed to a pharmaceutical compositions for treating, for example, mood disorders or conditions, psychotic disorders or conditions, or a combination thereof, in a mammal such as a human, the composition comprising (a) an atypical antipsychotic, a prodrug thereof or a pharmaceutically acceptable salt of the atypical antipsychotic or prodrug thereof, (b) a corticotropin releasing factor antagonist, a prodrug thereof, or pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or prodrug thereof, and optionally (c) a pharmaceutically acceptable vehicle, carrier or diluent.

The present invention is also directed to:

a method for treating one or more disorders or conditions described in the previous paragraph, the method comprising administering to a mammal in need of such treatment components (a) and (b) described in the previous paragraph, wherein (a) and (b) are each optionally and independently administered together with a pharmaceutically acceptable vehicle, carrier or diluent;

a composition for treating, for example, a depressive symptom associated with one or more disorders or conditions described in the previous paragraph, the composition comprising components (a), (b), and optionally (c) described in the previous paragraph, wherein the

symptom is selected from the group consisting of depressed mood, irritability, sad effect, and circadian rhythm alteration;

a method for treating a depressive symptom associated with one or more disorders or conditions described in the previous paragraph, the method comprising administering to a mammal in need of such treatment components (a) and (b) described in the previous paragraph, wherein (a) and (b) are each optionally and independently administered together with a pharmaceutically acceptable vehicle, carrier or diluent;

a kit comprising an atypical antipsychotic, a prodrug thereof, or pharmaceutically acceptable salt of said atypical antipsychotic or prodrug thereof in a first unit dosage form; a corticotropin releasing factor antagonist, a prodrug thereof, or pharmaceutically acceptable salt of said atypical antipsychotic or prodrug thereof; in a second unit dosage form; and a container;

a kit for achieving, for example, a therapeutic effect for one or more disorders or conditions described in the previous paragraph, the kit comprising a pharmaceutical composition comprising a corticotropin releasing factor antagonist, a prodrug thereof, or pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or prodrug thereof, a package containing the composition, and a package insert that is optionally integral with the package, wherein it is stated on the package insert that the pharmaceutical composition is to be administered to the mammal simultaneously or in a specifically timed manner with a pharmaceutical composition containing an atypical antipsychotic, a prodrug thereof, or pharmaceutically acceptable salt of said atypical antipsychotic or prodrug thereof; and

a kit for achieving, for example, a therapeutic effect for one or more disorders or conditions described in the previous paragraph, the kit comprising a pharmaceutical composition comprising an atypical antipsychotic, a prodrug thereof, or pharmaceutically acceptable salt of said atypical antipsychotic, or prodrug thereof, a package containing the composition, and a package insert that is optionally integral with the package, wherein it is stated on the package insert that the pharmaceutical composition is to be administered to the mammal simultaneously or in a specifically timed manner with a pharmaceutical composition containing corticotropin releasing factor antagonist, a prodrug thereof, or pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or prodrug thereof.

A further feature of the present invention is that the amount of the atypical antipsychotic used to treat mood disorders or conditions, psychotic disorders or conditions, or a combination thereof is a lower amount than the amount of the atypical antipsychotic used to treat such disorders or conditions when the atypical antipsychotic is used in the absence of another therapeutically active agent. The reduced amount of the atypical antipsychotic permits better management of drug-related toxicity and side effects. The amount of the

atypical antipsychotic in the composition of the invention that is used to achieve the same or a similar psychotropic effect as when the atypical antipsychotic is used in the absence of another therapeutically active agent is lower by about 25-90%, for example, about 40-80% and typically about 50-70%. The reduction in amount of the atypical antipsychotic required may depend on the amount of the corticotropin releasing factor antagonist.

The term 'mood disorders' refers to a group of heterogeneous illnesses including unipolar (depressive) and bipolar (manic-depressive) disorders that are characterized by pervasive mood disturbances, psychomotor dysfunction, and vegetative symptoms. Depression and elation are the core affective components, but anxiety and irritability are equally common, explaining the continued popularity of the broader rubric "affective disorders", the previous official designation. Types of depression that may be treated by the compositions, methods and kits of this invention include, inter alia: depression in cancer patients, depression in Parkinson's patients, Postmyocardial Infarction depression, depression in patients with human immunodeficiency virus (HIV), Subsyndromal Symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, DSM-IV major depression, treatment-resistant depression, treatment-refractory major depression, severe depression, psychotic depression, post-stroke depression, neuropathic pain, manic depressive illness, including manic depressive illness with mixed episodes and manic depressive illness with depressive episodes, seasonal affective disorder, bipolar depression BP I, bipolar depression BP II, and major depression with dysthymia. Types of anxiety that may be treated by the compositions, methods and kits of this invention include, inter alia: generalized anxiety disorder, panic disorder, post-traumatic stress disorder (PTSD), social anxiety disorder, treatment-resistant obsessive-compulsive disorder, treatment-resistant anxiety disorder, treatment-resistant generalized anxiety disorder, treatment-resistant post-traumatic stress disorder.

Examples of psychotic disorders that can be treated according to the present invention include, but are not limited to, schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; personality disorder of the schizoid type; psychotic disorder not otherwise specified.

Schizophrenia as used herein refers to a disorder that lasts for at least 6 months and includes at least one month of active-phase symptoms (i.e., two [or more] of the following:

delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms) (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Schizophreniform disorder is defined as a disorder characterized by a symptomatic presentation that is equivalent to schizophrenia except for its duration (i.e., the disturbance lasts from 1 to 6 months) and the absence of a requirement that there be a decline in functioning (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Schizoaffective disorder is defined as a lifetime pattern of social and interpersonal deficits characterized by an inability to form close interpersonal relationships, eccentric behavior, and mild perceptual distortions.

For example, "treating schizophrenia, or schizophreniform or schizoaffective disorder" as used herein also encompasses treating one or more symptoms (positive, negative, and other associated features) of said disorders, for example treating, delusions and/or hallucination associated therewith. Examples of symptoms of schizophrenia and schizophreniform and schizoaffecctive disorders also include disorganized speech, affective flattening, alogia, anhedonia, inappropriate affect, dysphoric mood (in the form of, for example, depression, anxiety or anger), and some indications of cognitive dysfunction.

Delusional disorder as referred to herein is characterized by at least 1 month of nonbizarre delusions without other active-phase symptoms of schizophrenia. (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Brief psychotic disorder is a disorder that lasts more than 1 day and remits by 1 month. (Diagnostic and Statistical Manual of Mental Disorders , DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Shared psychotic disorder is characterized by the presence of a delusion in an individual who is influenced by someone else who has a longer-standing delusion with similar content. (Diagnostic and Statistical Manual of Mental Disorders , DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Psychotic disorder due to a general medical condition is characterized by psychotic symptoms judged to be a direct physiological consequence of a general medical condition. (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Psychotic disorder not otherwise specified is a psychotic presentation that does not meet the criteria for any of the specific psychotic disorders defined in the DSM-IV-TR (American Psychiatric Assoc., Washington, DC, 2002).

The present invention is also useful to treat other disorders that may present psychotic symptoms as associated features such as dementia of the Alzheimer's type; substance-induced delirium; and major depressive disorder with psychotic features.

Other disorders and conditions that may be treated by the compositions, methods and kits of this invention include, inter alia:

phobias, including agoraphobia, social phobia and simple phobias;

sexual dysfunction, including premature ejaculation;

eating disorders, including anorexia nervosa and bulimia nervosa;

chemical dependencies, including addictions to alcohol, cocaine, heroin, phenolbarbitol, nicotine and benzodiazepines;

memory disorders, including dementia, amnestic disorders, and age-related cognitive decline (ARCD);

Parkinson's diseases, including dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias;

endocrine disorders, including hyperprolactinaemia;

vasospasm, including a vasospasm in the cerebral vasculature;

gastrointestinal tract disorders, including gastrointestinal tract disorders involving changes in motility and secretion;

cancer, including small cell lung carcinoma; and

headache, including headache associated with vascular disorders. The compositions, methods and kits of the present invention may also used for treating or preventing osteoporosis or frailty associated with aging or obesity, cardiovascular or heart related disease, in particular hypertension, tachycardia, and congestive heart failure, accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or of patients having undergone major surgery.

The meanings attributed to the different types and subtypes of mood disorders not defined herein are as stated in DSM-IV-TR under depressive disorders (" unipolar depression") and bipolar disorders, generalized anxiety disorder, and more specific anxiety disorders such as agoraphobia, panic disorder and social phobia, obsessive-compulsive disorder and post traumatic stress disorder (PTSD), the contents of which are incorporated by reference herein. (Diagnostic and Statistical Manual of Mental Disorders", 4th ed, American Psychiatric Assoc., Washington, DC, 2002, p. 345-484). Similarly, the meanings attributed to the different types and subtypes of and psychotic disorders are as stated in DSM-IV-TR.

The methods of this invention also encompass treating the diseases or conditions described herein by the co-administration of two separate pharmaceutical compositions. In

this latter embodiment, a first composition comprises a CRF antagonist, and a second composition comprises an atypical antipsychotic. These first and second compositions are preferably co-administered either simultaneously, or in a specifically timed manner.

The term "affective disorder" as used herein is interchangeable with the term "mood disorders" and refers to disorders that are characterized by changes in mood as the primary clinical manifestation, for example, depression.

The term "treatment-resistant" is used herein to define a condition wherein a patient having that condition does not respond to treatment with at least one antidepressant over a period of at least six weeks. For example, the term "treatment-resistant" may define a condition wherein a patient having that condition does not respond to treatment with two or more antidepressants over a period of six to eight weeks.

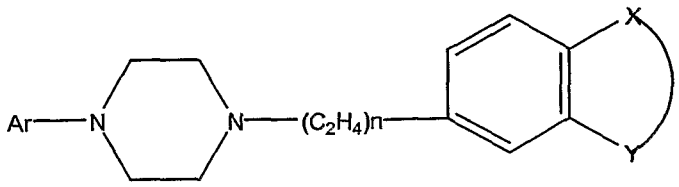
The term "prodrug" refers to compounds that are drug precursors which, following administration, release the drug in vivo via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form). A prodrug of any or all of the compounds (i.e., a CRF antagonist, or an atypical antipsychotic) may be used in the methods, kits, and compositions of the instant invention. In general, prodrugs are functional derivatives of these compounds which are readily convertible in vivo. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985 and can be achieved using methods well known to those skilled in the art. All such prodrugs are within the scope of the combinations, pharmaceutical compositions, methods and kits of this invention.

Upon cleavage, exemplary prodrugs release the corresponding free acid (where applicable), and such hydrolyzable ester-forming residues of the prodrugs of this invention include but are not limited to carboxylic acid substituents wherein the free hydrogen is replaced by $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_{12})$alkanoyloxymethyl, $(C_4\text{-}C_9)$1-(alkanoyloxy)ethyl, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-$(C_1\text{-}C_2)$alkylamino$(C_2\text{-}C_3)$alkyl (such as N,N-dimethylaminoethyl), carbamoyl-$(C_1\text{-}C_2)$alkyl, N,N-di$(C_1\text{-}C_2)$-alkylcarbamoyl-$(C_1\text{-}C_2)$alkyl, piperidino-, pyrrolidino-, or morpholino$(C_2\text{-}C_3)$alkyl, and the like.

Other exemplary prodrugs (where applicable) are derivatives of an alcohol of the compounds used in this invention wherein the free hydrogen of a hydroxyl substituent is replaced by $(C_1\text{-}C_6)$alkanoyloxymethyl, 1-(($C_1\text{-}C_6$)alkanoyloxy)ethyl, 1-methyl-1-(($C_1\text{-}C_6$)alkanoyloxy)ethyl, $(C_1\text{-}C_6)$alkoxycarbonyloxymethyl, N-($C_1\text{-}C_6$)alkoxy-carbonylamino-

methyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacetyl, α-aminoacyl, α-aminoacyl-.α-aminoacyl wherein said α-aminoacyl moieties are independently any of the naturally occurring L-amino acids found in proteins, --P(O)(OH)$_2$, --P(O)(O(C_1-C_6)alkyl)$_2$, glycosyl (the radical resulting from detachment of the hydroxyl of the hemiacetal of a carbohydrate), or the like.

Atypical antipsychotics which may be used in the present invention include olanazapine, clozapine, aripiprazole, quetiapine, amisulpride, risperidone, sertindole; the compounds represented by the structure **A**



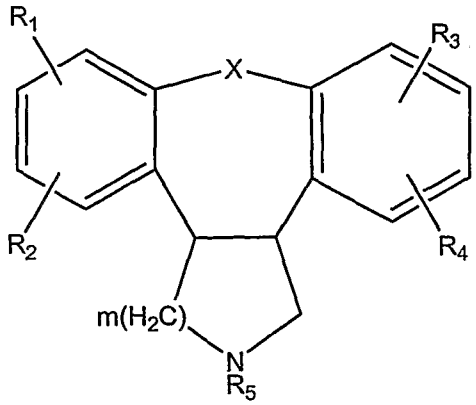
A

wherein Ar is benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by one fluoro, chloro, trifluoromethyl, methoxy, cyano, or nitro;

n is 1 or 2;

and X and Y together with the phenyl to which they are attached form benzothiazolyl; 2-aminobenzothiazolyl; benzoisothiazolyl; indazolyl; 2-hydroxyindazolyl; indolyl; oxindolyl optionally substituted by one to three of (C_1 –C_3)alkyl, or one of chloro, fluoro or phenyl, said phenyl optionally substituted by one chloro or fluoro; benzoxazolyl; 2-aminobenzoxazolyl; benzoxazolonyl; 2-aminobenzoxazolinyl; benzothiazolonyl; bezoimidazolonyl; or benzotriazolyl;

and the compounds represented by the structure **B**:



B

or pharmaceutically acceptable salts thereof, wherein

R_1, R_2, R_3 and R_4 each represent hydrogen, hydroxy, halogen, a C_1-C_6 alkyl group, an alkoxy or alkylthio group in which the alkyl group contains 1-6 carbon atoms, or a trifluoromethyl group,

R_5 represents hydrogen, a C_1-C_6 alkyl group carbon atoms or an aralkyl group with 7-10 carbon atoms,

m is 1 or 2,

X represents oxygen, sulphur, the group -N(R_6)- or the group -CH_2-, and

R_6 represents hydrogen or a C_1-C_4 alkyl group.

