SELECTIVE SEROTONIN RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR DISEASE

Background of the Invention

Field of the Invention

[0001] The present invention relates to novel combinations of compounds that are effective as therapeutic agents in the treatment of depression, mania, or social phobia, and other psychotic disorders. The combinations include inverse serotonin agonists and another antidepressant, anti-maniac, anti-phobia, or antipsychotic agent.

Description of the Related Art

[0002] Serotonin or 5-hydroxytryptamine (5-HT) plays a significant role in the functioning of the mammalian body. In the central nervous system, 5-HT is an important neurotransmitter and neuromodulator that is implicated in such diverse behaviors and responses as sleeping, eating, locomotion, perceiving pain, learning and memory, sexual behavior, controlling body temperature and blood pressure. In the spinal column, serotonin plays an important role in the control systems of the afferent peripheral nociceptors (Moulignier, *Rev. Neurol.* 150:3-15, (1994)). Peripheral functions in the cardiovascular, hematological and gastrointestinal systems have also been ascribed to 5-HT. 5-HT has been found to mediate a variety of contractile, secretory, and electrophysiologic effects including vascular and nonvascular smooth muscle contraction, and platelet aggregation. (Fuller, *Biology of Serotonergic Transmission*, 1982; Boullin, *Serotonin In Mental Abnormalities* 1:316 (1978); Barchas, et al., *Serotonin and Behavior*, (1973)). The 5-HT2A receptor subtype (also referred to as subclass) is widely yet discretely expressed in the human brain, including many cortical, limbic, and forebrain regions postulated to be involved in the modulation of higher cognitive and affective functions. This receptor subtype is also expressed on mature platelets where it mediates, in part, platelet aggregation, one of the initial steps in the process of vascular thrombosis.

[0003] Given the broad distribution of serotonin within the body, it is understandable that tremendous interest in drugs that affect serotonergic systems exists (Gershon, et al., *The Peripheral Actions of 5-Hydroxytryptamine*, 246 (1989); Saxena, et al., *J. Cardiovascular Pharmacol.* 15: Supp. 7 (1990)). Serotonin receptors are members of a large human gene family of membrane-spanning proteins that function as transducers

of intercellular communication. They exist on the surface of various cell types, including neurons and platelets, where, upon their activation by either their endogenous ligand serotonin or exogenously administered drugs, they change their conformational structure and subsequently interact with downstream mediators of cellular signaling. Many of these receptors, including the 5-HT2A subclass, are G-protein coupled receptors (GPCRs) that signal by activating guanine nucleotide binding proteins (G-proteins), resulting in the generation, or inhibition of, second messenger molecules such as cyclic AMP, inositol phosphates, and diacylglycerol. These second messengers then modulate the function of a variety of intracellular enzymes, including kinases and ion channels, which ultimately affect cellular excitability and function.

[0004] At least 15 genetically distinct 5-HT receptor subtypes have been identified and assigned to one of seven families (5-HT1-7). Each subtype displays a unique distribution, preference for various ligands, and functional correlate(s).

[0005] Serotonin may be an important component in various types of pathological conditions such as certain psychiatric disorders (depression, aggressiveness, panic attacks, obsessive compulsive disorders, psychosis, schizophrenia, suicidal tendency), certain neurodegenerative disorders (Alzheimer-type dementia, Parkinsonism, Huntington's chorea), anorexia, bulimia, disorders associated with alcoholism, cerebral vascular accidents, and migraine (Meltzer, *Neuropsychopharmacology*, 21:106S-115S (1999); Barnes & Sharp, *Neuropharmacology,* 38:1083-1152 (1999); Glennon, *Neurosci. Biobehavioral Rev.*, 14:35 (1990)). Recent evidence strongly implicates the 5-HT2 receptor subtype in the etiology of such medical conditions as hypertension, thrombosis, migraine, vasospasm, ischemia, depression, anxiety, psychosis, schizophrenia, sleep disorders and appetite disorders.

[0006] Schizophrenia is a particularly devastating neuropsychiatric disorder that affects approximately 1% of the human population. It has been estimated that the total financial cost for the diagnosis, treatment, and lost societal productivity of individuals affected by this disease exceeds 2% of the gross national product (GNP) of the United States. Current treatment primarily involves pharmacotherapy with a class of drugs known as antipsychotics. Antipsychotics are effective in ameliorating positive symptoms (e.g., hallucinations and delusions), yet they frequently do not improve negative symptoms (e.g., social and emotional withdrawal, apathy, and poverty of speech).

[0007] Currently, nine major classes of antipsychotics are prescribed to treat psychotic symptoms. Use of these compounds is limited, however, by their side effect profiles. Nearly all of the "typical" or older generation compounds have significant adverse effects on human motor function. These "extrapyramidal" side effects, so termed due to their effects on modulatory human motor systems, can be both acute (e.g., dystonic reactions, a potentially life threatening but rare neuroleptic malignant syndrome) and chronic (e.g., akathisias, tremors, and tardive dyskinesia). Drug development efforts have, therefore, focused on newer "atypical" agents free of these adverse effects.

[0008] Antipsychotic drugs have been shown to interact with a large number of central monoaminergic neurotransmitter receptors, including dopaminergic, serotonergic, adrenergic, muscarinic, and histaminergic receptors. It is likely that the therapeutic and adverse effects of these drugs are mediated by distinct receptor subtypes. The high degree of genetic and pharmacological homology between these receptor subtypes has hampered the development of subtype-selective compounds, as well as the determination of the normal physiologic or pathophysiologic role of any particular receptor subtype. Thus there is a need to develop drugs that are selective for individual receptor classes and subclasses amongst monoaminergic neurotransmitter receptors.

[0009] The prevailing theory for the mechanism of action of antipsychotic drugs involves antagonism of dopamine D2 receptors. Unfortunately, it is likely that antagonism of dopamine D2 receptors also mediates the extrapyramidal side effects. Antagonism of 5-HT2A is an alternate molecular mechanism for drugs with antipsychotic efficacy, possibly through antagonism of heightened or exaggerated signal transduction through serotonergic systems. 5-HT2A antagonists are therefore good candidates for treating psychosis without extrapyramidal side effects.

[0010] Traditionally, these receptors have been assumed to exist in a quiescent state unless activated by the binding of an agonist (a drug that activates a receptor). It is now appreciated that many, if not most, of the GPCR monoamine receptors, including serotonin receptors, can exist in a partially activated state in the absence of their endogenous agonists. This increased basal activity (constitutive activity) can be inhibited by compounds called inverse agonists. Both agonists and inverse agonists possess intrinsic activity at a receptor, in that they alone can activate or inactivate these molecules, respectively. In contrast, classic or neutral antagonists compete against agonists and

inverse agonists for access to the receptor, but do not possess the intrinsic ability to inhibit elevated basal or constitutive receptor responses.

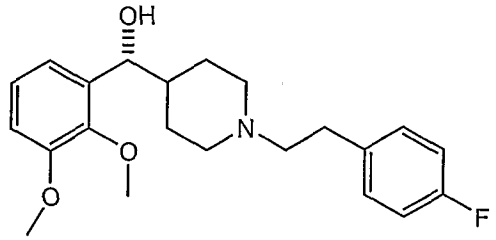
[0011] Recently, an important aspect of 5-HT2A receptor function was elucidated by applying the Receptor Selection and Amplification Technology (U.S. Patent 5,707,798, 1998; *Chem Abstr.* 128:111548 (1998) and citations therein), to the study of the 5-HT2 subclass of serotonin receptors. R-SAT is a phenotypic assay of receptor function that involves the heterologous expression of receptors in mammalian fibroblasts. Using this technology, it was demonstrated that native 5-HT2A receptors possess significant constitutive, or agonist-independent, receptor activity (U.S. Patent No. 6,358,698, herein incorporated by reference). Furthermore, by directly testing a large number of centrally acting medicinal compounds with known clinical activity in neuropsychiatric disease, it was determined that compounds with antipsychotic efficacy all shared a common molecular property. Nearly all of these compounds, which are used by psychiatrists to treat psychosis, were found to be potent 5-HT2A inverse agonists. This unique clinico-pharmacologic correlation at a single receptor subtype is compelling evidence that 5-HT2A receptor inverse agonism is a molecular mechanism of antipsychotic efficacy in humans.

[0012] Detailed pharmacological characterization of a large number of antipsychotic compounds revealed that they possess broad activity at multiple related receptor subtypes. Most of these compounds display agonist, competitive antagonist, or inverse agonist activity at multiple monoaminergic receptor subtypes, including serotoninergic, dopaminergic, adrenergic, muscarinic and histaminergic receptors. This broad activity is likely responsible for the sedating, hypotensive, and motor side effects of these compounds. It would therefore be of great advantage to develop compounds that are selective inverse agonists of the 5-HT2A receptor, but which have little or no activity on other monamine receptors subtypes, especially dopamine D2 receptors. Such compounds may be useful in the treatment of human disease (e.g., as anti-psychotics), and may avoid the adverse side effects associated with non-selective receptor interactions.