In an exemplary embodiment, pharmaceutical combinations and methods of treatment include ziprasidone as the atypical antipsychotic of Structure A. Ziprasidone (5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloroindolin-2-one hydrochloride hydrate) is a benzisothiazolyl piperazine-type atypical antipsychotic with in vitro activity as a 5-HT_{1A} receptor agonist and an inhibitor of serotonin and norepinephrine reuptake (See e.g. U.S. Pat. No. 4,831,031). The postsynaptic 5-HT_{1A} receptor has been implicated in both depressive and anxiety disorders (NM Barnes, T Sharp, 38 Neuropharmacology 1083-152,1999). Oral bioavailability of ziprasidone taken with food is approximately 60%, half-life is approximately 6-7 hours, and protein binding is extensive.

Ziprasidone is efficacious for the treatment of patients with schizophrenia and schizomood disorders, refractory schizophrenia, cognitive impairment in schizophrenia, affective and anxiety symptoms associated with schizoaffective disorder and bipolar disorder. Ziprasidone is considered a safe and efficacious atypical antipsychotic (Charles Caley & Chandra Cooper, 36 Ann. Pharmacother. 839-51, 2002).

The present invention is useful in treating mental disorders and conditions the treatment of which is facilitated by the administration of ziprasidone. Thus, the present invention has application where ziprasidone use is indicated as, e.g., in U.S. Pat. Nos. 6,245,766; 6,245,765; 6,387,904; 5,312,925; 4,831,031; and European EP 0901789 published March 17, 1999, all of which are incorporated herein by reference.

In an exemplary embodiment, pharmaceutical combinations and methods of treatment include trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino-[4, 5-c]pyrrole as the atypical antipsychotic of Structure B. Trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino-[4,5-c]pyrrole is also referred to herein as asenapine. Asenapine is described, for example, in U.S. Patent No. 4,145,434. A method of treatment of mental disorders such as psychosis and schizophrenia is described in U.S. Patent No. 5,763,476. A method of synthesis of asenapine and its maleate salt is shown in Scheme I below.

Other atypical antipsychotics which can be used in the present invention include, but are not limited to, the compounds described in the following paragraphs.

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzo-diazepine, is a known compound and is described in U.S. Pat. No. 5,229,382 as being useful

for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis.

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Pat. No. 3,539,573. Clinical efficacy in the treatment of schizophrenia is described (Hanes, et al., Psychopharmacol. Bull., 24, 62 (1988)).

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Pat. No. 4,804,663

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Pat. No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Pat. Nos. 5,112,838 and 5,238,945.

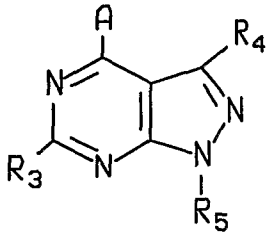
Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl -1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Pat. No. 4,879,288. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt.

Aripiprazole, 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro carbostyril or 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro -2(1H)-quinolinone, is an atypical antipsychotic agent used for the treatment of schizophrenia and described in U.S. Pat. No. 4,734,416 and U.S. Pat. No. 5,006,528.

Amisulpride is an atypical antipsychotic agent described in U.S. Pat. No. 4,401,822.

The CRF antagonist may be, for example,

I. a compound of the following formula, described in WO 94/13677:



and the pharmaceutically acceptable acid addition salts thereof, wherein

A is NR_1R_2, $CR_1R_2R_{11}$, or $C(=CR_1R_{12})R_2$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_6 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, O-C(O)-(C_1-C_6 alkyl), O-C(O)-N(C_1-C_4 alkyl)(C_1-C_2 alkyl); amino, NH(C_1-C_4 alkyl), S(C_1-C_6 alkyl), OC(O)NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)C(O)(C_1-C_4 alkyl), NHC(O)(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl), C(O)NH(C_1-C_4 alkyl), C(O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4

alkyl); $SO_2(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), and said $C_1\text{-}C_6$ alkyl may have one or two double or triple bonds;

R^2 is $C_1\text{-}C_{12}$ alkyl, aryl or ($C_1\text{-}C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1\text{-}C_6$ alkylene) cycloalkyl, wherein said cycloalkyl may have one or two of O, S or N-Z, wherein Z is hydrogen, substituted , independently, for one or two carbons of said cycloalkyl, $C_1\text{-}C_4$ alkyl, benzyl or $C_1\text{-}C_4$ alkanoyl, wherein R^2 may be substituted independently by from one to three of chloro, fluoro, or $C_1\text{-}C_4$ alkyl, or one of hydroxy, bromo, iodo, $C_1\text{-}C_6$ alkoxy, $OC(O)(C_1\text{-}C_6$ alkyl), $O\text{-}C\text{-}N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $S(C_1\text{-}C_6$ alkyl), NH_2, $NH(C_1\text{-}C_2$ alkyl), $N(C_1\text{-}C_4$ alkyl) $C(O)(C_1\text{-}C_4$ alkyl), $NHC(O)(C_1\text{-}C_4$ alkyl), COOH, $C(O)O(C_1\text{-}C_4$ alkyl), $C(O)NH(C_1\text{-}C_4$ alkyl), $C(O)N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), SH, CN, NO_2, $SO(C_1\text{-}C_4$ alkyl), $SO_2(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), and wherein said $C_1\text{-}C_{12}$ alkyl or $C_1\text{-}C_{10}$ alkylene may have one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a 4- to 8-membered ring optionally having one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, benzyl, or $C_1\text{-}C_4$ alkanoyl;

R_3 is hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, $O(C_1\text{-}C_6$ alkyl), $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), SH, $S(C_1\text{-}C_4$ alkyl), $SO(C_1\text{-}C_4$ alkyl), or $SO_2(C_1\text{-}C_4$ alkyl), wherein said $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl may have one or two double or triple bonds and may be substituted by from 1 to 3 R_7 substituents independently selected from the group consisting of hydroxy, amino, $C_1\text{-}C_3$ alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, $NHC(O)CH_3$, fluoro, chloro or $C_1\text{-}C_3$ thioalkyl;

R_4 is hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1\text{-}C_6$ alkoxy, amino, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl) $(C_1\text{-}C_2$ alkyl), $SO_n(C_1\text{-}C_6$ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said $C_1\text{-}C_6$ alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, $NHC(O)(C_1\text{-}C_4$ alkyl), $NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $C(O)O(C_1\text{-}C_4$ alkyl), $C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, piperazinyl, piperidinyl, or tetrazolyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, cyclopropyl, $NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $COO(C_1\text{-}C_4$ alkyl), $CO(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), SO_2NH_2, $NHSO_2(C_1\text{-}C_4$

alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may have one double or triple bond and may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro, COO(C_1-C_2 alkyl), cyano, or CO(C_1-C_2 alkyl); and

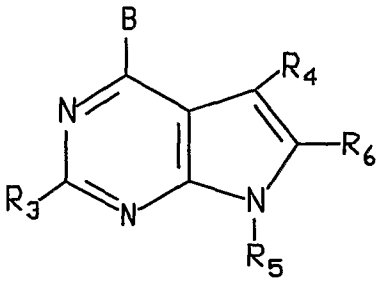
R_{12} is hydrogen or C_1-C_4 alkyl;

(a) A is not straight chain C_1-C_{12} alkyl;

(b) when R_3 is hydrogen, A is benzyl or phenethyl, and R_4 is fluoro, chloro, bromo or iodo, then R_5 is not 5'-deoxy-ribofuranosyl or 5'-amino-5'-deoxy-ribofuranosyl; and

(c) when R^5 is phenyl, said phenyl is substituted by two or three substituents.

II. The invention also relates to use of a CRF antagonist of the following formula, described in WO 94/13676:



and the acid addition salts thereof, wherein

B is XA wherein X is $(CH_2)_n$ in which n is 0, 1 or 2, NH, O, S, N(C_1-C_4 alkyl);

A is NR_1R_2, $CR_1R_2R_{11}$, or $C(=CR_2R_{12})R_1$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, O-C(=O)-(C_1-C_6 alkyl), O-C(=O)NH(C_1-C_4 alkyl), O-C(=O)-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_6 alkyl), N(C_1-C_4alkyl)C(=O)(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), COOH, C(=O)O(C_1-C_4 alkyl), C(=O)NH(C_1-C_4 alkyl), C(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or

one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, O-C(=O)-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl) (C_1-C_4 alkyl), N(C_1-C_4)- C(=O)(C_1-C_4 alkyl), NHC(=O)(C_1-C_4), COOH, C(=O)O(C_1-C_4 alkyl), C(=O)NH(C_1-C_4 alkyl), C(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkyl may contain one to three double or triple bonds; or

when A is NR_1R_2 or $CR_1R_2R_{11}$, then R_1 and R_2 taken together with the atom to which they are attached may form a saturated 4- to 8-membered optionally containing one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain from one or two double or triple bonds and may be substituted by from 1 to 3 substituents R_8 independently selected from the group consisting of hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, $NHCH_3$, fluoro, chloro or C_1-C_3 thioalkyl;

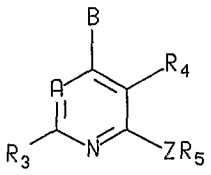
R_4 and R_6 are each independently hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NHC(=O)(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), C(=O)O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

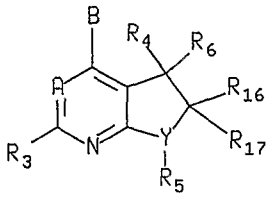
R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to four of fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of bromo, iodo, cyano, nitro, amino, NH(C_1-C_4 alkyl), N(C_1-C_4)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl;

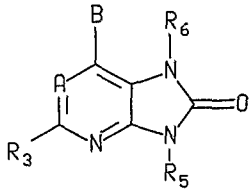
R_{11} is hydrogen, hydroxy, fluoro, chloro, COO(C_1-C_2 alkyl), cyano, or CO(C_1-C_2 alkyl); and

R_{12} is hydrogen or C_1-C_4 alkyl; with the proviso that (1) when R_5 is 4-bromophenyl, R_3 is hydrogen, and R_4 and R_6 are methyl, then B is not methylamino or ethyl, and (2) when R_5 is 4-bromophenyl, and R_3, R_4 and R_6 are methyl, then B is not 2-hydroxyethylamino.

III. It is also possible to employ a CRF antagonist that has a structure selected from the group shown below, and pharmaceutically acceptable salts and esters thereof, as described in WO 95/33750:







wherein

A is CR_7 or N;

B is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCHR_1R_2$, $OCHR_1R_2$, $SCHR_1R_2$, CHR_2OR_{12}, CHR_2SR_{12}, $C(S)R_2$ or $C(O)R_2$;

Y is CH or N;

Z is NH, O, S, N (C_1-C_2 alkyl), or $CR_{13}R_{14}$, wherein R_{13} and R_{14} are each independently hydrogen, trifluoromethyl, or C_1-C_4 alkyl, or one of R_{13} and R_{14} may be cyano, chloro, bromo, iodo, fluoro, hydroxy, O(C_1-C_2 alkyl), amino, NH(C_1-C_2 alkyl), or $CR_{13}R_{14}$ may be C=O or cyclopropyl;

R_1 is C_1-C_6 alkyl which may be substituted by one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, O-CO-(C_1-C_4 alkyl), O-CO-NH(C_1-C_4 alkyl), O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_4 alkyl), N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), NHCO(C_1-C_4 alkyl), COO(C_1-C_4 alkyl), CONH(C_1-C_4 alkyl), CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_4 alkyl), CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), and said C_1-C_6 alkyl or C_1-C_4 alkyl may contain one double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene)cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-R_9 wherein R_9 is hydrogen, or C_1-C_4 alkyl, wherein the above defined R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of bromo, iodo, C_1-C_6 alkoxy, O-CO-(C_1-C_6 alkyl), O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), CN, NO_2, SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_4 alkylene may contain one double or triple bond; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a saturated 5- to 8-membered carbocyclic ring which may contain one or two double bonds or one or two of O or S;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, amino, nitro, $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $SO_n(C_1$-C_4 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, $CO(C_1$-C_4 alkyl), CHO, or $COO(C_1$-C_4 alkyl), wherein said C_1-C_4 alkyl may contain one or two double or triple bonds and may be substituted by one or two of hydroxy, amino, carboxy, $NHCOCH_3$, $NH(C_1$-C_2 alkyl), $N(C_1$-C_2 alkyl)$_2$, $COO(C_1$-C_4 alkyl), $CO(C_1$-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each one of the above groups R_5 is substituted independently by from one to three of fluoro, chloro, C_1-C_6 alkyl, or C_1-C_6 alkoxy, or one of hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $NH(C_1$-C_4 alkyl), $N(C_1$-$C_6)(C_1$-C_2 alkyl), COOH, $COO(C_1$-C_4 alkyl), $CO(C_1$-C_4 alkyl), $SO_2NH(C_1$-C_4 alkyl), $SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2(C_1$-C_4 alkyl), $S(C_1$-C_6 alkyl), or $SO_2(C_1$-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, hydroxy, amino, methylamino, dimethylamino or acetyl;

R_6 is hydrogen, or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl may be substituted by one hydroxy, methoxy, ethoxy or fluoro;

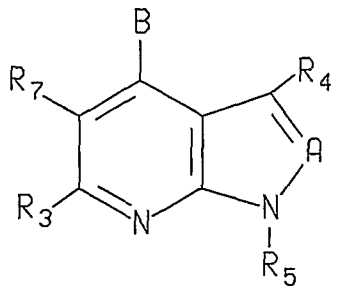
R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, $O(C_1$-C_4 alkyl), $C(O)(C_1$-C_4 alkyl), or $C(O)O(C_1$-C_4 alkyl), wherein the C_1-C_4 alkyl groups may be substituted with one hydroxy, chloro or bromo, or one to three fluoro;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

R_{12} is hydrogen or C_1-C_4 alkyl; and

R_{16} and R_{17} are each independently hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that they are not both methoxy or ethoxy, and CR_4R_6 and $CR_{16}R_{17}$ each independently may be C=O.

IV. It also possible to employ a CRF antagonist of the following formula, disclosed in WO 95/34563:



and the pharmaceutically acceptable acid addition salts thereof, wherein

A is N or -CR_6;

B is -NR_1R_2, -$CR_1R_2R_{11}$, -$C(=CR_2R_{12})R_1$, -$NHCHR_1R_2$, -$OCHR_1R_2$, -$SCHR_1R_2$, -CHR_2OR_{12}, -CHR_2SR_{12}, -$C(S)R_1$ or -$C(O)R_1$;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), and wherein any of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl, -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, oxazolyl, or benzoxazolyl; or 3- to 8-membered cycloalkyl or -(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-Z wherein Z is hydrogen; or C_1-C_4 alkyl, and wherein each of said groups R_2 may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -S(C_1-C_6 alkyl), -COO(C_1-C_4 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 may form a saturated 5- to 8-membered heterocyclic ring, or -CHR_1R_2 may form a saturated 5- to 8-membered carbocyclic ring, wherein each of these rings may optionally contain one or two carbon-carbon double bonds and wherein one or two of the carbon atoms of each of these rings may optionally be replaced with a sulfur or oxygen atom;

R_3 is C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, -CH_2OH, -CH_2OCH_3, -O(C_1-C_3 alkyl), -S(C_1-C_3 alkyl), or -SO_2(C_1-C_3 alkyl), wherein said C_1-C_3 alkyl may optionally contain one carbon-carbon double or triple bond;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, amino, -$NHCH_3$, -$N(CH_3)_2$, -CH_2OH, -CH_2OCH_3, or -SO_n(C_1-C_4 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, or -COO(C_1-C_4 alkyl) wherein the C_1-C_4 alkyl moieties in the foregoing R_4 groups may optionally contain one carbon-carbon double or triple bond;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, pyrimidyl, benzofuranyl, pyrazinyl or benzothiazolyl, wherein each one of said groups R_5 may optionally be substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6

alkoxy, or by one substituent selected from iodo, hydroxy, bromo, formyl, cyano, nitro, amino, trifluoromethyl, -NH(C_1-C_4 alkyl), -N(C_1-C_6)(C_1-C_2 alkyl), -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), wherein each of said C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one to three fluorine atoms;

R_6 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, -CH_2OH, -CH_2OCH_3, or C_1-C_4 alkoxy;

R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, -O(C_1-C_4 alkyl), cyano, -CH_2OH, -CH_2O(C_1-C_2 alkyl), -CO(C_1-C_2 alkyl), or -COO(C_1-C_2 alkyl);

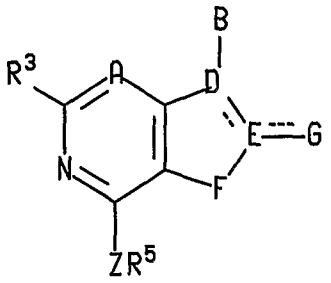
R_{11} is hydrogen, hydroxy, fluoro, or methoxy; and

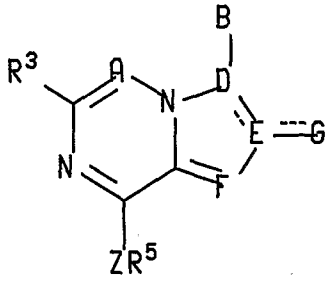
R_{12} is hydrogen or C_1-C_4 alkyl;

with the proviso that when A is N, then: (a) B is not unsubstituted alkyl; (b) R_5 is not unsubstituted phenyl or monosubstituted phenyl; and (c) R_3 is not unsubstituted alkyl;

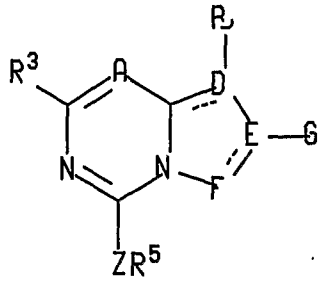
or a pharmaceutically acceptable salt of such compound.

V. In another embodiment, the CRF antagonist is of the following formula, disclosed in EP 778277:





or



or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

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

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is either double bonded to E in formulas I and II or double bonded to the adjacent carbon atom common to both fused rings in formula III, or D is CH and is single bonded to E in formulas I and II;

E is nitrogen, CH or carbon;

F is oxygen, sulfur, CHR^4 or NR^4 when it is single bonded to E and F is nitrogen or CR^4 when it is double bonded to E;

G, when single bonded to E, is hydrogen, C_1-C_4 alkyl, $-S(C_1$-C_4 alkyl), $-O(C_1$-C_4 alkyl), NH_2, $-NH(C_1$-C_4 alkyl) or $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), wherein each of the C_1-C_4 alkyl groups of G may optionally be substituted with one hydroxy, $-O(C_1$-C_2 alkyl) or fluoro group; G, when double bonded to E, is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D or F, is absent;

R^1 is hydrogen, C_1-C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, $-C(=O)O$-(C_1-C_4)alkyl, $-OC(=O)(C_1$-C_4 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-NHCO(C_1$-C_4 alkyl), -COOH, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_4 alkyl), -CN, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

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

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

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

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl) wherein each of the (C_1-C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substituted with one substituent R^9 selected from hydroxy, fluoro and (C_1-C_2 alkoxy);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4)alkyl, -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl), wherein each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoing R^4 groups may optionally contain one or two double or triple bonds and may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH_3, fluoro, chloro, C_1-C_3 thioalkyl, -CN, -COOH, -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl) and -NO_2;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein Z^4 is hydrogen, C_1-C_4 alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{12} wherein one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, -CF_3, -NO_2, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, C_1-C_4 alkyl, halo, cyano, hydroxy, -O(C_1-C_4 alkyl) -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4alkyl), -OCF_3, -CF_3, -CH_2OH, -CH_2O(C_1-C_4 alkyl);

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

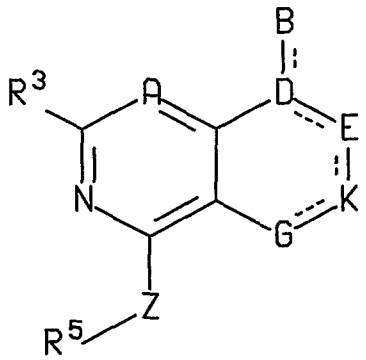
R^{11} is hydrogen or C_1-C_4 alkyl; and

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), -NC(=O)(C_1-C_2 alkyl), NC(=O)O(C_1-C_2alkyl) or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14}can be cyano;

with the proviso that: (a) in the five membered rings of structures I, II and III, there can not be two double bonds adjacent to each other; and (b) when R^4 is attached to nitrogen, it is not halo, cyano or nitro;

or a pharmaceutically acceptable salt of such compound.

VI. The CRF antagonist can also be of the following formula, disclosed in WO 98/05661:



wherein the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

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

D is nitrogen or CR^4 and is single bonded to all atoms to which it is attached, or D is carbon and is double bonded to E or double bonded to B;

E is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6; or E is a two atom spacer, wherein one of the atoms is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6, and the other is CR^6R^{12} or CR^9;

K and G are each, independently, C=O, C=S, sulfur, oxygen, CHR^8 or NR^8 when single bonded to both adjacent ring atoms, or nitrogen or CR^8 when it is double bonded to an adjacent ring atom;

the 6- or 7-membered ring that contains D, E, K and G may contain from one to three double bonds, from zero to two heteroatoms selected from oxygen, nitrogen and sulfur, and from zero to two C=O or C=S groups, wherein the carbon atoms of such groups are part of the ring and the oxygen and sulfur atoms are substituents on the ring;

R^1 is C_1-C_6 alkyl optionally substituted with from one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, -C(=O)(C_1-C_4alkyl), -C(=O)-O-(C_1-C_4)alkyl, -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4

alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl may optionally and independently be replaced by an oxygen or sulfur and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

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

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl);

R^4 is hydrogen, C_1-C_2 alkyl, hydroxy or fluoro;

each R^6, R^8 and R^9 that is attached to a carbon atom is selected, independently, from hydrogen, C_1-C_2 alkyl, fluoro, chloro, bromo, iodo, hydroxy, hydroxymethyl, formyl, trifluoromethyl, cyano, amino, nitro, -O(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_2 alkyl), -S(C_1-C_2 alkyl), -CO(C_1-C_2 alkyl), -C(=O)H or -C(=O)O(C_1-C_2 alkyl), wherein each of the C_1-C_2 alkyl moieties in the foregoing R^6, R^8, and R^9 groups may optionally contain one double or triple bond; and each R^6, R^8, and R^9 that is attached to a nitrogen atom is selected, independently, from hydrogen and C_1-C_4 alkyl;

R^5 is substituted phenyl, naphthyl, pyridyl or pyrimidyl, wherein each of the foregoing R^5 groups is substituted with from two to four substituents R^{15}, wherein from one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl, -O(C_1-C_6 alkyl) and -(C_1-C_6alkylene)O(C_1-C_6alkyl), and wherein one of said substituents may be selected, independently,

from bromo, iodo, formyl, cyano, trifluoromethyl, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, methyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, methoxy, -C(=O)(C_1-C_2 alkyl), -C(=O)O(C_1-C_2 alkyl), trifluoromethoxy, hydroxymethyl, trifluoromethyl or formyl;

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

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

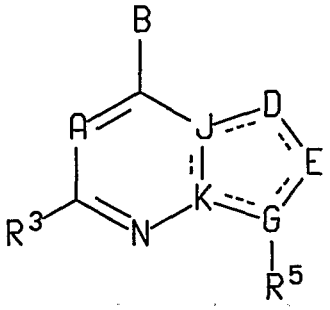
R^{12} is, hydrogen or methyl; and

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, and methyl with the exception that one of R^{13} and R^{14} may optionally be cyano;

with the proviso that: (a) in the six or seven membered rings of structures in formula I, there can not be two double bonds adjacent to each other; and (b) when D is carbon and is double bonded to B, then B is CR^1R^2;

or a pharmaceutically acceptable salt of such compound.

VII. The CRF antagonist can also be of the following formula, disclosed in WO 98/08847:



or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

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

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

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

G is nitrogen or carbon;

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

R^1 is C_1-C_6 alkyl optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, -O-(C_1-C_4 alkyl), CF_3, -C(=O)O-(C_1-C_4alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

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

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

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

R^6 is hydrogen, methyl or ethyl;

R^8 is hydrogen or C_1-C_4 alkyl;

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

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

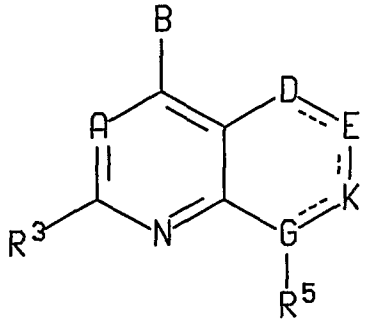
R^{10} is hydrogen, hydroxy, methoxy or fluoro;

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

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

and the pharmaceutically acceptable salts of such compounds.