Summary of the Invention

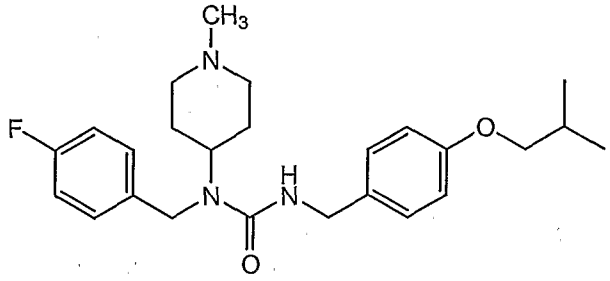
[0013] Disclosed herein is a pharmaceutical composition comprising: a first compound selected from the group consisting of an inverse agonist of a serotonin receptor, an antagonist of a serotonin receptor, and pharmaceutically acceptable salts

thereof; and a second compound selected from the group consisting of a SSRI, a SNRI, a MAO-I, a TCA, an antipsychotic agent, a norepinephrine reuptake inhibitor, a dopamine agonist, an anti-insomnia drug, an anti-manic drug, an anti-phobia drug, the compound of Formula (II)



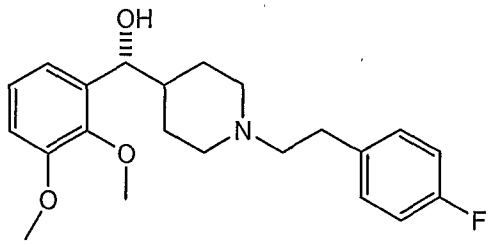
(II)

and pharmaceutically acceptable salts thereof. In some embodiments, the serotonin receptor is a 5HT2A receptor. In some embodiments, the first compound is a compound of Formula (I):



(I)

In some embodiments, the first compound is a compound of Formula (II):

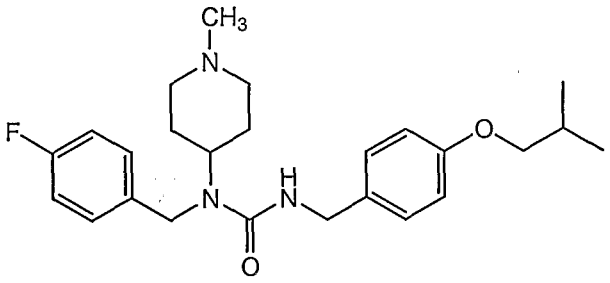


(II)

and the second compound selected from the group consisting of a SSRI, a SNRI, a MAO-I, a TCA, an antipsychotic agent, a norepinephrine reuptake inhibitor, a dopamine agonist, an anti-insomnia drug, an anti-manic drug, an anti-phobia drug. In some embodiments, the SSRI is selected from the group consisting of bupropion (Wellbutrin, Zyban), citalopram (Celexa), duloxetine, escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertaline (Zoloft),

sibutramine, trazodone (Dividose), and venlafaxine. In some embodiments, the SNRI is selected from the group consisting of citalopram (Celexa), dulexetine, escitalopram (Lexapro), fluvoxamine (Luvox), and venfalaxine (effexor). In some embodiments, the MAO-I is selected from the group consisting of tranylcypromine (Parnate), phenelzine (Nardil), maprotiline, and isocarboxazid (Marplan). In some embodiments, the TCA is selected from the group consisting of amitryptiline (Norpramine), amoxapineclomipramine (Anafranil), desipramine, doxepin (Sinequan), imipramine (Tofranil), maprotiline, (Elavil), protryptiline, and trimipramine. In some embodiments, the antipsychotic agent is selected from the group consisting of a phenothiazine, a phenylbutylpiperadine, a debenzapine, a benzisoxidil, and a salt of lithium. In some embodiments, the phenothiazine is selected from the group consisting of chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), and thioridazine (MellarilIn some embodiments, the phenylbutylpiperadine is selected from the group consisting of haloperidol (Haldol®) and pimozide (Orap®). In some embodiments, the debenzapine is selected from the group consisting of clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®), and quetiapine (Seroquel®). In some embodiments, the benzisoxidil is selected from the group consisting of resperidone (Resperidal®) and ziprasidone (Geodon®). In some embodiments, the salt of lithium is lithium carbonate. In some embodiments, the antipsychotic agent is selected from the group consisting of Aripiprazole (Abilify), Etrafon Haldol, Inapsine, Mellaril, Moban, Navane, Permitil, Prolixin, Phenergan, Reglan, Risperdal, Stelazine, Taractan, Triavil, and Trilafon. In some embodiments, the norepinephrine reuptake inhibitor is selected from the group consisting of thionisoxetine and reboxetine. In some embodiments, the dopamine agonist is selected from the group consisting of sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine. In some embodiments, the anti-insomnia drug is selected from the group consisting of alprazolam (Xanax), chlordiazepoxide (Librium, Limbitrol), clorazepate (Tranxene), estazolam (ProSom), flurazepam (Dalmane), hydroxyzine (Atarax), lorazepam (Ativan), pentobarbital (Nembutal), quazepam (Doral), secobarbital (Seconal), temazepam (Restoril), triazolam (Halcion), valium, zaleplon (Sonata), zolpidem (Ambien), and the benzodiazepine family of drugs. In some embodiments, the anti-insomina drug is an H1 antagonist or inverse agonist. In some embodiments, the H1 antagonist or inverse agonist is selected from the

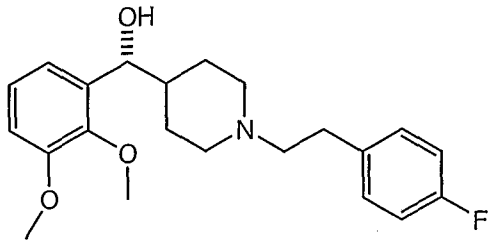
group consisting of azatadine, astemizole, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, ktotifen, leocabastine, meclizine, mepramine, manserin, promethazine, tipelennamine, triprolidine, acrivastine, cetrizine, desloratadine, fexofenadine, and loratidine. In some embodiments, the anti-manic drug is selected from the group consisting of divalproex (Depakote), lithium carbonate (Eskalith), and lithium citrate. In some embodiments, the anti-phobia drug is D-cycloserine. In some embodiments, the pharmaceutical composition further comprises physiologically acceptable carrier, diluent, or excipient, or a combination thereof. In one embodiment, the first compound is the compound of Formula (I):



(I)

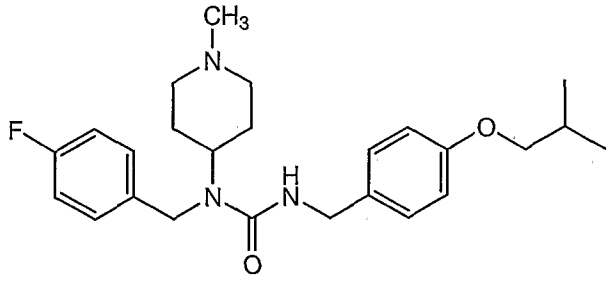
and the second compound is fluoxetine.

[0014] Also disclosed herein is a method of treating a disorder in a patient, the disorder selected from the group consisting of depression, mania, social phobia, psychosis, insomnia, and a neuropsychiatric disorder, the method comprising: identifying a patient in need of the treatment, and administering to the patient a therapeutically effective amount of a combination of a first compound and a second compound, the first compound selected from the group consisting of an inverse agonist of a serotonin receptor, an antagonist of a serotonin receptor, and pharmaceutically acceptable salts thereof, as described above and the second compound selected from the group consisting of a SSRI, a SNRI, a MAO-I, a TCA, an antipsychotic agent, a norepinephrine reuptake inhibitor, a dopamine agonist, an anti-insomnia drug, an anti-manic drug, an anti-phobia drug, the compound of Formula (II):



(II)

and pharmaceutically acceptable salts thereof, as described above. In some embodiments, the neuropsychiatric disorder is selected from the group consisting of schizophrenia and related idiopathic psychoses, anxiety, sleep disorders, appetite disorders, affective disorders, Tourette's Syndrome, drug-induced psychoses, and psychoses secondary to neurodegenerative disorders. In some embodiments, the affective disorders are selected from the group consisting of major depression, bipolar disorder, and depression with psychotic features. In some embodiments, the neurodegenerative disorders are selected from the group consisting of Alzheimer's and Huntington's Disease. In one embodiment, the disorder is depression, the first compound is the compound of Formula (I):

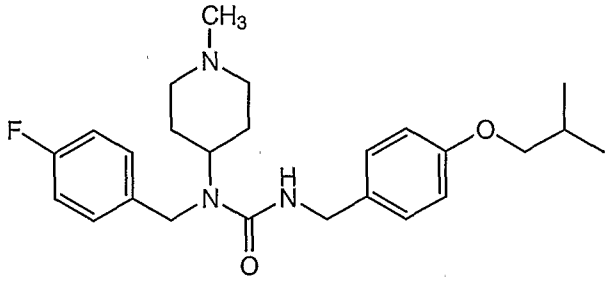


(I)

and the second compound is fluoxetine.

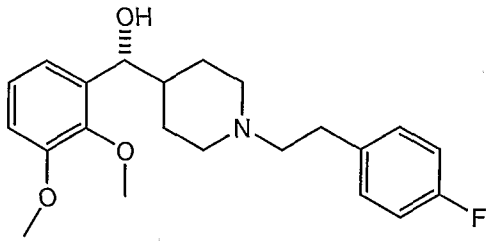
[0015] Also disclosed herein is use of a first compound and a second compound for the preparation of a medicament for treating a disorder selected from the group consiting of depression, mania, social phobia, psychosis, insomnia, and a neuropsychiatric disorder, wherein the first compound and second compound are as described above.

[0016] Also disclosed herein is a pharmaceutical composition comprising the compound of Formula (I):



(I)

and a compound selected from the group consisting of a SSRI, a SNRI, a MAO-I, a TCA, an antipsychotic agent, a norepinephrine reuptake inhibitor, a dopamine agonist, an anti-insomnia drug, an anti-manic drug, an anti-phobia drug, the compound of Formula (II):

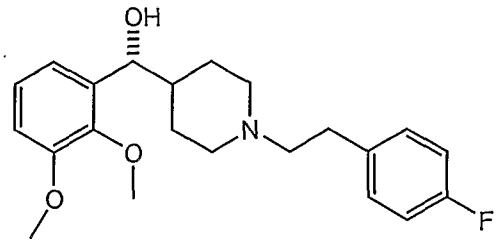


(II)

and pharmaceutically acceptable salts thereof. In some embodiments, the SSRI is selected from the group consisting of bupropion (Wellbutrin, Zyban), citalopram (Celexa), duloxetine, escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertaline (Zoloft), sibutramine, trazodone (Dividose), and venlafaxine. In some embodiments, the SNRI is selected from the group consisting of citalopram (Celexa), dulexetine, escitalopram (Lexapro), fluvoxamine (Luvox), and venfalaxine (effexor). In some embodiments, the MAO-I is selected from the group consisting of tranylcypromine (Parnate), phenelzine (Nardil), maprotiline, and isocarboxazid (Marplan). In some embodiments, the TCA is selected from the group consisting of amitryptiline (Norpramine), amoxapineclomipramine (Anafranil), desipramine, doxepin (Sinequan), imipramine (Tofranil), maprotiline, (Elavil), protryptiline, and trimipramine. In some embodiments, the antipsychotic agent is selected from the group consisting of a phenothiazine, a phenylbutylpiperadine, a debenzapine, a benzisoxidil, and a salt of lithium. In some embodiments, the phenothiazine is selected from the group consisting of chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), and thioridazine (MellarilIn some embodiments, the phenylbutylpiperadine is selected from the group consisting of haloperidol (Haldol®) and