VIII. Other useful CRF antagonists are of the following formula, disclosed in WO 98/08846:



wherein the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

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

G is nitrogen or CR^4 and is single bonded to all atoms to which it is attached, or G is carbon and is double bonded to K;

K is nitrogen or CR^6 when double bonded to G or E, or K is oxygen, sulfur, C=O, C=S, CR^6R^{12} or NR^8 when single bonded to both adjacent ring atoms, or K is a two atom spacer, wherein one of the two ring atoms of the spacer is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6, and the other is CR^6R^{12} or CR^9;

D and E are each, independently, C=O, C=S, sulfur, oxygen, CR^4R^6 or NR^8 when single bonded to both adjacent ring atoms, or nitrogen or CR^4 when it is double bonded to an adjacent ring atom;

the 6- or 7-membered ring that contains D, E, K and G may contain from one to three double bonds, from zero to two heteroatoms selected from oxygen, nitrogen and sulfur, and from zero to two C=O or C=S groups, wherein the carbon atoms of such groups are part of the ring and the oxygen and sulfur atoms are substituents on the ring;

R^1 is C_1-C_6 alkyl optionally substituted with from one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, -C(=O)(C_1-C_4alkyl), -C(=O)-O-(C_1-C_4)alkyl, -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl may optionally and independently be replaced by an oxygen or sulfur atom or by NZ wherein Z is hydrogen, C_1-C_4 alkyl or benzyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or $CR^1R^2R^{10}$ may form a ring selected from saturated 3 to 8 membered rings, the 5 to 8 membered rings of which may optionally contain one or two double bonds, and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally

and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is hydrogen, benzyl or C_1-C_4 alkyl;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl);

each R^8, R^9 and R^{12} is selected, independently, from hydrogen and C_1-C_2 alkyl;

each R^4 and R^6 that is attached to a carbon atom is selected, independently, from hydrogen and C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, hydroxy (C_1-C_2 alkyl), trifluoromethyl, cyano, amino, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CH_2SCH_3, -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4 alkyl), wherein each of the C_1-C_2 alkyl moieties in the foregoing R^4 and R^6 groups may optionally contain one double or triple bond; and R^6, when attached to a nitrogen atom, is selected from hydrogen and C_1-C_4 alkyl;

R^5 is substituted phenyl, naphthyl, pyridyl or pyrimidyl, wherein each of the foregoing R^5 groups is substituted with from two to four substituents R^{13}, wherein up to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl, -O(C_1-C_6 alkyl) and -(C_1-C_6 alkylene)O(C_1-C_6alkyl), and wherein one of said substituents may be selected, independently, from bromo, iodo, formyl, cyano, trifluoromethyl, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -(C_0-C_1alkylene)-S-(C_1-C_2alkyl), -(C_0-C_1alkylene)-SO-(C_1-C_2alkyl), -(C_0-C_1alkylene)-SO_2-(C_1-C_2alkyl) and -(C_1-C_4alkylene)-OH, and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, methyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, methoxy, -C(=O)(C_1-C_2 alkyl), -C(=O)O(C_1-C_2 alkyl), hydroxymethyl, trifluoromethyl or formyl;

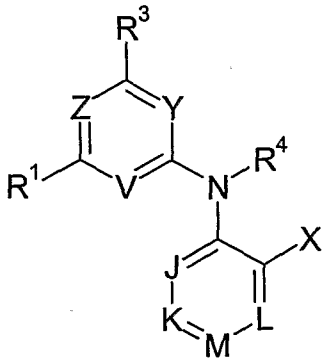
R^{10} is hydrogen, hydroxy, methoxy or fluoro; and

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

with the proviso that in the ring containing D, E, K and G of formula I, there can not be two double bonds adjacent to each other;

and the pharmaceutically acceptable salt of such compound.

IX. The CRF antagonist may also be of the following formula, disclosed in WO 95/10506:



or a pharmaceutically, acceptable salt or prodrug thereof, wherein Y is CR^{3a}, N, or CR^{29};

when Y is CR^{3a} or N:

R^1 is independently selected at each occurrence from the group consisting of C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halogen, C_1-C_2 haloalkyl, NR^6R^7, OR^8, and $S(O)_nR^8$; R^3 is C_1-C_4 alkyl, aryl, C_3-C_6 cycloalkyl, C_1-C_2 haloalkyl, halogen, nitro, NR^6R^7, OR^8, $S(O)_nR^8$ $C(=O)R^9$, $C(=O)NR^6R^7$, $C(=S)NR^6R^7$, $-(CHR^{16})_kNR^6R^7$, $(CH_2)_kOR^8$, $C(=O)NR^{10}CH(R^{11})CO_2R^{12}$, $-C(OH)(R^{25})(R^{25a})$, $-(CH_2)_pS(O)_n$-alkyl, $-(CHR^{16})R^{25}$, $-C(CN)(R^{25})(R^{16})$ provided that R^{25} is not -NH- containing rings, $-C(=O)R^{25}$, $-CH(CO_2R^{16})_2$, $NR^{10}C(=O)CH(R^{11})NR^{10}R^{12}$, $NR^{10}CH(R^{11})CO_2R^{12}$; substituted C_1-C_4 alkyl, substituted C_2-C_4 alkenyl, substituted C_2-C_4 alkynyl, substituted C_1-C_4 alkoxy, aryl-(substituted C_1-C_4) alkyl, aryl-(substituted C_1-C_4) alkoxy, substituted C_3-C_6 cycloalkyl, amino-(substituted C_1-C_4)alkyl, substituted C_1-C_4 alkylamino, where substitution by R^{27} can occur on any carbon containing substituent; 2-pyridinyl, imidazolyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 4-methyl-3-pyridinyl, furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 4-pyrazinyl, azetidinyl, phenyl, 1*H*-indazolyl, 2-pyrrolidonyl, 2*H*,6*H*-1,5,2-dithiazinyl, 2*H*-pyrrolyl, 3*H*-indolyl, 4-piperidonyl, 4*aH*-carbazolyl, 4*H*-quinolizinyl, 6*H*-1,2,5-thiadiazinyl, acridinyl, azocinyl, azepinyl, benzofuranyl, benzothiophenyl, carbazolyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, furazanyl, imidazolidinyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, benzimidazolyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxazolidinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, β-carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thianthrenyl, thiazolyl, thiophenyl, triazinyl, xanthenyl; or 1-tetrahydroquinolinyl or 2-tetrahydroisoquinolinyl either of which can be substituted with 0-3 groups chosen from keto and C_1-C_4 alkyl; J, K, and L are independently selected at each occurrence from the group of N, CH, and CX';

M is CR^5 or N;

V is CR^{1a} or N;

Z is CR^2 or N;

R^{1a}, R^2, and R^{3a} are independently selected at each occurrence from the group consisting of hydrogen, halo, halomethyl, C_1-C_3 alkyl, and cyano;

R^4 is $(CH_2)_mOR^{16}$, C_1-C_4 alkyl, allyl, propargyl, $(CH_2)_mR^{13}$, or $-(CH_2)_mOC(O)R^{16}$;

X is halogen, aryl, heteroaryl, $S(O)_2R^8$, SR^8, halomethyl, $-(CH_2)_pOR^8$, cyano, $-(CHR^{16})_pNR^{14}R^{15}$, $-C(=O)R^8$, C_1-C_6 alkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_{10}alkenyl, C_2-C_{10}alkynyl, C_2-C_{10}alkoxy, aryl-(C_2-C_{10})-alkyl, C_3-C_6cycloalkyl, aryl-(C_1-C_{10})-alkoxy, nitro, thio-(C_1-C_{10})-alkyl, $-C(=NOR^{16})$-C_1-C_4-alkyl, $-C(=NOR^{16})H$, or $-C(=O)NR^{14}R^{15}$, where substitution by R^{18} can occur on any carbon containing substituents;

X' is independently selected at each occurrence from the group consisting of hydrogen, halogen, aryl, heteroaryl, $S(O)_nR^8$, halomethyl, $-(CHR^{16})_pOR^8$, cyano, $-(CHR^{16})_pNR^{14}R^{15}$, $C(=O)R^8$, C_1-C_6 alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_{10}alkoxy, aryl-(C_1-C_{10})-alkyl, C_3-C_6cycloalkyl, aryl-(C_1-C_{10})-alkoxy, nitro, thio-(C_1-C_{10})-alkyl, $-C(=NOR^{16})$-C_1-C_4-alkyl, $-C(=NOR^{16})H$, and $-C(=O)NR^{14}R^{15}$, where substitution by R^{16} can occur on any carbon containing substituents;

R^5 is halo, $-C(=NOR^{16})$-C_1-C_4-alkyl, C_1-C_4alkyl, C_1-C_3 haloalkyl, $-(CHR^{16})_pOR^8$, $-(CHR^{16})_pS(O)_nR^8$, $-(CHR^6)_pNR^{14}R^{15}$, C_3-C_6 cycloalkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, aryl-(C_2-C_{10})-akyl, aryl-(C_1-C_{10})-alkoxy, cyano, C_3-C_6 cycloalkoxy, nitro, amino- (C_2-C_{10})-alkyl, thio-(C_2-C_{10})-alkyl, $SO_n(R^8)$, $C(=O)R^8$ $-C(=NOR^{16})H$, or $-C(=O)NR^{14}R^{15}$, where substitution by R^{18} can occur on any carbon containing substituents;

R^6 and R^7 are independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxy, (C_4-C_{12})-cycloalkylalkyl, $-(CH_2)_kR^{13}$, $(CHR^{16})_pOR^8$, -(C_1-C_6alkyl)-aryl, heteroaryl, $-S(O)_z$-aryl or -(C_1-C_6alkyl)-heteroaryl or aryl, wherein the aryl or heteroaryl groups are optionally substituted with 1-3 groups selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, NHC(=O)(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, nitro, carboxy, CO_2(C_1-C_6 alkyl), cyano, and $S(O)_2$-(C_1-C_6-alkyl); or can be taken together to form $-(CH_2)_pA(CH_2)_r$-, optionally substituted with 0-3 R^{17}; or, when considered with the commonly attached nitrogen, can be taken together to form a heterocycle, said heterocycle being substituted on carbon with 1-3 groups consisting of hydrogen, C_1-C_6 alkyl, hydroxy, or C_1-C_6 alkoxy;

A is CH_2, O, NR^{25}, C(=O), $S(O)_n$, $N(C(=O)R^{17})$, $N(R^{19})$, $C(H)(NR^{14}R^{15})$, $C(H)(OR^{20})$, $C(H)(C(=O)R^{21})$, or $N(S(O)_nR^{21})$;

R^8 is independently selected at each occurrence from the group consisting of hydrogen; C_1-C_6 alkyl; $-(C_4$-$C_{12})$ cycloalkylalkyl; $(CH_2)_tR^{22}$; C_3-C_{10} cycloalkyl; $-NR^6R^7$; aryl; heteroaryl; $-NR^{16}(CH_2)_nR^6R^7$; $-(CH_2)_kR^{25}$; and $(CH_2)_t$heteroaryl or $(CH_2)_t$aryl, either of which can optionally be substituted with 1-3 groups selected from the group consisting of hydrogen,

halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, NHC(=O)(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, nitro, carboxy, CO_2(C_1-C_6 alkyl), cyano, and S(O)$_2$(C_1-C_6-alkyl);

R^9 is independently selected at each occurrence from R^{10}, hydroxy, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, aryl substituted with 0-3 R^{18}, and -(C_1-C_6 alkyl)-aryl substituted with 0-3 R^{18};

R^{10}, R^{16}, R^{24}, and R^2 are independently selected at each occurrence from hydrogen or C_1-C_4 alkyl;

R^{11} is C_1-C_4 alkyl substituted with 0-3 groups chosen from the following: keto, amino, sulfhydryl, hydroxyl, guanidinyl, p-hydroxyphenyl, imidazolyl, phenyl, indolyl, and indolinyl, or, when taken together with an adjacent R^{10}, are $(CH_2)_t$;

R^{12} is hydrogen or an appropriate amine protecting group for nitrogen or an appropriate carboxylic acid protecting group for carboxyl;

R^{13} is independently selected at each occurrence from the group consisting of CN, OR^{19}, SR^{19}, and C_3-C_6 cycloalkyl;

R^{14} and R^{15} are independently selected at each occurrence from the group consisting of hydrogen, C_4-C_{10}, cycloalkyl-alkyl, and R_{19};

R^{17} is independently selected at each occurrence from the group consisting of R^{10}, C_1-C_4 alkoxy, halo, OR^{23}, SR^{23}, $NR^{23}R^{24}$, and (C_1-C_6) alkyl (C_1-C_4) alkoxy;

R_{18} is independently selected at each occurrence from the group consisting of R^{10}, hydroxy, halogen, C_1-C_2 haloalkyl, C_1-C_4 alkoxy, $C(=O)R^{24}$, and cyano;

R^{19} is independently selected at each occurrence from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_wR^{22}$, and aryl substituted with 0-3 R^{18};

R^{20} is independently selected at each occurrence from the group consisting of R^{10}, $C(=O)R^{31}$, and C_2-C_4 alkenyl;

R^{21} is independently selected at each occurrence from the group consisting of R^{10}, C_1-C_4 alkoxy, $NR^{23}R^{24}$, and hydroxyl;

R^{22} is independently selected at each occurrence from the group consisting of cyano, OR^{24}, SR^{24}, $NR^{23}R^{24}$,C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_nR^{31}$, and $-C(=O)R^{25}$;

R^{25}, which can be optionally substituted with 0-3 R17, is independently selected at each occurrence from the group consisting of phenyl, pyrazolyl, imidazolyl, 2-methyl-3-pyridinyl, 4-methyl-3-pyridinyl, furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 4-pyrazinyl, azetidinyl, 1*H*-indazolyl, 2-pyrrolidonyl, 2*H*,6*H*-1,5,2-dithiazinyl, 2*H*-pyrrolyl, 3*H*-indolyl, 4-piperidonyl, 4a*H*-carbazolyl, 4*H*-quinolizinyl, 6*H*-1,2,5-thiadiazinyl, acridinyl, azocinyl, azepinyl, benzofuranyl, benzothiophenyl, carbazolyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, furazanyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl benzimidazolyl, isothiazolyl, isoxazolyl, morpholinyl,

naphthyridinyl, octahydroisoquinolinyl, oxazolidinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazolidinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, B-carbolinyl, tetrahydrofuranyl, tetrazolyl, thianthrenyl, thiazolyl, thiophenyl, triazinyl, xanthenyl; and 1 -tetrahydroquinolinyl or 2-tetrahydroisoquinolinyl either of which can be substituted with 0-3 groups chosen from keto and C_1-C_4 alkyl;

R^{25a}, which can be optionally substituted with 0-3 R^{17}, is independently selected at each occurrence from the group consisting of H and R^{25};

R^{27} is independently selected at each occurrence from the group consisting of C_1-C_3 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_2-C_4 alkoxy, aryl, nitro, cyano, halogen, aryloxy, and heterocycle optionally linked through 0;

R^{31} is independently selected at each occurrence from the group consisting of C_1-C_4 alkyl, C_3-C_7 cycloalkyl, C_4-C_{10} cycloalkyl-alkyl, and aryl-(C_1-C_4) alkyl;

k, m, and r are independently selected at each occurrence from 1-4;

n is independently, selected at each occurrence from 0-2,

p, q, and z are independently selected at each occurrence from 0-3;

t and w are independently selected at each occurrence from 1-6,

provided that when J is CX' and K and L are both CH, and M is CR^5, then

(A) when V and Y are N and Z is CH and R^1 and R^3 are methyl,

(1) and R^4 is methyl, then

(a) R^5 can not be methyl when X is OH and X' is H;

(b) R^5 can not be $-NHCH_3$, or $-N(CH_3)_2$ when X and X' are $-OCH_3$; and

(c) R^5 can not be $-N(CH_3)_2$ when X and X' are $-OCH_2CH_3$;

(2) and R^4 is ethyl, then

(a) R^5 can not be methylamine when X and X′ are $-OCH_3$;

(b) R^5 can not be OH when X is Br and X′ is OH; and

(c) R^5 can not be $-CH_2OH$ or $-CH_2N(CH_3)_2$ when X is $-SCH_3$ and X' is H;

(B) when V and Y are N, Z is CH, R^4 is ethyl, R^5 is iso-propyl, X is Br, X' is H, and

(1) R^1 is CH_3, then

(a) R^3 can not be OH, piperazin-1-yl, $-CH_2$,-piperidin-1-yl, $-CH_2$-(N-4-methylpiperazi n-1-yl), -C(O)NH-phenyl, $-CO_2H$, $-CH_2O$-(4-pyridyl), $-C(O)NH_2$, 2-indolyl, $-CH_2O$-(4-carboxyphenyl), $-N(CH_2CH_3)$(2-bromo-4-isopropylphenyl);

(2) R^2 is $-CH_2CH_2CH_3$ then R^3 can not be $-CH_2CH_2CH_3$

(C) when V, Y and Z are N, R^4 is ethyl, and

(1) R^5 is iso-propyl, X is bromo, and X' is H, then

(a) R^3 can not be OH or $-OCH_2CN$ when R^1 is CH_3 and

(b) R^3 can not be $-N(CH_3)_2$ when R^1 is $-N(CH_3)_2$;

(2) R^5 is $-OCH_3$, X is $-OCH_3$, and X' is H, then R^3 and R^1 can not both be chloro; further provided that when J, K, and L are all CH and M is CR^5, then

(D) at least one of V, Y, and Z must be N;

(E) when V is CR^{1a}, Z and Y can not both be N;

(F) when Y is CR^{3a}, Z and V can not both be N;

(G) when Z is CR^2, V and Y must both be N;

(H) Z can be N only when both V and Y are N or when V is CR^{1a} and Y is CR^{3a};

(I) when V and Y are N, Z is CR^2, and R^2 is H or C_1-C_3 alkyl, and R^4 is C_1-C_3 alkyl, R^3 can not be 2-pyridinyl, indolyl, indolinyl, imidazolyl, 3-pyridinyl, 4-pyridinyl, 2-rnethyl-3-pyridinyl, 4-methyl-3-pyridinyl, furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, or 4-pyrazinyl;

(J) when V and Y are N; Z is CR^2; R^2 is H or C_1-C_3 alkyl; R^4 is C_1-C_4 alkyl, R^5, X, and/or X' are OH, halo, CF_3, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, cyano, amino, carbamoyl, or C_1-C_4 alkanoyl; and R^1 is C_1-C_4 alkyl, then R^4 can not be -NH(substituted phenyl) or -N(C_1-C_4 alkyl) (substituted phenyl);

and wherein, when Y is CR^{29}:

J, K, L, M, Z, A, k, m, n, p, q, r, t, w, R^3, R^{10}, R^{11}, R^{12}, R^{13}, R^{16}, R^{18}, R^{19}, R^{21}, R^{23}, R^{24}, R^{25}, and R^{27} are as defined above and R^{25a}, in addition to being as defined above, can also be C_1-C_4 alkyl, but

V is N;

R^1 is C_1-C_2 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_2-C_4 alkoxy, halogen, amino, methylamino, dimethylamino, aminomethyl, or N-methylaminomethyl;

R^2 is independently selected at each occurrence from the group consisting of hydrogen, halo, C_1-C_3, alkyl, nitro, amino, and $-CO_2R^{10}$;

R_4 is taken together with R^{29} to form a 5-membered ring and is $-C(R^{26})=$ or -N= when R^{29} is $-C(R^{30})=$ or -N=, or $-CH(R^{26})-$ when R^{29} is $-CH(R^{30})-$;

X is Cl, Br, I, S(O)nR^8, OR^8, halomethyl, $-(CHR^{16})_pOR^8$, cyano, $-(CHR^{16})_pNR^{14}R^{15}$, $C(=O)R^8$, C_1-C_6 alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10}, alkoxy, aryl-(C_1-C_{10})-alkyl, C_3-C_6 cycloalkyl, aryl-(C_1-C_{10})-alkoxy, nitro, thio-(C_1-C_{10})-alkyl, $-C(=NOR^{16})$-C_1-C_4-alkyl,

-C(=NOR^{16})H, or C(=O)NR^{14}R^{15} where substitution by R^{18} can occur on any carbon containing substituents;

X' is hydrogen, Cl, Br, I, S(O)$_n$R^8, -(CHR^{16})$_p$OR^8, halomethyl, cyano, -(CHR^{16})$_p$NR^{14}R^{15}, C(=O)R^8, C$_1$-C$_6$ alkyl, C$_2$-C$_{10}$alkenyl, C$_2$-C$_{10}$, alkynyl, C$_1$-C$_{10}$ alkoxy, aryl-(C$_1$-C$_{10}$)-alkyl, C$_3$-C$_6$ cycloalkyl, aryl-(C$_2$-C$_{10}$)-alkoxy, nitro, thio-(C$_2$-C$_{10}$)-alkyl, -C(=NOR^{16})-C$_1$-C$_4$-alkyl, -C(=NOR^{16})H, or C(=O)NR^{8}R^{15} where substitution by R^{18} can occur on any carbon containing substituents;

R^5 is halo, -C(=NOR^{16})-C$_1$-C$_4$-alkyl, C$_1$-C$_6$ alkyl, C$_1$-C$_3$ haloalkyl, C$_1$-C$_6$ alkoxy, (CHR^{16})$_p$OR^5, (CHR^{16})$_p$S(O)$_n$R^8, (CHR^{16})$_p$NR^{14}R^{15}, C$_3$-C$_6$ cycloalkyl, C$_2$-C$_{10}$ alkenyl, C$_2$-C$_{10}$ alkynyl, aryl-(C$_2$-C$_{10}$)-alkyl, aryl-(C$_1$-C$_{10}$)-alkoxy, cyano, C$_3$-C$_6$ cycloalkoxy, nitro, amino-(C$_1$-C$_{10}$)-alkyl, thio-(C$_1$-C$_{10}$)-alkyl, SO$_n$(R^8), C(=O)R^8, -C(=NOR^{16})H, or C(=O)NR^{8}R^{15} where substitution by R^{18} can occur on any carbon containing substituents;

R^6 and R^7 are independently selected at each occurrence from the group consisting of hydrogen, C$_1$-C$_6$ alkyl, C$_3$-C$_{10}$ cycloalkyl, -(CH$_2$)$_k$R^{13}, (C$_4$-C$_{12}$)-cycloalkylalkyl, C$_1$-C$_6$ alkoxy, -(C$_1$-C$_6$ alkyl)-aryl, heteroaryl, aryl, -S(O)$_z$-aryl or -(C$_1$-C$_6$ alkyl)-heteroaryl or aryl wherein the aryl or heteroaryl groups are optionally substituted with 1-3 groups selected from hydrogen, halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ alkoxy, amino, NHC(=O)(C$_1$-C$_6$ alkyl), NH(C$_1$-C$_6$ alkyl), N(C$_1$-C$_6$ alkyl)$_2$, nitro, carboxy, CO$_2$(C$_1$-C$_6$ alkyl), and cyano; or can be taken together to form -(CH$_2$)qA(CH$_2$)$_r$-, optionally substituted with 0-3 R^{17}; or, when considered with the commonly attached nitrogen, can be taken together to form a heterocycle, said heterocycle being substituted on carbon with 1-3 groups consisting of hydrogen, C$_1$-C$_6$ alkyl, hydroxy, or C$_1$-C$_6$ alkoxy;

R^8 is independently selected at each occurrence from the group consisting of hydrogen, C$_1$-C$_6$ alkyl, -(C$_4$-C$_{12}$) cycloalkylalkyl, (CH$_2$)$_t$R^{22}, C$_3$-C$_{10}$ cycloalkyl, -(C$_1$-C$_6$ alkyl)-aryl, heteroaryl, -NR^{16}, -N(CH$_2$)$_n$NR^{6}R^7; -(CH$_2$)$_k$R^{25}, -(C$_1$-C$_6$ alkyl)-heteroaryl or aryl optionally substituted with 1-3 groups selected from hydrogen, halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ alkoxy, amino, NHC(=O)(C$_1$-C$_6$ alkyl), NH(C$_1$-C$_6$ alkyl), N(C$_1$-C$_6$alkyl)$_2$, nitro, carboxy, CO$_2$(C$_1$-C$_6$ alkyl), and cyano;

R^9 is independently selected at each occurrence from R^{10}, hydroxy, C$_1$-C$_4$ alkoxy, C$_3$-C$_6$ cycloalkyl, C$_2$-C$_4$ alkenyl, and aryl substituted with 0-3 R^{18};

R^{14} and R^{15} are independently selected at each occurrence from the group consisting of hydrogen, C$_1$-C$_6$ alkyl, C$_3$-C$_6$ cycloalkyl, (CH$_2$)$_t$R^{22}, and aryl substituted with 0-3 R^{18};

R^{17} is independently selected at each occurrence from the group consisting of R^{10}, C$_1$-C$_4$ alkoxy, halo, OR^{23}, SR^{23}, and NR^{23}R^{24};

R^{20} is independently selected at each occurrence from the group consisting of R^{10} and C(=O)R^{31};

R^{22} is independently selected at each occurrence from the group consisting of cyano, OR^{24}, SR^{24}, $NR^{23}R^{24}$, C_3-C_6 cycloalkyl, $-S(O)_nR^{31}$, and $-C(=O)R^{25}$;

R^{26} is hydrogen or halogen;

R^{28} is C_1-C_2, alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, hydrogen, C_1-C_2 alkoxy, halogen, or C_2-C_4 alkylamino;

R^{29} is taken together with R^4 to form a five membered ring and is: $-CH(R^{30})-$ when R^4 is $-CH(R^{28})-$, $-C(R^{30})=$ or $-N=$ when R^4 is $-C(R^{28})=$ or $-N=$;

R^{30} is hydrogen, cyano, C_1-C_2 alkyl, C_1-C_2 alkoxy, halogen, C_1-C_2 alkenyl, nitro, amido, carboxy, or amino;

R^{31} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, or aryl-(C_1-C_4) alkyl; provided that when J, K, and L are all CH, M is CR^5, Z is CH, R^3 is CH_3, R^{28} is H, R^5 is isopropyl, X is Br, X' is H, and R^1 is CH_3, then R^{30} can not be H, $-CO_2H$, or $-CH_2NH_2$; and further provided that when J, K and L are all CH; M is CR^5; Z is N; and

(A) R^{29} is $-C(R^{30})=$; then one of R^{28} or R^{30} is hydrogen;

(B) R^{29} is N; then R^3 is not halo, NH_2, NO_2, CF_3, CO_2H, CO_2-alkyl, alkyl, acyl, alkoxy, OH, or $-(CH_2)_m$Oalkyl;

(C) R^{29} is N; then R^{28} is not methyl if X or X' are bromo or methyl and R^5 is nitro; or

(D) R^{29} is N; and R^1 is CH_3; and R^3 is amino; then R^5 is not halogen or methyl.

Preferred compounds of this group include those wherein:

i) V is N, R^1 is methyl; and R^3 is aryl, NR^6R^7, or OR^8;

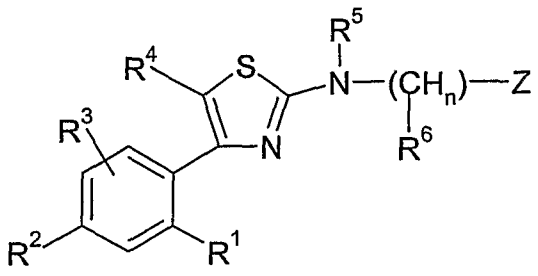
ii) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7, or OR^8; and R^4 is methyl or ethyl;

iii) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7, or OR^8; R^4 is methyl or ethyl; and X is O(C_1-C_4 alkyl), Br, or C_1-C_4 alkyl;

iv) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7, or OR^8; R^4 is methyl, ethyl; X is OMe, Br, or (C_1-C_4 alkyl), M is C_1-C_4 alkyl, Br, Cl, or O(C_1-C_4 alkyl); and

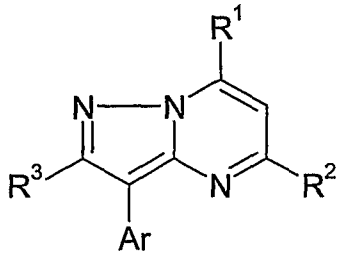
v) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7, OR^8; or R^4 is methyl, ethyl; X is OMe, Br, or C_1-C_4 alkyl, M is C_1-C_4 alkyl, Br, Cl, or O(C_1-C_4 alkyl); and L is CH, or N.