pimozide (Orap®). In some embodiments, the debenzapine is selected from the group consisting of clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®), and quetiapine (Seroquel®). In some embodiments, the benzisoxidil is selected from the group consisting of resperidone (Resperidal®) and ziprasidone (Geodon®). In some embodiments, the salt of lithium is lithium carbonate. In some embodiments, the antipsychotic agent is selected from the group consisting of Aripiprazole (Abilify), Etrafon Haldol, Inapsine, Mellaril, Moban, Navane, Permitil, Prolixin, Phenergan, Reglan, Risperdal, Stelazine, Taractan, Triavil, and Trilafon. In some embodiments, the norepinephrine reuptake inhibitor is selected from the group consisting of thionisoxetine and reboxetine. In some embodiments, the dopamine agonist is selected from the group consisting of sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine. In some embodiments, the anti-insomnia drug is selected from the group consisting of alprazolam (Xanax), chlordiazepoxide (Librium, Limbitrol), clorazepate (Tranxene), estazolam (ProSom), flurazepam (Dalmane), hydroxyzine (Atarax), lorazepam (Ativan), pentobarbital (Nembutal), quazepam (Doral), secobarbital (Seconal), temazepam (Restoril), triazolam (Halcion), valium, zaleplon (Sonata), zolpidem (Ambien), and the benzodiazepine family of drugs. In some embodiments, the anti-insomina drug is an H1 antagonist or inverse agonist. In some embodiments, the H1 antagonist or inverse agonist is selected from the group consisting of azatadine, astemizole, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, ktotifen, leocabastine, meclizine, mepramine, manserin, promethazine, tipelennamine, triprolidine, acrivastine, cetrizine, desloratadine, fexofenadine, and loratidine. In some embodiments, the anti-manic drug is selected from the group consisting of divalproex (Depakote), lithium carbonate (Eskalith), and lithium citrate. In some embodiments, the anti-phobia drug is D-cycloserine. In some embodiments, the pharmaceutical composition further comprises physiologically acceptable carrier, diluent, or excipient, or a combination thereof. In some embodiments, a method is provided for treating a disorder in a patient, the disorder selected from the group consisting of depression, mania, social phobia, psychosis, and a neuropsychiatric disorder, the method comprising: identifying a patient in need of the treatment, and administering to the patient a therapeutically effective amount of the composition described above.

[0017] Also disclosed herein is a pharmaceutical composition comprising a compound of Formula (II):



(II)

and a compound selected from the group consisting of a SSRI, a SNRI, a MAO-I, a TCA, an antipsychotic agent, a norepinephrine reuptake inhibitor, a dopamine agonist, an anti-insomnia drug, an anti-manic drug, an anti-phobia drug, and pharmaceutically acceptable salts thereof. In some embodiments, the SSRI is selected from the group consisting of bupropion (Wellbutrin, Zyban), citalopram (Celexa), duloxetine, escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertaline (Zoloft), sibutramine, trazodone (Dividose), and venlafaxine. In some embodiments, the SNRI is selected from the group consisting of citalopram (Celexa), dulexetine, escitalopram (Lexapro), fluvoxamine (Luvox), and venfalaxine (effexor). In some embodiments, the MAO-I is selected from the group consisting of tranylcypromine (Parnate), phenelzine (Nardil), maprotiline, and isocarboxazid (Marplan). In some embodiments, the TCA is selected from the group consisting of amitryptiline (Norpramine), amoxapineclomipramine (Anafranil), desipramine, doxepin (Sinequan), imipramine (Tofranil), maprotiline, (Elavil), protryptiline, and trimipramine. In some embodiments, the antipsychotic agent is selected from the group consisting of a phenothiazine, a phenylbutylpiperadine, a debenzapine, a benzisoxidil, and a salt of lithium. In some embodiments, the phenothiazine is selected from the group consisting of chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), and thioridazine (MellarilIn some embodiments, the phenylbutylpiperadine is selected from the group consisting of haloperidol (Haldol®) and pimozide (Orap®). In some embodiments, the debenzapine is selected from the group consisting of clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®), and quetiapine (Seroquel®). In some embodiments, the benzisoxidil is selected from the group consisting of resperidone (Resperidal®) and ziprasidone (Geodon®). In some embodiments, the salt of lithium is lithium carbonate. In some embodiments, the

antipsychotic agent is selected from the group consisting of Aripiprazole (Abilify), Etrafon Haldol, Inapsine, Mellaril, Moban, Navane, Permitil, Prolixin, Phenergan, Reglan, Risperdal, Stelazine, Taractan, Triavil, and Trilafon. In some embodiments, the norepinephrine reuptake inhibitor is selected from the group consisting of thionisoxetine and reboxetine. In some embodiments, the dopamine agonist is selected from the group consisting of sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine. In some embodiments, the anti-insomnia drug is selected from the group consisting of alprazolam (Xanax), chlordiazepoxide (Librium, Limbitrol), clorazepate (Tranxene), estazolam (ProSom), flurazepam (Dalmane), hydroxyzine (Atarax), lorazepam (Ativan), pentobarbital (Nembutal), quazepam (Doral), secobarbital (Seconal), temazepam (Restoril), triazolam (Halcion), valium, zaleplon (Sonata), zolpidem (Ambien), and the benzodiazepine family of drugs. In some embodiments, the anti-insomina drug is an H1 antagonist or inverse agonist. In some embodiments, the H1 antagonist or inverse agonist is selected from the group consisting of azatadine, astemizole, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, ktotifen, leocabastine, meclizine, mepramine, manserin, promethazine, tipelennamine, triprolidine, acrivastine, cetrizine, desloratadine, fexofenadine, and loratidine. In some embodiments, the anti-manic drug is selected from the group consisting of divalproex (Depakote), lithium carbonate (Eskalith), and lithium citrate. In some embodiments, the anti-phobia drug is D-cycloserine. In some embodiments, the pharmaceutical composition further comprises physiologically acceptable carrier, diluent, or excipient, or a combination thereof. In some embodiments, a method is provided for treating a disorder in a patient, the disorder selected from the group consisting of depression, mania, social phobia, psychosis, and a neuropsychiatric disorder, the method comprising: identifying a patient in need of the treatment, and administering to the patient a therapeutically effective amount of the composition described above.

Detailed Description of the Preferred Embodiment

Definitions

[0018] For the purpose of the current disclosure, the following definitions shall in their entireties be used to define technical terms, and shall also, in their entireties,

be used to define the scope of the composition of matter for which protection is sought in the claims.

[0019] "Constitutive activity" is defined as the elevated basal activity of a receptor that is independent of the presence of an agonist. Constitutive activity of a receptor may be measured using a number of different methods, including cellular (e.g., membrane) preparations (see, e.g., Barr &. Manning, *J. Biol. Chem.* 272:32979-87 (1997)), purified reconstituted receptors with, or without the associated G-protein in phospholipid vesicles (Cerione et al., *Biochemistry* 23:4519-25 (1984)), and functional cellular assays (U.S. Patent Application Ser. No. 60/103,317) or any other method known in the art.

[0020] "Agonist" is defined as a compound that increases the basal activity of a receptor when it contacts the receptor.

[0021] An "antagonist" is defined as a compound that competes with an agonist or inverse agonist for binding to a receptor, thereby blocking the action of an agonist or inverse agonist on the receptor. However, an antagonist (also known as a "neutral" antagonist) has no effect on constitutive receptor activity.

[0022] An "inverse agonist" is defined as a compound that decreases the basal activity of a receptor (i.e., signaling mediated by the receptor). Such compounds are also known as negative antagonists. An inverse agonist is a ligand for a receptor that causes the receptor to adopt an inactive state relative to a basal state occurring in the absence of any ligand. Thus, while an antagonist can inhibit the activity of an agonist, an inverse agonist is a ligand that can alter the conformation of the receptor in the absence of an agonist. The concept of an inverse agonist has been explored by Bond et al. in *Nature* 374:272 (1995). More specifically, Bond et al. have proposed that unliganded β_2-adrenoceptor exists in an equilibrium between an inactive conformation and a spontaneously active conformation. Agonists are proposed to stabilize the receptor in an active conformation. Conversely, inverse agonists are believed to stabilize an inactive receptor conformation. Thus, while an antagonist manifests its activity by virtue of inhibiting an agonist, an inverse agonist can additionally manifest its activity in the absence of an agonist by inhibiting the spontaneous conversion of an unliganded receptor to an active conformation.

[0023] The "5-HT2A receptor" is defined as a receptor, having an activity corresponding to the activity of the human serotonin receptor subtype, which was

characterized through molecular cloning and pharmacology as detailed in Saltzman et al., *Biochem. Biophys. Res. Comm.* 181:1469-78; and Julius et al., *Proc. Natl. Acad. Sci. USA* 87:928-932, the disclosures of which are incorporated herein by reference in their entireties.

[0024] The term "subject" refers to an animal, preferably a mammal, most preferably a human, who is the object of treatment, observation or experiment.

[0025] "Selective" is defined as a property of a compound whereby an amount of the compound sufficient to effect a desired response from a particular receptor type, subtype, class or subclass with significantly less or substantially little or no effect upon the activity other receptor types. For example, a selective compound may have at least a 10-fold greater effect on activity of the desired receptor than on other receptor types. In some cases, a selective compound may have at least a 20-fold greater effect on activity of the desired receptor than on other receptor types, or at least a 50-fold greater effect, or at least a 100-fold greater effect, or at least a 1000-fold greater effect, or at least a 10,000-fold greater effect, or at least a 100,000-fold greater effect, or more than a 100,000-fold greater effect. "Selectivity" or "selective," as an inverse agonist is understood as a property of the compound of the invention whereby an amount of compound that effectively inversely agonizes the 5-HT2A receptor, and thereby decreases its activity, causes little or no inverse agonistic or antagonistic activity at other, related or unrelated, receptors. In particular, in one embodiment, a compound has surprisingly been found not to interact strongly with other serotonin receptors (5-HT 1A, 1B, 1D, 1E, 1F, 2B, 2C, 4A, 6, and 7) at concentrations where the signaling of the 5-HT2A receptor is strongly or completely inhibited. In one embodiment, the compound is also selective with respect to other monoamine-binding receptors, such as the dopaminergic, histaminergic, adrenergic and muscarinic receptors. Compounds that are highly selective for 5-HT2A receptors may have a beneficial effect in the treatment of psychosis, schizophrenia or similar neuropsychiatric disorders, while avoiding adverse effects associated with drugs hitherto suggested for this purpose.