X. The invention also encompasses use of aminothiazole derivatives of the following formula, disclosed in WO 97/00868:



wherein each of R^1 and R^2 is independently a halogen atom; a C_1-C_5 hydroxyalkyl radical; C_1-C_5 alkyl; C_7-C_{10} aralkyl; C_1-C_5 alkoxy; trifluoromethyl; nitro; nitrile; a group –SR where R is hydrogen, a C_1-C_5 alkyl radical or a C_7-C_{10} aralkyl radical; a group S-CO-R where R is a C_1-C_5 alkyl radical or aralkyl in which the aryl portion is C_6-C_8 and the alkyl portion is C_1-C_4; a group –COOR′ where R′ is hydrogen or C_1-C_5 alkyl; a group -CONR′R″ where R′ and R″ are as defined above for R′; a group -NR′R″ where R′ and R″ are as previously defined for R′; a group –CONRaRb or NRaRb, where Ra and Rb, taken together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclic ring; or a group –NHCO-NR′R″, where R′ and R″ are as defined above for R′; R^3 is hydrogen or as defined for R^1 and R^2 is a hydrogen atom; C_{1-5} alkyl; halogen; a hydroxymethyl group; or a formyl group; R^5 is C_1-C_5 alkyl; a C_3-C_7 cycloalkyl group; a cycloalkylalkyl group in which the cycloalkyl portion is C_3-C_7 and the alkyl portion is C_1-C_5; or C_5-C_6 alkenyl; n is 0 or 1; R^6 is C_{1-5} alkyl; alkoxyalkyl in which the alkyl portions are C_1-C_5; C_3-C_7 cycloalkyl; a cycloalkylalkyl group in which the cycloalkyl portion is C_3-C_7 and the alkyl portion is C_1-C_5; a cycloalkyloxyalkyl radical in which the cycloalkyl is C_3-C_7 and the alkyl is C_1-C_4; a hydroxyalkyloxyalkyl radical in which the alkyls are C_2-C_{10}; or an alkoxyalkyloxyalkyl radical in which the alkyls are C_3-C_{12}; and Z is an optionally substituted bi- or tricyclic aromatic or heteroaromatic group; and stereoisomers and/or addition salts thereof.

XI. CRF antagonists of the following formula, disclosed in WO 97/29109, may also be employed:



including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

R^1 is NR^4R^5 or OR^5;

R^2 is C_1-C_6alkyl, C_1-C_6alkyloxy or C_1-C_6alkylthio,

R^3 is hydrogen, C_1-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylsulfoxy or C_1-C_6alkylthio;

R^4 is hydrogen, C_1-C_6alkyl, mono- or di(C_3-C_6cyloalkylmethyl, C_3-C_6cyloalkyl, C_3-C_6alkenyl, hydroxyC_1-C_6alkyl, C_1-C_6akylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl;

R^5 is C_1-C_8alkyl, mono- or di(C_3-C_6cycloalkyl)methyl, Ar^1CH_2, C_3-C_6alkenyl, C_1-C_6alkyloxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, thienylmethyl, furanylmethyl, C_1-C_6alkylthioC_1-C_6alkyl, morpholinyl, mono- or di(C_1-C_6alkyl)aminoC_{1-6}alkyl, di(C_1-C_6alkyl)amino, C_1-

C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl substituted with imidazolyl; or a radical of formula -Alk-O-CO-Ar^1;

or R^4 and R^5 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl; and

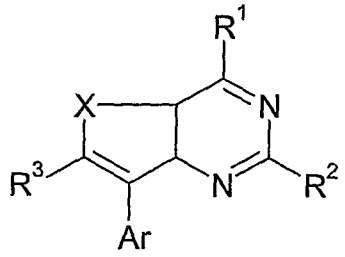
Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino and mono- or di(C_1-C_6alkyl)amino; pyridinyl; pyridinyl substituted with 1 ~ 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino, mono- or di(C_1-C_6alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_6alkyl, C_1-C_6alkyloxy, di(C_1-C_6alkyl)aminoC_1-C_6alkyl, trifluoromethyl and C_1-C_6alkyl substituted with morpholinyl; or pyridinyl; and Alk is C_1-C_6alkanediyl;

with the proviso that 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo[1,5-a]-pyrimidine and 2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo[1,5-a]pyrimidine are not included.

Preferred compounds of this formula are those wherein R^2 is methyl; R^3 is hydrogen, or C_1-C_6 alkyl; and Ar is substituted phenyl or 3-pyridyl.

XII. CRF antagonists of the following formula, disclosed in WO 97/29110, may also be employed:



including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

X is S. SO or SO_2;

R^1 is NR^4R^5 or OR^5;

R^2 is C_1-C_6alkyl, C_1-C_6alkyloxy or C_1-C_6alkylthio;

R^3 is hydrogen, C_1-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylsulfoxy or C_1-C_6alkylthio;

R^4 is hydrogen, C_{1-6}alkyl, mono- or di(C_3-C_6cycloalkyl)methyl, C_3-C_6cycloalkyl, C_3-C_6alkenyl, hydroxyC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl;

R^5 is C_1-C_8alkyl, mono- or di(C_3-C_6cycloalkyl)methyl, Ar^1CH_2, C_3-C_6alkenyl, C_1-C_6alkyloxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, thienylmethyl, furanylmethyl, C_1-C_6alkylthioC_1-

C_6alkyl, morpholinyl, mono- or di(C_1-C_6alkyl)aminoC_1-C_6alkyl, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl substituted with imidazolyl; or a radical of formula -Alk-O-CO-Ar I; or R^4 and R^5 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_1-C_6alkyl or C_1-C_6alkyloxyC_1-C_6alkyl;

Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino and mono- or di(C_1-C_6alkyl)amino; pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents independently selected from halo, C_1-C_6alkyl, trifluoromethyl, hydroxy, cyano, C_1-C_6alkyloxy, benzyloxy, C_1-C_6alkylthio, nitro, amino, mono- or di(C_1-C_6alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;

$Ar^1$is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_6alkyl, C_1-C_6alkyloxy, di(C_1-C_6alkyl)aminoC_1-C_6alkyl trifluoromethyl, and C_1-C_6alkyl substituted with morpholinyl; or pyridinyl; and

Alk is C_1-C_6alkanediyl.

Preferred compounds of this group include those wherein:

i) R^2 is methyl;

ii) R^2 is methyl; and Ar is substituted phenyl or 3-pyridyl;

iii) R^2 is methyl; R^3 is methyl; and Ar is substituted phenyl or 3-pyridyl.

Specific CRF antagonists useful in the practice of the invention, include, without limitation, the following compounds:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;

(3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine;

(3,6-dimethyl-2-(4-chloro-2,6-dimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-cholorophenyl)-1-4-dihydro-2H-3-oxa-1,8-diazanaphthalene;

butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amino;

4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one;

4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;

N-butyl-N-ethyl-2,5-dimethyl-NN-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;

[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;

6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one;

3-{(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;

diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;

dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-amine;

butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine;

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;

4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;

butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-ethylamine;

[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;

4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;

(1-ethylpropyl)-[3,5,6-trimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-amine;

4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;

4-(1-ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;

4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo[2,3-b]pyridine;

2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;

1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

9-(1-ethylpropyl)-2-methyl-6-(2,4,6-trimethylphenylamino)-7,9-dihydro-purin-8-one;

1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-imidazo[4,5-c]pyridine;

1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-pyrido[3,4-b]pyrazin-3-one;

1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-pyrido[3,4-b]pyrazin-3-one;

1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;

1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;

1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine-3-carboxylic acid methyl ester;

1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine-3-carboxylic acid isopropyl ester;

1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1H-[1,6]naphthyridin-2-one;

1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine;

1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;

1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;

1-(1-ethyl-propyl)-3,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1H-3-oxa-[1,6]-naphthyridin-2-one;

1-(1-ethyl-propyl)-3,3,6-trimethyl-4-(2,4,6-trimethyl-phenoxy)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido [2,3-d]pyrimidin-7-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b] pyrazin-2-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido [2,3-b]pyrazine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;

5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;

8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

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

4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

4-(butyl-ethyl-amino)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

(butyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;

(propyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;

(diethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido [2,3-d]pyrimidin-4-yl]-amine;

(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;

(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine;

4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido [2,3-d]pyrimidin-7-one;

(butyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;

(propyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;

(diethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;

(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;

(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidine;

8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-3,4-dihydro-1H-pyrido [2,3-b]pyrazin-2-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinoline;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,2-dihydro-3-oxa-1, 8-diaza-naphthalen-4-one;

8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinolin-4-yl]-amine;

4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-chloro-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinoline;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;

8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinolin-4-yl]-amine;

8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b] pyrazin-2-one;

8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido [2,3-b]pyrazin-2-one;

8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido [2,3-b]pyrazine;

8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

4-(1-hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;

4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

4-(1-ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

4-diethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

4-(ethyl-propyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

5-(1-hydroxymethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-hydroxymethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-ethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-diethylamino-5-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(ethyl-propyl-amino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

4-(2,4-dichlorophenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;

oxalate of 4-(2,4-dichlorophenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methylisoquinol-5-yl)-N-propylamino]thiazole;

4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-methoxycarbonylmethylindol-5-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-chloroisoquinol-5-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;

4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-1-methoxynaphth-2-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-trifluoromethylphenyl)-5-methyl-2-[N-6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2-ethoxynaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2[N-(2,3-dimethylnaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-bromo-2-methoxynaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2,6-dimethylnaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(cyclopropyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;

3-(2,4-dichlorophenyl)-5-methyl-7(N-propyl-N-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;

3-(2,4-dichlorophenyl)-5-methyl-7-(N-allyl-N-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;

2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N,N-diallylamino)-pyrazolo[2,3-a]pyrimidine;

2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-butyl-N-cyclopropanemethylamino)pyrazolo[2,3-alpyrimidine;

2_methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-propyl-N-cyclopopanemethyl-amino) pyrazolo[2,3-a]pyrimidine;

2-methyl-3-(4-chlorophenyl)-5-methyl-7-(N,N-dipropylamino)-pyrazolo[2,3-a) pyrimidine;

3-[6-(dimethylamino)-3-pyridinyl-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a]pyrimidin-7-amine;

3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropyl-pyrazolo[2,3-a]pyrimidine-7-amine;

3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(N-propyl-N-methyloxyethylamino)-pyrazolo (2,3-a)pyrimidine;

7-(N-diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine;

7-(N-(3-cyanopropyl)-N-propylamino-2,5,dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;

[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine;

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

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

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

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

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

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

4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester.

Methods for making the CRF antagonists described above are disclosed in international patent publication WO 95/33750 incorporated by reference herein.

Particularly preferred are those compositions, methods, and kits that contain one of the following CRF antagonists:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;

(3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine:

(3,6-dimethyl-2-(4-chloro-2,6-dimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine:

or

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-cholorophenyl)-1-4-dihydro-2H-3-oxa-1,8-diazanaphthalene;

and one of the following atypical antipsychotics: olanazapine, clozapine, ziprasidone, or pharmaceutically acceptable salts thereof.

In the preferred kits of the present invention, the pharmaceutical composition comprising a CRF antagonist is a pharmaceutical composition comprising one of the particularly preferred CRF antagonists as defined above, and the pharmaceutical composition comprising an atypical antipsychotic is a pharmaceutical composition comprising one of the particularly preferred atypical antipsychotics as defined above.

The preferred methods of treatment of the present invention are those methods that employ a particularly preferred CRF antagonist and particularly preferred atypical antipsychotic as defined above.

Also preferred are those methods that employ a particularly preferred CRF antagonist and a particularly preferred atypical antipsychotic or a pharmaceutical composition(s) of the present invention, as defined above, for treating osteoporosis or frailty associated with aging or obesity, cardiovascular or heart related disease, in particular hypertension, tachycardia, and congestive heart failure, accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or of patients having undergone major surgery.

The compounds used in the present invention may have optical centers and therefore may occur in different enantiomeric configurations. The compounds used in the present invention include all enantiomers, diastereomers, and other stereoisomers of the compounds, as well as racemic and other mixtures thereof. Individual isomers can be obtained by known methods, such as optical resolution, optically selective reaction, or chromatographic separation in the preparation of the final product or its intermediate.

Preferably, the combinations of pharmaceutically active compounds of the present invention show a synergistic effect and/or show less side effects, as compared to the individual compounds, when treating a mammal, preferably a human. Thus, in treating a particular disease, at a specific dosage level, the combinations of pharmaceutically active compounds of the present invention show a better activity than the activity which could be expected when administering the individual compounds, less or less severe side effects than could be expected when administering the individual compounds, or a combination of a better activity and of less or less severe side effects than could be expected when administering the individual compounds.

The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically-acceptable cationic salts" is intended to define but is not limited to such salts as the alkali metal salts, (e.g., sodium and potassium), alkaline earth metal salts (e.g., calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically-acceptable acid addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

DETAILED DESCRIPTION OF THE INVENTION

The compositions and combinations of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, or subcutaneous injection, or through an implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated with pharmaceutically acceptable carriers, vehicles, or diluents to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, granules, and the like, and for non-human mammals (cats and dogs are the presently preferred non-human mammals) the solid dosage forms can include admixtures with food and chewable forms. In such solid dosage forms, the compounds and combinations of this invention can be admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, starch, or the like. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings. In the case of chewable forms, the dosage form may comprise flavoring agents and perfuming agents.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants (such as wetting agents), emulsifying and suspending agents, sweetening agents, flavorings, perfuming agents, and the like. Ziprazidone formulations in the form of a suspension are described in U.S. Patent Application Serial No. 60/42195, filed October 25, 2002 and incorporated herein by reference in its entirety. Novel injectable depot formulations

of ziprasidone are described in U.S. Patent Application Serial No. 60/421473, filed October 25, 2002 and incorporated herein by reference in its entirety.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, emulsions, and the like. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories that may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The pharmaceutical compositions of the present invention can consist of a combination of immediate release and controlled release characteristics. Such compositions can take the form of combinations of the active ingredients that range in size from nanoparticles to microparticles or in the form of a plurality of pellets with different release rates. The tablet or capsule composition of the present invention can contain an atypical antipsychotic in sustained or controlled release form and the CRF antagonist in an immediate release form. Alternatively, the atypical antipsychotic can be in immediate release form and the CRF antagonist can be in sustained or controlled release form.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, methods of preparing pellets are described in Remington: The Science and Practice of Pharmacy, Mack Publishing Company, Easton, Pa., 19th Edition (1995). Prolonged release pellets are prepared by either coating immediate release pellets or via matrix systems. Coating may be carried out, for example, in coating pans or in fluid bed coater-driers. Extrusion and subsequent spheronization is a long-known method for the preparation of pharmaceutical pellets (J. W. Conine et al., Drug & Cosmetic Ind. 106, 38-41 (1970)). However, other methods such as pelletization may be utilized. Particles may be agglomerated to form spherical granules or pellets, in a high-speed mixer granulator, or rotary fluid bed agglomerator. These methods are described by K. W. Olson and A. M. Mehta, Int.J.Pharm.Tech&.Prod.Mfr. 6 18-24, 1985. Pellets may be also prepared by extrusion of wet

masses or melts followed by spheronisation, for example as described in C. Vervaet, L. Baert & J. P. Remon Int.J.Pharm. 116 (1995) 131-146. Excipients used are typically those with plastic qualities such as microcrystalline cellulose, but also mannitol. Small quantities of a polymeric binder are generally added. Surfactants such as sodium dodecyl sulphate may also be incorporated to give easier extrusion.