[0026] Serotonin or 5-hydroxytryptamine (5-HT) plays a significant role in the functioning of the mammalian body. In the central nervous system, 5-HT is an important neurotransmitter and neuromodulator that is implicated in such diverse behaviors and responses as sleeping, eating, locomotion, perceiving pain, learning and memory, sexual behavior, controlling body temperature and blood pressure. In the spinal column,

serotonin plays an important role in the control systems of the afferent peripheral nociceptors (Moulignier, *Rev. Neurol.* 150:3-15, (1994)). Peripheral functions in the cardiovascular, hematological, and gastrointestinal systems have also been ascribed to 5-HT. 5-HT has been found to mediate a variety of contractile, secretory, and electrophysiologic effects including vascular and nonvascular smooth muscle contraction, and platelet aggregation. (Fuller, *Biology of Serotonergic Transmission,* 1982; Botillin, *Serotonin In Mental Abnormalities* 1:316 (1978); Barchas, et al., *Serotonin and Behavior,* (1973)). The 5-HT2A receptor subtype (also referred to as subclass) is widely yet discretely expressed in the human brain, including many cortical, limbic, and forebrain regions postulated to be involved in the modulation of higher cognitive and affective functions. This receptor subtype is also expressed on mature platelets where it mediates, in part, platelet aggregation, one of the initial steps in the process of vascular thrombosis.

[0027] Given the broad distribution of serotonin within the body, it is understandable that tremendous interest in drugs that affect serotonergic systems exists (Gershon, et at, The *Peripheral Actions of 5-Hydroxytryptamine,* 246 (1989); Saxena, et at, *J. Cardiovascular Pharmacol.* 15: Supp. 7 (1990)). Serotonin receptors are members of a large human gene family of membrane-spanning proteins that function as transducers of intercellular communication. They exist on the surface of various cell types, including neurons and platelets, where, upon their activation by either their endogenous ligand serotonin or exogenously administered drugs, they change their conformational structure and subsequently interact with downstream mediators of cellular signaling. Many of these receptors, including the 5-HT2A subclass, are G-protein coupled receptors (GPCRs) that signal by activating guanine nucleotide binding proteins (G-proteins), resulting in the generation, or inhibition of, second messenger molecules such as cyclic AMP, inositol phosphates, and diacylglycerol. These second messengers then modulate the function of a variety of intracellular enzymes, including kinases and ion channels, which ultimately affect cellular excitability and function.

[0028] At least 15 genetically distinct 5-HT receptor subtypes have been identified and assigned to one of seven families (5-HTl-7). Each subtype displays a unique distribution, preference for various ligands, and functional correlate(s). Serotonin may be an important component in various types of pathological conditions such as certain psychiatric disorders (depression, aggressiveness, panic attacks, obsessive compulsive disorders, psychosis, schizophrenia, suicidal tendency), certain

neurodegenerative disorders (Alzheimer-type dementia, Parkinsonism, Huntington's chorea), anorexia, bulimia, disorders associated with alcoholism, cerebral vascular accidents, and migraine (Meltzer, *Neuropsychopharmacology,* 21:106S-115S (1999); Barnes & Sharp, *Neuropharmacology,* 38:1083-1152 (1999); Glennon, *Neurosci. Biobehavioral Rev.,* 14:35 (1990)). Recent evidence strongly implicates the 5-HT2 receptor subtype in the etiology of such medical conditions as hypertension, thrombosis, migraine, vasospasm, ischemia, depression, anxiety, psychosis, schizophrenia, sleep disorders and appetite disorders.

[0029] In one aspect, the present invention relates to a method of treating depression in a patient comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of a first compound in combination with a therapeutically effective amount of a second compound.

[0030] In another aspect, the present invention relates to a method of treating mania in a patient comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of a first compound in combination with a therapeutically effective amount of a second compound.

[0031] In yet another aspect, the present invention relates to a method of treating social phobia in a patient comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of a first compound in combination with a therapeutically effective amount of a second compound.

[0032] In a further aspect, the present invention relates to a method of treating psychosis in a patient comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of a first compound in combination with a therapeutically effective amount of a second compound.

[0033] In another aspect, the present invention relates to a method of treating a neuropsychiatric disorder in a patient comprising identifying a patient in need thereof, and administering to said patient a therapeutically effective amount of a first compound in combination with a therapeutically effective amount of a second compound. In some embodiments, the neuropsychiatric disorder is selected from the group consisting of schizophrenia and related idiopathic psychoses, anxiety, sleep disorders, appetite disorders, affective disorders such as major depression, bipolar disorder, and depression with psychotic features, and Tourette's Syndrome, drug-induced psychoses, psychoses secondary to neurodegenerative disorders such Alzheimer's or Huntington's Disease.

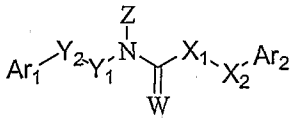
[0034] In still another aspect, the present invention relates to a method of treating insomnia in a patient comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of a first compound in combination with a therapeutically effective amount of a second compound.

[0035] The term "therapeutically effective amount" as used herein means an amount of an active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation, amelioration, or lessening of the symptoms of the disease being treated, or prevents or slows the progress of the disease or increase of the symptoms.

[0036] In certain embodiments, the patient may be a mammal. The mammal may be selected from the group consisting of mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, primates, such as monkeys, chimpanzees, and apes, and humans. In some embodiments, the patient is a human.

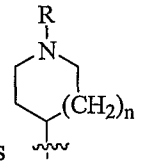
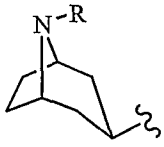
[0037] In some embodiments, the first compound in the above methods is an inverse agonist selective for a serotonin receptor. In certain embodiments, the serotonin receptor is a 5HT2A receptor, while in other embodiments the serotonin receptor is a 5HT2C receptor. In other embodiments, the inverse agonists binds to a 5HT2A receptor and a 5HT2C receptor.

[0038] In some embodiments, the first compound is a compound of formula (III)



III

where

Z is  or , wherein R is a hydrogen, a cyclic or straight-chained or branched acyclic organyl group, a lower hydroxyalkyl group, a lower aminoalkyl group, or an aralkyl or heteroaralkyl group; and n is 1;

X_1 is methylene, vinylene, or an NH or N(lower alkyl) group; and X_2 is methylene; or, when X_1 is methylene or vinylene, X_2 is methylene or a bond; or when X_1 is methylene, X_2 is O, S, NH, or N(lower alkyl) or a bond;

Y_1 is methylene and Y_2 is methylene, vinylene, ethylene, propylene, or a bond; or

Y_1 is a bond and Y_2 is vinylene; or

Y_1 is ethylene and Y_2 is O, S, NH, or N(lower alkyl);

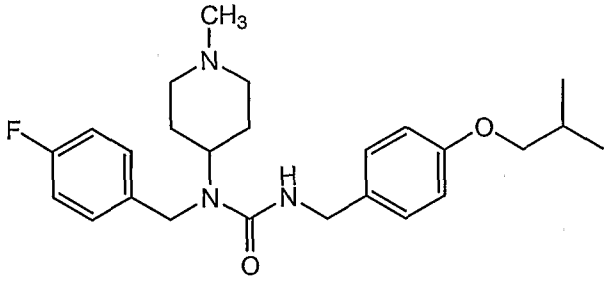
Ar_1 and Ar_2 independently are unsubstituted or substituted aryl or heteroaryl groups, provided that Ar_1 and Ar_2 are not simultaneously unsubstituted phenyl; and

W is oxygen; or

a pharmaceutically acceptable salt or prodrug thereof.

[0039] In other embodiments, the first compound is a compound disclosed in U.S. Patent Application Publication Serial No. 2002/0004513 A1, published on January 10, 2002, by Andersson et al., and entitled "AZACYCLIC COMPOUNDS," which is the publication of the U.S. Application Serial No. 09/800,096, or in U.S. Patent Application Publication Serial No. 2003/0220316 A1, published on November 27, 2003, by Andersson et al., and entitled "AZACYCLIC COMPOUNDS," which is the publication of the U.S. Application Serial No. 10/409,782, or in U.S. Application Serial No. 10/802,970, filed on March 16, 2004, by Andersson et al., and entitled "AZACYCLIC COMPOUNDS," the entire disclosure of all of which is hereby incorporated by reference herein in their entirety, including any drawings.

[0040] In another embodiment, the first compound is N-(1-methylpiperidin-4-yl)-N-(4-fluorophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide, which is the compound of Formula (I):



(I)

[0041] In another embodiment, the first compound in the above methods is an antagonist selective for a serotonin receptor. In certain embodiments, the serotonin receptor is a 5HT2A receptor, while in other embodiments the serotonin receptor is a

5HT2C receptor. In other embodiments, the antagonists binds to a 5HT2A receptor and a 5HT2C receptor.

[0042] In some embodiments, the second compound in the above methods is a selective serotonin reuptake inhibitor (SSRI). Examples of SSRIs include, but are not limited to, bupropion (Wellbutrin, Zyban), citalopram (Celexa), duloxetine, escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertaline (Zoloft), sibutramine, trazodone (Dividose), and venlafaxine. Any other SSRI currently known or later developed are within the scope of the present disclosure.

[0043] In other embodiments, the second compound in the above methods is a serotonin/norepinephrine reuptake inhibitor (SNRI). Examples of SNRIs include, but are not limited to, citalopram (Celexa), dulexetine, escitalopram (Lexapro), fluvoxamine (Luvox), and venfalaxine (effexor). Any other SNRI currently known or later developed are within the scope of the present disclosure.

[0044] In further embodiments, the second compound in the above methods is a monoamine oxidase inhibitor (MAO-I). Examples of MAO-Is include, but are not limited to, tranylcypromine (Parnate), phenelzine (Nardil), maprotiline, and isocarboxazid (Marplan). Any other MAO-I currently known or later developed are within the scope of the present disclosure.

[0045] In yet other embodiments, the second compound in the above methods is a tricyclic antidepressant (TCA). Examples of TCAs include, but are not limited to, amitryptiline (Norpramine), amoxapineclomipramine (Anafranil), desipramine, doxepin (Sinequan), imipramine (Tofranil), maprotiline, (Elavil), protryptiline, and trimipramine. Any other TCA currently known or later developed are within the scope of the present disclosure.

[0046] In some other embodiments, the second compound in the above methods is a compound selected from aripiprazole (Abilify), clozapine, fluoxetine/olanzapine (Symbyax), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakote), and ziprasidone (Geodon). Any other atypical antidepressant currently known or later developed are within the scope of the present disclosure.

[0047] In some embodiments, the second compound in the above methods is a compound selected from chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), thioridazine (Mellaril®), haloperidol (Haldol®),

pimozide (Orap®), clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®), quetiapine (Seroquel®), resperidone (Resperidal®), ziprasidone (Geodon®), lithium carbonate, Aripiprazole (Abilify), Clozapine, Clozaril, Compazine, Etrafon, Geodon, Haldol, Inapsine, Loxitane, Mellaril, Moban, Navane, Olanzapine (Zyprexa), Orap, Permitil, Prolixin, Phenergan, Quetiapine (Seroquel), Reglan, Risperdal, Serentil, Seroquel, Stelazine, Taractan, Thorazine, Triavil, Trilafon, and Zyprexa.

[0048] In some embodiments, the second compound in the above methods is an antipsychotic agent. The antipsychotic agent may be selected from the group consisting of a phenothiazine, phenylbutylpiperadine, debenzapine, benzisoxidil, and salt of lithium. The phenothiazine group of compounds may be selected from the group consisting of chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), and thioridazine (Mellaril®). The phenylbutylpiperadine group of compounds may be selected from the group consisting of haloperidol (Haldol®), and pimozide (Orap®). The debenzapine group of compounds may be selected from the group consisting of clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®) and quetiapine (Seroquel®). The benzisoxidil group of compounds may be selected from the group consisting of resperidone (Resperidal®) and ziprasidone (Geodon®). The salt of lithium may be lithium carbonate. In some embodiments, the antipsychotic agent may be selected from the group consisting of Aripiprazole (Abilify), Clozapine, Clozaril, Compazine, Etrafon, Geodon, Haldol, Inapsine, Loxitane, Mellaril, Moban, Navane, Olanzapine (Zyprexa), Orap, Permitil, Prolixin, Phenergan, Quetiapine (Seroquel), Reglan, Risperdal, Serentil, Seroquel, Stelazine, Taractan, Thorazine, Triavil, Trilafon, and Zyprexa, or pharmaceutically acceptable salts thereof.

[0049] In other embodiments, the second compound in the above methods is a norepinephrine reuptake inhibitor. The norepinephrine reuptake inhibitor is selected from the group consisting of thionisoxetine and reboxetine.

[0050] In further embodiments, the second compound in the above methods is a dopamine agonist. The dopamine agonist may be selected from the group consisting of sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine.

[0051] In yet another embodiment, the second compound in the above methods is an anti-insomnia drug. Examples of anti-insomnia drugs include, but are not limited to, alprazolam (Xanax), chlordiazepoxide (Librium, Limbitrol), clorazepate

(Tranxene), estazolam (ProSom), flurazepam (Dalmane), hydroxyzine (Atarax), lorazepam (Ativan), pentobarbital (Nembutal), quazepam (Doral), secobarbital (Seconal), temazepam (Restoril), triazolam (Halcion), valium, zaleplon (Sonata), zolpidem (Ambien), and the benzodiazepine family of drugs. Any other anti-insomnia drug currently known or later developed are within the scope of the present disclosure.

[0052] In other embodiments, the second compound in the above methods is an anti-manic drug. Examples of anti-manic drugs include, but are not limited to, divalproex (Depakote), lithium carbonate (Eskalith), and lithium citrate. Any other anti-manic drug currently known or later developed are within the scope of the present disclosure.

[0053] In some embodiments, the second compound in the above methods is an anti-phobia drug. An example of anti-phobia drugs includes, but is not limited to, D-cycloserine. Those of skill in the art recognize that some of the other drugs disclosed herein also work as anti-phobia drugs. Any other anti-manic drug currently known or later developed are within the scope of the present disclosure.

[0054] Insomnia is a heterogeneous, highly prevalent condition that is associated with increased risk of new or recurrent psychiatric disorders, increased daytime sleepiness with consequent cognitive impairment, poorer prognoses, reduced quality of life and high healthcare-related financial burden. Emerging data suggest that resolution of insomnia may improve psychiatric outcomes. The nature of insomnia can differ among individuals with some individuals presenting with difficulties in falling asleep (sleep induction), difficulties staying asleep (sleep maintenance) or a combination of both. It is difficult to titrate the sleep inducing effects from the sleep maintenance effects when a single anti-insomnia drug is used. Therefore, some patients with only sleep induction or only sleep maintenance difficulties may be treated with a drug that treats both kinds of sleep disturbances. Another way to tailor a sleep medications to the specific sleep complaint of a patient is to use two different anti-insomnia drugs in combination, ideally one drug would primarily induce sleep and a second drug would primarily improve sleep maintenance. A sleep inducing agent may be selected from the general classes of barbiturates, benzodiazepines, direct GABA agonists, positive allosteric modulators of GABA receptors, histamine receptor antagonists, histamine receptor inverse agonists and others. Sleep maintenance agents can be selected from drugs that are antagonist or are inverse agonist at the general class of 5-HT2 receptors, more specifically agents that are

antagonists and/or inverse agonists at the 5-HT2A and/or 5-HT2C receptors. These include: drugs like ritanserin, ketanserin, MDL 100,907, eplivanserin, the compound of formula I and others.

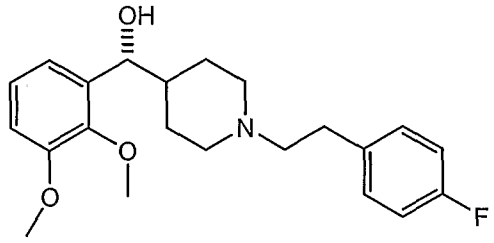
[0055] The treatment of insomnia involves primarily pharmacological interventions. Until recently the treatments of choice have been the benzodiazepines. However, this class of drugs has been associated with a number of adverse effects including tolerance, dependence, withdrawal and abuse potential, impairment in daytime cognitive and psychomotor performance (including an increased risk of accidents and falls), adverse effects on respiration and the disruption of normal sleep architecture with reduction in both slow wave sleep and rapid eye movement. More recently newer non-benzodiazepine hypnotics have emerged including zolpidem, zopiclone, eszopiclone (Lunesta), zaleplon, gaboxadol, indiplon, and beta carbolines like abecarnil. These agents primarily act by enhancing the activity of the GABA(A) receptor. These therapies have proven effective with reducing time to sleep onset, decreasing wake time after sleep onset and sleep maintenance and reducing the number of nighttime awakenings. However, these newer drugs still produce side effects that ultimately may limit their use.

[0056] An extensive body of research exists on CNS effects of H1-antagonists. These include both subjective (e.g., self-rating of increased drowsiness) and objective (e.g. EEG measurement of sleep latency) estimates of sedation, and from simple (e.g., critical flicker fusion) to the complex tasks (e.g., impaired driving). There is a distinction between the older first-generation H1-antagonists and the newer second-generation ones. At the recommended dosages, all the second-generation H1-antagonists are less sedating in more patients than their predecessors. This is largely attributable to poor brain penetrating properties of the newer medications when compared to the older H1 antagonists. However, higher dose of even the newer H1 antagonists also induce sleep. The common sedative properties produced by most H1-antagonists remain a major concern and, therefore, these compounds are no longer medications of choice in the treatment of allergic rhinitis, allergic conjunctivitis, or urticaria. However, these drugs may find a new utility in treating sleep induction problems. Particularly, when used in combination with sleep maintenance agents.

[0057] Accordingly, in one embodiment, the second compound in the above methods is an anti-insomnia drug that is an H1 antagonist or inverse agonist. Examples of H1 antagonists include, but are not limited to azatadine, astemizole, brompheniramine,

carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, ktotifen, leocabastine, meclizine, mepramine, manserin, promethazine, tipelennamine, triprolidine, acrivastine, cetrizine, desloratadine, fexofenadine, and loratidine. Any other H1 antagonist or inverse agonist currently known or later developed are also within the scope of the present disclosure.

[0058] In other embodiments, the first or second compound in the above methods is a serotonin 2A antagonist. The serotonin 2A antagonist may be M 100,907 or an analog thereof. By "M 100,907," it is meant the compound of Formula II.



(II)

[0059] In some embodiments, a first compound of Formula (I) is administered in combination with a second compound of Formula (II). In other embodiments, a first compound of Formula (II) is administered in combination with a second compound selected from the group consisting of a SSRI including but not limited to bupropion (Wellbutrin, Zyban), citalopram (Celexa), duloxetine, escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertaline (Zoloft), sibutramine, trazodone (Dividose), and venlafaxine; a SNRI including but not limited to citalopram (Celexa), dulexetine, escitalopram (Lexapro), fluvoxamine (Luvox), and venfalaxine (effexor); a MAO-I including but are not limited to tranylcypromine (Parnate), phenelzine (Nardil), maprotiline, and isocarboxazid (Marplan); a TCA including but not limited to amitryptiline (Norpramine), amoxapineclomipramine (Anafranil), desipramine, doxepin (Sinequan), imipramine (Tofranil), maprotiline, (Elavil), protryptiline, and trimipramine; aripiprazole (Abilify); clozapine; fluoxetine/olanzapine (Symbyax); olanzapine (Zyprexa); quetiapine (Seroquel); risperidone (Risperdal); valproic acid (Depakote); ziprasidone (Geodon); chlorpromazine (Thorazine®); mesoridazine (Serentil®); prochlorperazine (Compazine®); thioridazine (Mellaril®); haloperidol (Haldol®); pimozide (Orap®); clozapine (Clozaril®); loxapine (Loxitane®); olanzapine (Zyprexa®); quetiapine (Seroquel®); resperidone (Resperidal®); ziprasidone (Geodon®); lithium carbonate; Aripiprazole (Abilify); Clozapine; Clozaril;