Pharmaceutical compositions according to the invention can contain 0.1%-95% of the therapeutic agents of this invention, preferably 1%-70%. In any event, the composition or formulation to be administered will contain a quantity of therapeutic agent(s) according to the invention in an amount effective to treat the condition or disease of the subject being treated.

The two active ingredients of the composition this invention can be co-administered simultaneously or sequentially in any order, or as a single pharmaceutical composition.

Pharmaceutical compositions of use in the present invention preferably comprise one or both active compound(s) in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampyules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredients are mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

When referring to these preformulation compositions as homogeneous, it is meant that the active ingredients is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 2000 mg of each of the active ingredients of the present invention. Typical unit dosage forms contain from 1 to 300 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric

layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The dosage of active ingredients in the compositions and methods of this invention may be varied; however, it is necessary that the amount of the active ingredients in such compositions be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, the particular compounds administered, the duration of the treatment, and other factors. All dosage ranges and dosage levels mentioned herein refer to each pharmaceutically active compound present in the pharmaceutical compositions and kits of the present invention, as well as those used in the methods of the present invention. Generally, dosage levels of between 0.0001 to 100 mg/kg of body weight daily are administered to humans and other animals, e.g., mammals. A preferred dosage range in humans is 0.01 to 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses. A preferred dosage range in mammals other than humans is 0.01 to 10.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses. A more preferred dosage range in mammals other than humans is 0.1 to 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

In general, the pharmaceutical compositions, methods and kits of this invention, will be administered at dosages of a therapeutically effective amount of the first and of the second therapeutic agent in single or divided doses. The term "therapeutically effective amount" as used herein refers to a sufficient amount of the compound to treat mood disorders and psychotic disorders or conditions at a reasonable benefit/risk ratio applicable to any medical treatment.

The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age. However, some variation in dosage will necessarily occur depending upon the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The following dosage amounts and other dosage amounts set forth elsewhere in this description and in the appendant claims are for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine the dosage amount required for a subject whose weight falls outside the 65 kg to 70 kg range, based upon the medical history of the subject. All doses set forth herein, and in the appendant claims, are daily doses.

The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition. Dosage amount and interval can be

adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain therapeutic effects.

More particularly, the dosages may be as described in the patents listed herein for ziprasidone, olanzapine, clozapine, risperidone, sertindole, quetiapine, or the Physicians' Desk Reference, 57th ed., Thompson, 2003 which are expressly incorporated herein by reference. Desirably, when ziprasidone is selected as the active agent, the daily dose in the composition of the invention contains from about 5 mg to about 460 mg. More preferably, each dose of the first component contains about 20 mg to about 320 mg of the ziprasidone, and even more preferably, each dose contains from about 20 mg to about 160 mg of ziprasidone. Pediatric dosages may be less. This dosage form permits the full daily dosage to be administered in one or two oral doses, for example.

General outlines of the dosages for the atypical antipsychotics and some preferred dosages are provided herein. This list is not intended to be complete but is merely a guideline for any of the desired combinations of the present invention.

Olanzapine: from about 0.25 to about 100 mg, once/day; preferred, from about 1 to about 30 mg, once/day; and most preferably about 1 to about 25 mg once/day;

Clozapine: from about 12.5 to about 900 mg daily; preferred, from about 150 to about 450 mg daily;

Risperidone: from about 0.25 to about 16 mg daily; preferred from about 2-8 mg daily;

Sertindole: from about 0.0001 to about 1.0 mg/kg daily;

Quetiapine: from about 1.0 to about 40 mg/kg given once daily or in divided doses;

In more general terms, one would create a drug combination of the present invention by choosing a dosage of first and second component compounds according to the spirit of the above guideline.

Preferred dosage for the CRF antagonists in the composition of the invention is of about 0.01 – 100 mg / kg of the patient.

When administered in combination, either as a single or as separate pharmaceutical composition(s), the atypical antipsychotic and the CRF antagonist are present in a ratio which is consistent with the manifestation of the desired effect. In particular, the ratio by weight of ziprasidone to the a CRF antagonist will suitably be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to 1 and 100 to 1.

The pharmaceutical combinations may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day, and most especially once daily.

The present invention also encompasses treatment with a combination of active ingredients which may be administered separately. Accordingly, the invention also relates to combining separate pharmaceutical compositions in kit form. Thus, in one embodiment, the

kit comprises two separate pharmaceutical compositions: a corticotropin releasing factor antagonist, a prodrug thereof, or a pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or said prodrug; and an atypical antipsychotic, a prodrug thereof, or a pharmaceutically acceptable salt of said atypical antipsychotic or said prodrug. The kit also comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil that is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably, the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the dosage form so specified should be ingested. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. Also, a daily dose of a corticotropin releasing factor antagonist, a prodrug thereof, or a pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or said prodrug can consist of one tablet or capsule, while a daily dose of the atypical antipsychotic, prodrug thereof, or pharmaceutically acceptable salt of said atypical antipsychotic or said prodrug can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter that indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

In another embodiment, the present invention comprises kits comprising a pharmaceutical composition, a package, and a package insert. The pharmaceutical composition of these kits contains either a corticotropin releasing factor antagonist or an atypical antipsychotic. The kits of the present invention containing a pharmaceutical composition containing a corticotropin releasing factor antagonist differ from known kits containing a pharmaceutical composition containing a corticotropin releasing factor antagonist in that on the package and/or on the package insert of the kits it is stated that the pharmaceutical composition is to be administered together with a pharmaceutical composition containing an atypical antipsychotic. The kits of the present invention containing a pharmaceutical composition containing an atypical antipsychotic differ from known kits containing a pharmaceutical composition containing an atypical antipsychotic in that on the package and/or on the package insert of the kits it is stated that the pharmaceutical composition is to be administered together with a pharmaceutical composition containing a corticotropin releasing factor antagonist.

The term "together with" as used in the immediately preceding paragraph is intended to encompass the simultaneous administration of the two pharmaceutical compositions (e.g., a tablet containing one pharmaceutical composition is to be administered orally while the other pharmaceutical composition is administered by way of infusion, two tablets or capsules are to be swallowed together, etc.). The term "together with" is also intended to include the administration of the two pharmaceutical compositions in a specifically timed manner, i.e., one pharmaceutical composition is to be administered a certain time period after administration of the other pharmaceutical composition. The time period in which the two pharmaceutical compositions are to be administered must be sufficiently short for the corticotropin releasing factor antagonist and the atypical antipsychotic to exhibit their activity contemporaneously, preferably in a synergistic manner. The exact time period depends on the specific compounds of the pharmaceutical compositions, the application route, the kind and severeness of the disease to be treated, the kind, age, and condition of the patient to be treated, etc., and can be determined by a physician using known methods in combination with the disclosure of the present invention. Generally, the two compositions are to be administered within one day,

preferably within 5 hours, more preferably within 2 hours, and even more preferably within one hour. Most preferably, the two compositions are to be administered at the same time or one immediately after the other.

Methods that may be used to determine CRF antagonist activity of the compounds employed to practice the present invention are as described in, e.g., Wynn et al., Endocrinology, 116:1653-59 (1985), and Grigoriadis et al., Peptides, 10:179-88 (1989). Methods that can be used to determine the CRF binding protein inhibiting activity of compounds employed to practice the present invention are described in Smith et al., Brain Research, 745(1,2):248-56 (1997). These methods determine the binding affinity of a test compound for a CRF receptor, which is highly related to its expected activity as a CRF antagonist.

The effectiveness of combinations of this invention, i.e., a corticotropin releasing factor antagonist and an atypical antipsychotic, may be tested for mood disorders or conditions and psychotic disorders or conditions may be demonstrated, for example, by measuring markers such as Positive or Negative Syndrome Scale (PANSS) and Scales for the Assessment of Negative Symptoms (SANS) or BPRS scores (Kay et al, 13 Schizophrenia Bulletin, 261-276; (1987)), or in various animal models such as PCP or methamphetamine induced locomotor test or the conditioned avoidance response test.

The products of the present invention have the advantage that they surprisingly provide relief from mood disorders or psychotic disorder more rapidly than would be expected from administration of either compound alone.

The invention is further illustrated by, but by no means limited to, the following examples.

EXAMPLE 1

A pharmaceutical composition is prepared by combining ziprasidone with a CRF antagonist which is either (a) 4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine, (b) (3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine, (c) (3,6-dimethyl-2-(4-chloro-2,6-dimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine, or (d) 5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-cholorophenyl)-1-4-dihydro-2H-3-oxa-1,8-diazanaphthalene; in a pharmaceutically acceptable carrier. The composition contains respective amounts of ziprasidone and the CRF antagonist to deliver on a daily basis between about 20mg to about 160 mg ziprasidone and between about 0.1 to 100 mg of the CRF antagonist. The composition is administered to a patient for the treatment of schizophrenia on a daily, twice daily, three times daily, or four times daily basis.

EXAMPLE 2

Administration of ziprasidone in combination with CRF antagonists.

A prospective, open-label, randomized, flexible-dose multicenter study is carried out comparing the efficacy of IM ziprasidone with and without a CRF antagonist in the dosages of the CRF antagonist described in Example 1 in improving agitation and psychopathology in patients with psychotic disorders. Ziprasidone is given IM at a dose of 10 or 20 mg, with an additional daily dose if needed to a maximum of 40 mg.

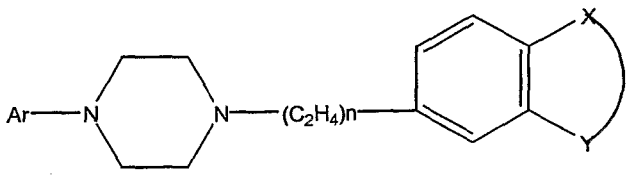
About half of ziprasidone treated patients receive at least one dose of a CRF antagonist of Example 1 during IM therapy. Primary efficacy outcomes are mean change from baseline in Brief Psychiatric Rating Scale (BPRS), CGI-S, and CGI-Improvement (CGI-I) scores. BPRS, CGI-S, and CGI-I are rated at baseline, once every 24 hours during IM treatment, and at the end of day three.

It should be understood that the invention is not limited to the particular embodiments described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

We claim:

1. A pharmaceutical compositions comprising (a) an atypical antipsychotic, a prodrug thereof or a pharmaceutically acceptable salt of the atypical antipsychotic or prodrug thereof, (b) a corticotropin releasing factor antagonist, a prodrug thereof, or pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or prodrug thereof, and optionally (c) a pharmaceutically acceptable vehicle, carrier or diluent.

2. The composition of claim 1, wherein the atypical antipsychotic is a compound represented by the formula A



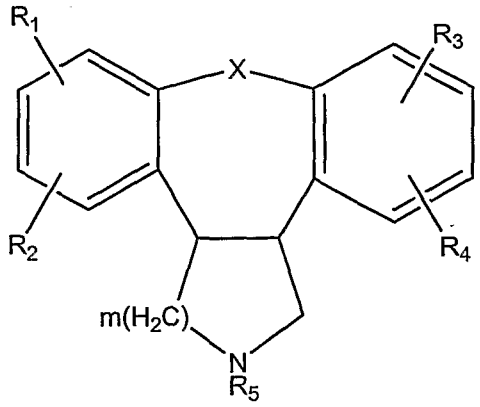
A

wherein Ar is benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by one fluoro, chloro, trifluoromethyl, methoxy, cyano, or nitro;

n is 1 or 2;

and X and Y together with the phenyl to which they are attached form benzothiazolyl; 2-aminobenzothiazolyl; benzoisothiazolyl; indazolyl; 2-hydroxyindazolyl; indolyl; oxindolyl optionally substituted by one to three of (C.sub.1 -C.sub.3)alkyl, or one of chloro, fluoro or phenyl, said phenyl optionally substituted by one chloro or fluoro; benzoxazolyl; 2-aminobenzoxazolyl; benzoxazolonyl; 2-aminobenzoxazolinyl; benzothiazolonyl; bezoimidazolonyl; or benzotriazolyl.

3. The composition of claim 1, wherein the atypical antipsychotic is a compound represented by the formula B



B

or pharmaceutically acceptable salts thereof, wherein

R_1, R_2, R_3 and R_4 each represent hydrogen, hydroxy, halogen, a C_1-C_6 alkyl group, an alkoxy or alkylthio group in which the alkyl group contains 1-6 carbon atoms, or a trifluoromethyl group,

R_5 represents hydrogen, a C_1-C_6 alkyl group carbon atoms or an aralkyl group with 7-10 carbon atoms,

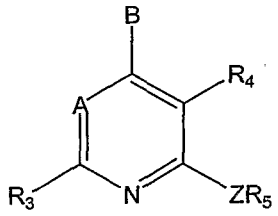
m is 1 or 2,

X represents oxygen, sulphur, the group -N(R_6)- or the group -CH_2-, and

R_6 represents hydrogen or a C_1-C_4 alkyl group.

4. The composition of claim 1, wherein the atypical antipsychotic is selected from the group consisting of olanazapine, clozapine, aripiprazole, quetiapine, amisulpride, risperidone, sertindole, asenapine, and ziprasidone.

5. The composition of claim 1 wherein said corticotropin releasing factor antagonist is a compound of the formula



wherein

A is CR_7 or N;

B is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCHR_1R_2$, $OCHR_1R_2$, $SCHR_1R_2$, CHR_2OR_{12}, CHR_2SR_{12}, $C(S)R_2$ or $C(O)R_2$;

Z is NH, O, S, N (C_1-C_2 alkyl), or $CR_{13}R_{14}$, wherein R_{13} and R_{14} are each independently hydrogen, trifluoromethyl, or C_1-C_4 alkyl, or one of R_{13} and R_{14} may be cyano, chloro, bromo, iodo, fluoro, hydroxy, O(C_1-C_2 alkyl), amino, NH(C_1-C_2 alkyl), or $CR_{13}R_{14}$ may be C=O or cyclopropyl;

R_1 is C_1-C_6 alkyl which may be substituted by one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, O-CO-(C_1-C_4 alkyl), O-CO-NH(C_1-C_4 alkyl), O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_4 alkyl), N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), NHCO(C_1-C_4 alkyl), COO(C_1-C_4 alkyl), CONH(C_1-C_4 alkyl), CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_4 alkyl), CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), and said C_1-C_6 alkyl or C_1-C_4 alkyl may contain one double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene)cycloalkyl, wherein said cycloalkyl

may contain one or two of O, S or N-R_9 wherein R_9 is hydrogen, or C_1-C_4 alkyl, wherein the above defined R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of bromo, iodo, C_1-C_6 alkoxy, O-CO-(C_1-C_6 alkyl), O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), CN, NO_2, SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_4 alkylene may contain one double or triple bond; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a saturated 5- to 8-membered carbocyclic ring which may contain one or two double bonds or one or two of O or S;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, amino, nitro, NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_n(C_1-C_4 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, CO(C_1-C_4 alkyl), CHO, or COO(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl may contain one or two double or triple bonds and may be substituted by one or two of hydroxy, amino, carboxy, $NHCOCH_3$, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl)$_2$, COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano or nitro;

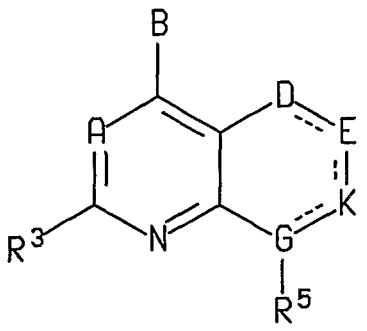
R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each one of the above groups R_5 is substituted independently by from one to three of fluoro, chloro, C_1-C_6 alkyl, or C_1-C_6 alkoxy, or one of hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, NH(C_1-C_4 alkyl), N(C_1-C_6)(C_1-C_2 alkyl), COOH, COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), or SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, hydroxy, amino, methylamino, dimethylamino or acetyl;

R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, O(C_1-C_4 alkyl), C(O)(C_1-C_4 alkyl), or C(O)O(C_1-C_4 alkyl), wherein the C_1-C_4 alkyl groups may be substituted with one hydroxy, chloro or bromo, or one to three fluoro;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy; and

R_{12} is hydrogen or C_1-C_4 alkyl.

6. The composition of claim 1 wherein said corticotropin releasing factor antagonist is a compound of the formula



wherein the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

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

G is nitrogen or CR^4 and is single bonded to all atoms to which it is attached, or G is carbon and is double bonded to K;

K is nitrogen or CR^6 when double bonded to G or E, or K is oxygen, sulfur, C=O, C=S, CR^6R^{12} or NR^8 when single bonded to both adjacent ring atoms, or K is a two atom spacer, wherein one of the two ring atoms of the spacer is oxygen, nitrogen, sulfur, C=O, C=S, CR^6R^{12}, NR^6 or CR^6, and the other is CR^6R^{12} or CR^9;

D and E are each, independently, C=O, C=S, sulfur, oxygen, CR^4R^6 or NR^8 when single bonded to both adjacent ring atoms, or nitrogen or CR^4 when it is double bonded to an adjacent ring atom;

the 6- or 7-membered ring that contains D, E, K and G may contain from one to three double bonds, from zero to two heteroatoms selected from oxygen, nitrogen and sulfur, and from zero to two C=O or C=S groups, wherein the carbon atoms of such groups are part of the ring and the oxygen and sulfur atoms are substituents on the ring;

R^1 is C_1-C_6 alkyl optionally substituted with from one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, $-C(=O)(C_1$-C_4alkyl), $-C(=O)$-O-(C_1-C_4)alkyl, $-OC(=O)(C_1$-C_4 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-NHCO(C_1$-C_4 alkyl), -COOH, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_4 alkyl), -CN, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

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

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

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

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl);

each R^8, R^9 and R^{12} is selected, independently, from hydrogen and C_1-C_2 alkyl;

each R^4 and R^6 that is attached to a carbon atom is selected, independently, from hydrogen and C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, hydroxy (C_1-C_2 alkyl), trifluoromethyl, cyano, amino, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CH_2SCH_3, -S(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4 alkyl), wherein each of the C_1-C_2 alkyl moieties in the foregoing R^4 and R^6 groups may optionally contain one double or triple bond; and R^6, when attached to a nitrogen atom, is selected from hydrogen and C_1-C_4 alkyl;

R^5 is substituted phenyl, naphthyl, pyridyl or pyrimidyl, wherein each of the foregoing R^5 groups is substituted with from two to four substituents R^{13}, wherein up to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl, -O(C_1-C_6 alkyl) and -(C_1-C_6 alkylene)O(C_1-C_6alkyl), and wherein one of said substituents may be selected, independently, from bromo, iodo, formyl, cyano, trifluoromethyl, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -(C_0-C_1alkylene)-S-(C_1-C_2 alkyl), -(C_0-C_1alkylene)-SO-(C_1-C_2alkyl), -(C_0-C_1alkylene)-SO_2-(C_1-C_2alkyl) and -(C_1-C_4 alkylene)-OH, and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, methyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, methoxy, -C(=O)(C_1-C_2 alkyl), -C(=O)O(C_1-C_2 alkyl), hydroxymethyl, trifluoromethyl or formyl;

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

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

with the proviso that in the ring containing D, E, K and G of formula I, there can not be two double bonds adjacent to each other.

7. The composition of claim 1 wherein said CRF antagonist is selected from the group consisting of:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;

(3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine;

(3,6-dimethyl-2-(4-chloro-2,6-dimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-cholorophenyl)-1-4-dihydro-2H-3-oxa-1,8-diazanaphthalene;

butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amino;

4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one;

4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;

N-butyl-N-ethyl-2,5-dimethyl-NN-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;

[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;

6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one;

3-{(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;

diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;

dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-amine;

butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine;

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;

4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;

butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-ethylamine;

[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;

4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;

(1-ethylpropyl)-[3,5,6-trimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-amine;

4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;

4-(1-ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;

4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo[2,3-b]pyridine;

2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;

1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

9-(1-ethylpropyl)-2-methyl-6-(2,4,6-trimethylphenylamino)-7,9-dihydro-purin-8-one;

1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-imidazo[4,5-c]pyridine;

1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;

1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-pyrido[3,4-b]pyrazin-3-one;

1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-pyrido[3,4-b]pyrazin-3-one;

1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;

1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;

1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine-3-carboxylic acid methyl ester;

1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine-3-carboxylic acid isopropyl ester;

1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1H-[1,6]naphthyridin-2-one;

1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine;

1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;

1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;

1-(1-ethyl-propyl)-3,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1H-3-oxa-[1,6]-naphthyridin-2-one;

1-(1-ethyl-propyl)-3,3,6-trimethyl-4-(2,4,6-trimethyl-phenoxy)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;

5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;

8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

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

4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

4-(butyl-ethyl-amino)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

(butyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;

(propyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;

(diethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido [2,3-d]pyrimidin-4-yl]-amine;

(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;

(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine;

4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido [2,3-d]pyrimidin-7-one;

(butyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;

(propyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;

(diethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;

(1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;

(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidine;

8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-3,4-dihydro-1H-pyrido [2,3-b]pyrazin-2-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinoline;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,2-dihydro-3-oxa-1, 8-diaza-naphthalen-4-one;

8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinolin-4-yl]-amine;

4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-chloro-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinoline;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;

8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

(1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinolin-4-yl]-amine;

8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b] pyrazin-2-one;

8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one

8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido [2,3-b]pyrazin-2-one;

8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido [2,3-b]pyrazine;

8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

4-(1-hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;

4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

4-(1-ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

4-diethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

4-(ethyl-propyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)- quinoline;

5-(1-hydroxymethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-hydroxymethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-ethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-diethylamino-5-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(ethyl-propyl-amino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

4-(2,4-dichlorophenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;

oxalate of 4-(2,4-dichlorophenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methylisoquinol-5-yl)-N-propylamino]thiazole;

4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-methoxycarbonylmethylindol-5-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-chloroisoquinol-5-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;

4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-1-methoxynaphth-2-yl)-N-propylamino]thiazole;

oxalate of 4-(2-chloro-4-trifluoromethylphenyl)-5-methyl-2-[N-6-methoxyisoquinol-5-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2-ethoxynaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2[N-(2,3-dimethylnaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate de 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-bromo-2-methoxynaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2,6-dimethylnaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(cyclopropyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;

3-(2,4-dichlorophenyl)-5-methyl-7(N-propyl-N-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;

3-(2,4-dichlorophenyl)-5-methyl-7-(N-allyl-N-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;

2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N,N-diallylamino)-pyrazolo[2,3-a]pyrimidine;

2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-butyl-N-cyclopropanemethyl-amino)pyrazolo[2,3-alpyrimidine; 2_methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-propyl-N-cyclopopanemethyl-amino) pyrazolo[2,3-a]pyrimidine;

2-methyl-3-(4-chlorophenyl)-5-methyl-7-(N,N-dipropylamino)-pyrazolo[2,3-a) pyrimidine;

3-[6-(dimethylamino)-3-pyridinyl-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a]pyrimidin-7-amine;

3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropyl-pyrazolo[2,3-a]pyrimidine-7-amine;

3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(N-propyl-N-methyloxyethylamino)-pyrazolo (2,3-a)pyrimidine;

7-(N-diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine;

7-(N-(3-cyanopropyl)-N-propylamino-2,5,dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;

[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine;

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

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

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

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

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

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

4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester.

8. The composition of claim 7, wherein the corticotropin releasing factor antagonist is selected from the group consisting of:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;

(3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine;

(3,6-dimethyl-2-(4-chloro-2,6-dimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine;

and 5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-cholorophenyl)-1-4-dihydro-2H-3-oxa-1,8-diazanaphthalene.

9. The composition of claim 8, wherein the atypical antipsychotic is selected from the group consisting of ziprasidone and asenapine.

10. A method for treating mood disorders or conditions, psychotic disorders or conditions, or a combination thereof, in a mammal, the method comprising administering to a mammal in need of such treatment (a) an atypical antipsychotic, a prodrug thereof or a pharmaceutically acceptable salt of the atypical antipsychotic or prodrug thereof, and (b) a corticotropin releasing factor antagonist, a prodrug thereof, or pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or prodrug thereof, wherein (a) and (b) are each optionally and independently administered together with a pharmaceutically acceptable vehicle, carrier or diluent.

11. The method of claim 10, wherein the corticotropin releasing factor antagonist is selected from the group consisting of:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;

(3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine;

(3,6-dimethyl-2-(4-chloro-2,6-dimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine; and 5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-cholorophenyl)-1-4-dihydro-2H-3-oxa-1,8-diazanaphthalene.

12. The method of claim 11, wherein the atypical antipsychotic is selected from the group consisting of ziprasidone and asenapine.

13. The method of claim 10 wherein the atypical antipsychotic and the corticotropin releasing factor antagonist are administered simultaneously or in a specifically timed manner.

14. A method for treating a depressive symptom associated with mood disorders or conditions, psychotic disorders or conditions, or a combination thereof, in a mammal, the method comprising administering to a mammal in need of such treatment (a) an atypical antipsychotic, a prodrug thereof or a pharmaceutically acceptable salt of the atypical antipsychotic or prodrug thereof, and (b) a corticotropin releasing factor antagonist, a prodrug thereof, or pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or prodrug thereof, wherein (a) and (b) are each optionally and independently administered together with a pharmaceutically acceptable vehicle, carrier or diluent, , wherein the symptom is selected from the group consisting of depressed mood, irritability, sad effect, and circadian rhythm alteration.

15. A kit comprising a pharmaceutical composition comprising a corticotropin releasing factor antagonist, a prodrug thereof, or pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or prodrug thereof, a package containing the composition, and a package insert that is optionally integral with the package, wherein it is stated on the package insert that the pharmaceutical composition is to be administered to the mammal simultaneously or in a specifically timed manner with a pharmaceutical composition containing an atypical antipsychotic, a prodrug thereof, or pharmaceutically acceptable salt of said atypical antipsychotic or prodrug thereof.