Compazine; Etrafon; Geodon; Haldol; Inapsine; Loxitane; Mellaril; Moban; Navane; Olanzapine (Zyprexa); Orap; Permitil; Prolixin; Phenergan; Quetiapine (Seroquel); Reglan; Risperdal; Serentil; Seroquel; Stelazine; Taractan; Thorazine; Triavil; Trilafon; Zyprexa; an antipsychotic agent including but not limited to a phenothiazine such as chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), and thioridazine (Mellaril®), a phenylbutylpiperadine such as haloperidol (Haldol®) and pimozide (Orap®), a debenzapine such as clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®) and quetiapine (Seroquel®), a benzisoxidil such as resperidone (Resperidal®) and ziprasidone (Geodon®), a salt of lithium such as lithium carbonate, Aripiprazole (Abilify), Etrafon Haldol, Inapsine, Mellaril, Moban, Navane, Permitil, Prolixin, Phenergan, Reglan, Risperdal, Stelazine, Taractan, Triavil, and Trilafon; a norepinephrine reuptake inhibitor including but not limited to thionisoxetine and reboxetine; a dopamine agonist including but not limited to sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine; an anti-insomnia drug including but not limited to alprazolam (Xanax), chlordiazepoxide (Librium, Limbitrol), clorazepate (Tranxene), estazolam (ProSom), flurazepam (Dalmane), hydroxyzine (Atarax), lorazepam (Ativan), pentobarbital (Nembutal), quazepam (Doral), secobarbital (Seconal), temazepam (Restoril), triazolam (Halcion), valium, zaleplon (Sonata), zolpidem (Ambien), the benzodiazepine family of drugs, azatadine, astemizole, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, ktotifen, leocabastine, meclizine, mepramine, manserin, promethazine, tipelennamine, triprolidine, acrivastine, cetrizine, desloratadine, fexofenadine, and loratidine; an anti-manic drug including but not limited to divalproex (Depakote), lithium carbonate (Eskalith), and lithium citrate; an anti-phobia drug including but not limited to D-cycloserine; and pharmaceutically acceptable salts thereof.

[0060] In some embodiments, the administering step in the above methods comprises administering the first compound and the second compound simultaneously. These embodiments include those in which the first compound and the second compound are in the same administrable composition, i.e., a single tablet, pill, or capsule, or a single solution for intravenous injection, or a single drinkable solution, or a single dragee formulation or patch, contains both compounds. The embodiments also include those in which each compound is in a separate administrable composition, but the patient is

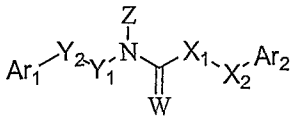
directed to take the separate compositions nearly simultaneously, i.e., one pill is taken right after the other or that one injection of one compound is made right after the injection of another compound, etc.

[0061] In other embodiments the administering step comprises administering one of the first compound and the second compound first and then administering the other one of the first compound and the second compound. In these embodiments, the patient may be administered a composition comprising one of the compounds and then at some time, a few minutes or a few hours, later be administered another composition comprising the other one of the compounds. Also included in these embodiments are those in which the patient is administered a composition comprising one of the compounds on a routine or continuous basis while receiving a composition comprising the other compound occasionally.

[0062] In another aspect, the present invention relates to a pharmaceutical composition comprising a first compound and a second compound.

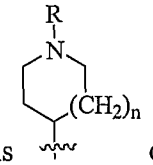
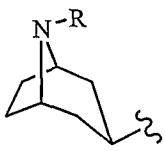
[0063] In some embodiments, the first compound in the above pharmaceutical composition is an inverse agonist selective for a serotonin receptor. In certain embodiments, the serotonin receptor is a 5HT2A receptor, while in other embodiments the serotonin receptor is a 5HT2C receptor. In other embodiments, the inverse agonists binds to a 5HT2A receptor and a 5HT2C receptor.

[0064] In some embodiments, the first compound is a compound of formula (III)



III

where

Z is  or , wherein R is a hydrogen, a cyclic or straight-chained or branched acyclic organyl group, a lower hydroxyalkyl group, a lower aminoalkyl group, or an aralkyl or heteroaralkyl group; and n is 1;

X_1 is methylene, vinylene, or an NH or N(lower alkyl) group; and X_2 is methylene; or, when X_1 is methylene or vinylene, X_2 is methylene or a bond; or when X_1 is methylene, X_2 is O, S, NH, or N(lower alkyl) or a bond;

Y_1 is methylene and Y_2 is methylene, vinylene, ethylene, propylene, or a bond; or

Y_1 is a bond and Y_2 is vinylene; or

Y_1 is ethylene and Y_2 is O, S, NH, or N(lower alkyl);

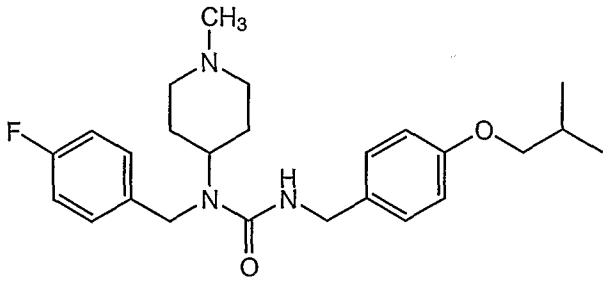
Ar_1 and Ar_2 independently are unsubstituted or substituted aryl or heteroaryl groups, provided that Ar_1 and Ar_2 are not simultaneously unsubstituted phenyl; and

W is oxygen; or

a pharmaceutically acceptable salt or prodrug thereof.

[0065] In other embodiments, the first compound is a compound disclosed in U.S. Patent Application Publication Serial No. 2002/0004513 A1, published on January 10, 2002, by Andersson et al., and entitled "AZACYCLIC COMPOUNDS," which is the publication of the U.S. Application Serial No. 09/800,096, or in U.S. Patent Application Publication Serial No. 2003/0220316 A1, published on November 27, 2003, by Andersson et al., and entitled "AZACYCLIC COMPOUNDS," which is the publication of the U.S. Application Serial No. 10/409,782, or in U.S. Application Serial No. 10/802,970, filed on March 16, 2004, by Andersson et al., and entitled "AZACYCLIC COMPOUNDS," the entire disclosures of all of which are hereby incorporated by reference herein in their entirety, including any drawings.

[0066] In another embodiment, the first compound is N-(1-methylpiperidin-4-yl)-N-(4-fluorophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide, which is the compound of Formula (I):



(I)

[0067] In another embodiment, the first compound in the above pharmaceutical composition is an antagonist selective for a serotonin receptor. In certain embodiments, the serotonin receptor is a 5HT2A receptor, while in other embodiments

the serotonin receptor is a 5HT2C receptor. In other embodiments, the antagonists binds to a 5HT2A receptor and a 5HT2C receptor.

[0068] In some embodiments, the second compound in the above pharmaceutical composition is a selective serotonin reuptake inhibitor (SSRI). Examples of SSRIs include, but are not limited to, bupropion (Wellbutrin, Zyban), citalopram (Celexa), duloxetine, escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertaline (Zoloft), sibutramine, trazodone (Dividose), and venlafaxine. Any other SSRI currently known or later developed are within the scope of the present disclosure.

[0069] In other embodiments, the second compound in the above pharmaceutical composition is a serotonin/norepinephrine reuptake inhibitor (SNRI). Examples of SNRIs include, but are not limited to, citalopram (Celexa), dulexetine, escitalopram (Lexapro), fluvoxamine (Luvox), and venfalaxine (effexor). Any other SNRI currently known or later developed are within the scope of the present disclosure.

[0070] In further embodiments, the second compound in the above pharmaceutical composition is a monoamine oxidase inhibitor (MAO-I). Examples of MAO-Is include, but are not limited to, tranylcypromine (Parnate), phenelzine (Nardil), maprotiline, and isocarboxazid (Marplan). Any other MAO-I currently known or later developed are within the scope of the present disclosure.

[0071] In yet other embodiments, the second compound in the above pharmaceutical composition is a tricyclic antidepressant (TCA). Examples of TCAs include, but are not limited to, amitryptiline (Norpramine), amoxapineclomipramine (Anafranil), desipramine, doxepin (Sinequan), imipramine (Tofranil), maprotiline, (Elavil), protryptiline, and trimipramine. Any other TCA currently known or later developed are within the scope of the present disclosure.

[0072] In some other embodiments, the second compound in the above pharmaceutical composition is a compound selected from aripiprazole (Abilify), clozapine, fluoxetine/olanzapine (Symbyax), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakote), and ziprasidone (Geodon). Any other atypical antidepressant currently known or later developed are within the scope of the present disclosure.

[0073] In some embodiments, the second compound in the above pharmaceutical composition is a compound selected from chlorpromazine (Thorazine®),

mesoridazine (Serentil®), prochlorperazine (Compazine®), thioridazine (Mellaril®), haloperidol (Haldol®), pimozide (Orap®), clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®), quetiapine (Seroquel®), resperidone (Resperidal®), ziprasidone (Geodon®), lithium carbonate, Aripiprazole (Abilify), Clozapine, Clozaril, Compazine, Etrafon, Geodon, Haldol, Inapsine, Loxitane, Mellaril, Moban, Navane, Olanzapine (Zyprexa), Orap, Permitil, Prolixin, Phenergan, Quetiapine (Seroquel), Reglan, Risperdal, Serentil, Seroquel, Stelazine, Taractan, Thorazine, Triavil, Trilafon, and Zyprexa.

[0074] In some embodiments, the second compound in the above pharmaceutical composition is an antipsychotic agent. The antipsychotic agent may be selected from the group consisting of a phenothiazine, phenylbutylpiperadine, debenzapine, benzisoxidil, and salt of lithium. The phenothiazine group of compounds may be selected from the group consisting of chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), and thioridazine (Mellaril®). The phenylbutylpiperadine group of compounds may be selected from the group consisting of haloperidol (Haldol®), and pimozide (Orap®). The debenzapine group of compounds may be selected from the group consisting of clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®) and quetiapine (Seroquel®). The benzisoxidil group of compounds may be selected from the group consisting of resperidone (Resperidal®) and ziprasidone (Geodon®). The salt of lithium may be lithium carbonate. In some embodiments, the antipsychotic agent may be selected from the group consisting of Aripiprazole (Abilify), Clozapine, Clozaril, Compazine, Etrafon, Geodon, Haldol, Inapsine, Loxitane, Mellaril, Moban, Navane, Olanzapine (Zyprexa), Orap, Permitil, Prolixin, Phenergan, Quetiapine (Seroquel), Reglan, Risperdal, Serentil, Seroquel, Stelazine, Taractan, Thorazine, Triavil, Trilafon, and Zyprexa, or pharmaceutically acceptable salts thereof.

[0075] In other embodiments, the second compound in the above pharmaceutical composition is a norepinephrine reuptake inhibitor. The norepinephrine reuptake inhibitor is selected from the group consisting of thionisoxetine and reboxetine.

[0076] In further embodiments, the second compound in the above pharmaceutical composition is a dopamine agonist. The dopamine agonist may be selected from the group consisting of sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine.

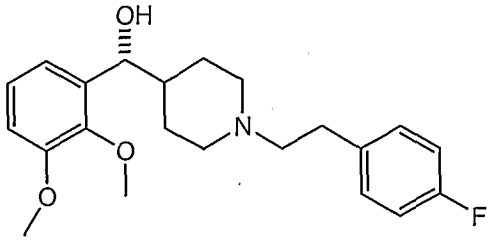
[0077] In yet another embodiment, the second compound in the above pharmaceutical composition is an anti-insomnia drug. Examples of anti-insomnia drugs include, but are not limited to, alprazolam (Xanax), chlordiazepoxide (Librium, Limbitrol), clorazepate (Tranxene), estazolam (ProSom), flurazepam (Dalmane), hydroxyzine (Atarax), lorazepam (Ativan), pentobarbital (Nembutal), quazepam (Doral), secobarbital (Seconal), temazepam (Restoril), triazolam (Halcion), valium, zaleplon (Sonata), zolpidem (Ambien), and the benzodiazepine family of drugs. Any other anti-insomnia drug currently known or later developed are within the scope of the present disclosure.

[0078] In some embodiments, the second compound in the above methods is an anti-insomnia drug that is an H1 antagonist or inverse agonist. Examples of H1 antagonists include, but are not limited to azatadine, astemizole, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, ktotifen, leocabastine, meclizine, mepramine, manserin, promethazine, tipelennamine, triprolidine, acrivastine, cetrizine, desloratadine, fexofenadine, and loratidine. Any other H1 antagonist or inverse agonist currently known or later developed are also within the scope of the present disclosure.

[0079] In other embodiments, the second compound in the above pharmaceutical composition is an anti-manic drug. Examples of anti-manic drugs include, but are not limited to, divalproex (Depakote), lithium carbonate (Eskalith), and lithium citrate. Any other anti-manic drug currently known or later developed are within the scope of the present disclosure.

[0080] In some embodiments, the second compound in the above pharmaceutical composition is an anti-phobia drug. An example of anti-phobia drugs includes, but is not limited to, D-cycloserine. Those of skill in the art recognize that some of the other drugs disclosed herein also work as anti-phobia drugs. Any other anti-manic drug currently known or later developed are within the scope of the present disclosure.

[0081] In another embodiment, the first or second compound in the above pharmaceutical composition is a serotonin 2A antagonist. The serotonin 2A antagonist may be M 100,907 or an analog thereof. By "M 100,907," it is meant the compound of Formula II.



(II)

[0082] In some embodiments, the first compound of the pharmaceutical composition is Formula (I) and the second compound of the composition is Formula (II). In other embodiments, the first compound of the pharmaceutical composition is Formula (II) and the second compound of the composition is selected from the group consisting of a SSRI including but not limited to bupropion (Wellbutrin, Zyban), citalopram (Celexa), duloxetine, escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertaline (Zoloft), sibutramine, trazodone (Dividose), and venlafaxine; a SNRI including but not limited to citalopram (Celexa), dulexetine, escitalopram (Lexapro), fluvoxamine (Luvox), and venfalaxine (effexor); a MAO-I including but are not limited to tranylcypromine (Parnate), phenelzine (Nardil), maprotiline, and isocarboxazid (Marplan); a TCA including but not limited to amitryptiline (Norpramine), amoxapineclomipramine (Anafranil), desipramine, doxepin (Sinequan), imipramine (Tofranil), maprotiline, (Elavil), protryptiline, and trimipramine; aripiprazole (Abilify); clozapine; fluoxetine/olanzapine (Symbyax); olanzapine (Zyprexa); quetiapine (Seroquel); risperidone (Risperdal); valproic acid (Depakote); ziprasidone (Geodon); chlorpromazine (Thorazine®); mesoridazine (Serentil®); prochlorperazine (Compazine®); thioridazine (Mellaril®); haloperidol (Haldol®); pimozide (Orap®); clozapine (Clozaril®); loxapine (Loxitane®); olanzapine (Zyprexa®); quetiapine (Seroquel®); resperidone (Resperidal®); ziprasidone (Geodon®); lithium carbonate; Aripiprazole (Abilify); Clozapine; Clozaril; Compazine; Etrafon; Geodon; Haldol; Inapsine; Loxitane; Mellaril; Moban; Navane; Olanzapine (Zyprexa); Orap; Permitil; Prolixin; Phenergan; Quetiapine (Seroquel); Reglan; Risperdal; Serentil; Seroquel; Stelazine; Taractan; Thorazine; Triavil; Trilafon; Zyprexa; an antipsychotic agent including but not limited to a phenothiazine such as chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), and thioridazine (Mellaril®), a phenylbutylpiperadine such as haloperidol (Haldol®) and pimozide (Orap®), a debenzapine such as clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®)

and quetiapine (Seroquel®), a benzisoxidil such as resperidone (Resperidal®) and ziprasidone (Geodon®), a salt of lithium such as lithium carbonate, Aripiprazole (Abilify), Etrafon Haldol, Inapsine, Mellaril, Moban, Navane, Permitil, Prolixin, Phenergan, Reglan, Risperdal, Stelazine, Taractan, Triavil, and Trilafon; a norepinephrine reuptake inhibitor including but not limited to thionisoxetine and reboxetine; a dopamine agonist including but not limited to sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine; an anti-insomnia drug including but not limited to alprazolam (Xanax), chlordiazepoxide (Librium, Limbitrol), clorazepate (Tranxene), estazolam (ProSom), flurazepam (Dalmane), hydroxyzine (Atarax), lorazepam (Ativan), pentobarbital (Nembutal), quazepam (Doral), secobarbital (Seconal), temazepam (Restoril), triazolam (Halcion), valium, zaleplon (Sonata), zolpidem (Ambien), the benzodiazepine family of drugs, azatadine, astemizole, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, ktotifen, leocabastine, meclizine, mepramine, manserin, promethazine, tipelennamine, triprolidine, acrivastine, cetrizine, desloratadine, fexofenadine, and loratidine; an anti-manic drug including but not limited to divalproex (Depakote), lithium carbonate (Eskalith), and lithium citrate; an anti-phobia drug including but not limited to D-cycloserine; and pharmaceutically acceptable salts thereof.

[0083] In some embodiments, the pharmaceutical compositions described herein are used to treat disorders disclosed in U.S. Patent Application Serial No. 10/759,561, filed on January 15, 2004, by Weiner et al., and entitled "SELECTIVE SEROTONIN 2A/2C RECEPTOR INVERSE AGONISTS AS THERAPEUTICS FOR NEURODEGENERATIVE DISEASES," which is hereby incorporated by reference herein in its entirety, including any drawings.

[0084] It is understood by those of skill in the art that the compounds disclosed herein may be present as the compounds themselves, or as pharmaceutically acceptable salts, esters, amides, or prodrugs thereof, all of which are contemplated by the present invention.

[0085] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound of the invention

with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can also be obtained by reacting a compound of the invention with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

[0086] The term "ester" refers to a chemical moiety with formula $-(R)_n-COOR'$, where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1.

[0087] An "amide" is a chemical moiety with formula $-(R)_n-C(O)NHR'$ or $-(R)_n-NHC(O)R'$, where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1. An amide may be an amino acid or a peptide molecule attached to a molecule of the present invention, thereby forming a prodrug.

[0088] Any amine, hydroxy, or carboxyl side chain on any of the compounds disclosed herein can be esterified or amidified. The procedures and specific groups to be used to achieve this end are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein in its entirety.

[0089] A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further

example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

[0090] In some embodiments, the pharmaceutical composition described herein further comprises a physiologically acceptable carrier, diluent, or excipient, or a combination thereof.

[0091] The term "pharmaceutical composition" refers to a mixture of a compound of the invention with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0092] The term "carrier" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

[0093] The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

[0094] The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

[0095] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

[0096] Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

[0097] Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly in the renal or cardiac area, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

[0098] The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

[0099] Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

[0100] For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0101] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with pharmaceutical combination of the invention, optionally grinding the resulting mixture, and processing the mixture of

granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0102] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0103] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[0104] For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0105] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0106] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0107] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0108] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0109] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0110] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0111] A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A common cosolvent system used is the VPD co-solvent system, which is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. Naturally, the proportions of a co-solvent system may be

varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0112] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0113] Many of the compounds used in the pharmaceutical combinations of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acid or base forms.

[0114] Pharmaceutical compositions suitable for use in the present invention include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0115] The exact formulation, route of administration and dosage for the pharmaceutical compositions of the present invention can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The

Pharmacological Basis of Therapeutics", Ch. 1 p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.5 to 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient. Note that for almost all of the specific compounds mentioned in the present disclosure, human dosages for treatment of at least some condition have been established. Thus, in most instances, the present invention will use those same dosages, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compounds, a suitable human dosage can be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0116] Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.1 mg and 500 mg of each ingredient, preferably between 1 mg and 250 mg, e.g. 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of each ingredient between 0.01 mg and 100 mg, preferably between 0.1 mg and 60 mg, e.g. 1 to 40 mg of each ingredient of the pharmaceutical compositions of the present invention or a pharmaceutically acceptable salt thereof calculated as the free base, the composition being administered 1 to 4 times per day. Alternatively the compositions of the invention may be administered by continuous intravenous infusion, preferably at a dose of each ingredient up to 400 mg per day. Thus, the total daily dosage by oral administration of each ingredient will typically be in the range 1 to 2000 mg and the total daily dosage by parenteral administration will typically be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years.

[0117] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

[0118] Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0119] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0120] The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

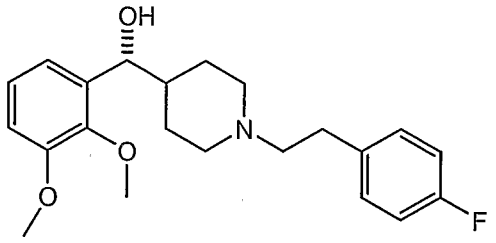
[0121] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

a first compound selected from the group consisting of an inverse agonist of a serotonin receptor, an antagonist of a serotonin receptor, and pharmaceutically acceptable salts thereof; and

a second compound selected from the group consisting of a SSRI, a SNRI, a MAO-I, a TCA, an antipsychotic agent, a norepinephrine reuptake inhibitor, a dopamine agonist, an anti-insomnia drug, an anti-manic drug, an anti-phobia drug, the compound of Formula (II)

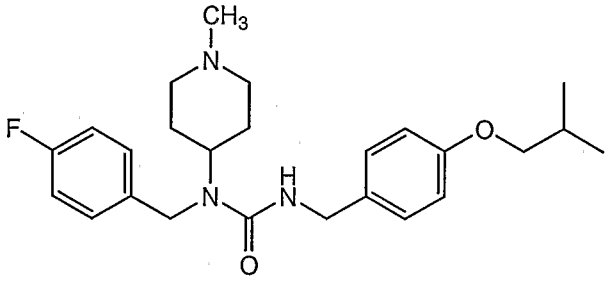


(II)

and pharmaceutically acceptable salts thereof.

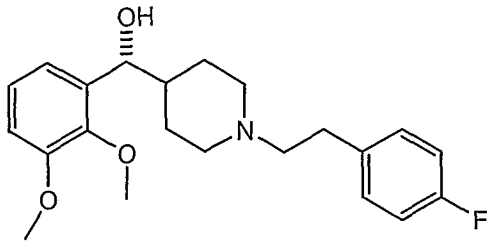
2. The pharmaceutical composition of claim 1, wherein the serotonin receptor is a 5HT2A receptor.

3. The pharmaceutical composition of claim 2, wherein the first compound is a compound of Formula (I):



(I)

4. The pharmaceutical composition of claim 2, wherein the first compound is a compound of Formula (II):



(II)

and the second compound selected from the group consisting of a SSRI, a SNRI, a MAO-I, a TCA, an antipsychotic agent, a norepinephrine reuptake inhibitor, a dopamine agonist, an anti-insomnia drug, an anti-manic drug, and an anti-phobia drug.

5. The pharmaceutical composition of claim 1, wherein the SSRI is selected from the group consisting of bupropion (Wellbutrin, Zyban), citalopram (Celexa), duloxetine, escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertaline (Zoloft), sibutramine, trazodone (Dividose), and venlafaxine.

6. The pharmaceutical composition of claim 1, wherein the SNRI is selected from the group consisting of citalopram (Celexa), dulexetine, escitalopram (Lexapro), fluvoxamine (Luvox), and venfalaxine (effexor).

7. The pharmaceutical composition of claim 1, wherein the MAO-I is selected from the group consisting of tranylcypromine (Parnate), phenelzine (Nardil), maprotiline, and isocarboxazid (Marplan).

8. The pharmaceutical composition of claim 1, wherein the TCA is selected from the group consisting of amitryptiline (Norpramine), amoxapineclomipramine (Anafranil), desipramine, doxepin (Sinequan), imipramine (Tofranil), maprotiline, (Elavil), protryptiline, and trimipramine.

9. The pharmaceutical composition of claim 1, wherein the antipsychotic agent is selected from the group consisting of a phenothiazine, a phenylbutylpiperadine, a debenzapine, a benzisoxidil, and a salt of lithium.

10. The pharmaceutical composition of claim 9, wherein the phenothiazine is selected from the group consisting of chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), and thioridazine (Mellaril®).

11. The pharmaceutical composition of claim 9, wherein the phenylbutylpiperadine is selected from the group consisting of haloperidol (Haldol®) and pimozide (Orap®).

12. The pharmaceutical composition of claim 9, wherein the debenzapine is selected from the group consisting of clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®), and quetiapine (Seroquel®).

13. The pharmaceutical composition of claim 9, wherein the benzisoxidil is selected from the group consisting of resperidone (Resperidal®) and ziprasidone (Geodon®).

14. The pharmaceutical composition of claim 9, wherein the salt of lithium is lithium carbonate.

15. The pharmaceutical composition of claim 1, wherein the antipsychotic agent is selected from the group consisting of Aripiprazole (Abilify), Etrafon Haldol, Inapsine, Mellaril, Moban, Navane, Permitil, Prolixin, Phenergan, Reglan, Risperdal, Stelazine, Taractan, Triavil, and Trilafon.

16. The pharmaceutical composition of claim 1, wherein the norepinephrine reuptake inhibitor is selected from the group consisting of thionisoxetine and reboxetine.

17. The pharmaceutical composition of claim 1, wherein the dopamine agonist is selected from the group consisting of sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine.

18. The pharmaceutical composition of claim 1, wherein the anti-insomnia drug is selected from the group consisting of alprazolam (Xanax), chlordiazepoxide (Librium, Limbitrol), clorazepate (Tranxene), estazolam (ProSom), flurazepam (Dalmane), hydroxyzine (Atarax), lorazepam (Ativan), pentobarbital (Nembutal), quazepam (Doral), secobarbital (Seconal), temazepam (Restoril), triazolam (Halcion), valium, zaleplon (Sonata), zolpidem (Ambien), and the benzodiazepine family of drugs.

19. The pharmaceutical composition of claim 1, wherein the anti-insomnia drug is an H1 antagonist or inverse agonist.

20. The pharmaceutical composition of claim 19, wherein the H1 antagonist or inverse agonist is selected from the group consisting of azatadine, astemizole, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, ktotifen, leocabastine,

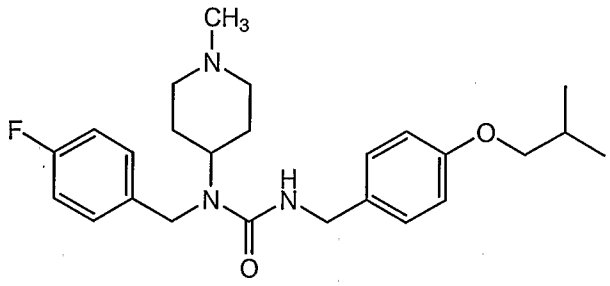
meclizine, mepramine, manserin, promethazine, tipelennamine, triprolidine, acrivastine, cetrizine, desloratadine, fexofenadine, and loratidine.

21. The pharmaceutical composition of claim 1, wherein the anti-manic drug is selected from the group consisting of divalproex (Depakote), lithium carbonate (Eskalith), and lithium citrate.

22. The pharmaceutical composition of claim 1, wherein the anti-phobia drug is D-cycloserine.

23. The pharmaceutical composition of claim 1, further comprising physiologically acceptable carrier, diluent, or excipient, or a combination thereof.

24. The pharmaceutical composition of claim 1 wherein the first compound is the compound of Formula (I):



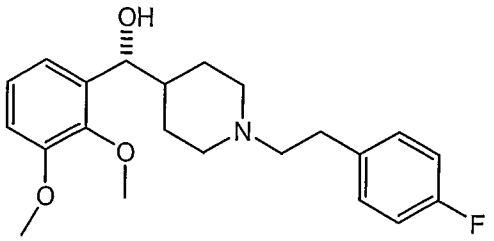
(I)

and the second compound is fluoxetine.

25. A method of treating a disorder in a patient, the disorder selected from the group consisting of depression, mania, social phobia, psychosis, insomnia, and a neuropsychiatric disorder, the method comprising:

identifying a patient in need of said treatment, and

administering to said patient a therapeutically effective amount of a combination of a first compound and a second compound, the first compound selected from the group consisting of an inverse agonist of a serotonin receptor, an antagonist of a serotonin receptor, and pharmaceutically acceptable salts thereof, the second compound selected from the group consisting of a SSRI, a SNRI, a MAO-I, a TCA, an antipsychotic agent, a norepinephrine reuptake inhibitor, a dopamine agonist, an anti-insomnia drug, an anti-manic drug, an anti-phobia drug, the compound of Formula (II)



(II)

and pharmaceutically acceptable salts thereof.

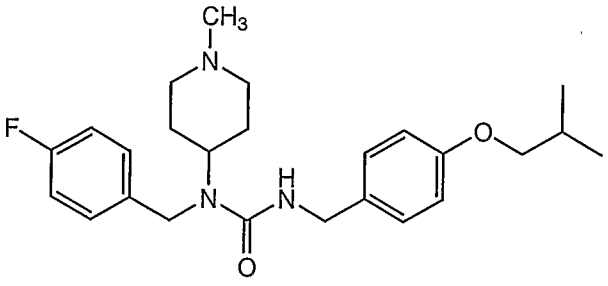
26. The method of claim 25, wherein the neuropsychiatric disorder is selected from the group consisting of schizophrenia and related idiopathic psychoses, anxiety, sleep disorders, appetite disorders, affective disorders, Tourette's Syndrome, drug-induced psychoses, and psychoses secondary to neurodegenerative disorders.

27. The method of claim 26, wherein said affective disorders is selected from the group consisting of major depression, bipolar disorder, and depression with psychotic features.

28. The method of claim 26, wherein said neurodegenerative disorders are selected from the group consisting of Alzheimer's and Huntington's Disease

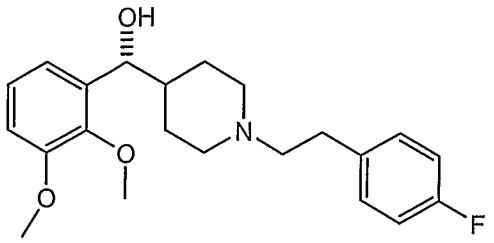
29. The method of claim 25, wherein the serotonin receptor is a 5HT2A receptor.

30. The method of claim 29, wherein the first compound is a compound of Formula (I):



(I)

31. The method of claim 29, wherein the first compound is a compound of Formula (II):



(II)

32. The method of claim 25, wherein the SSRI is selected from the group consisting of bupropion (Wellbutrin, Zyban), citalopram (Celexa), duloxetine, escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertaline (Zoloft), sibutramine, trazodone (Dividose), and venlafaxine.

33. The method of claim 25, wherein the SNRI is selected from the group consisting of citalopram (Celexa), dulexetine, escitalopram (Lexapro), fluvoxamine (Luvox), and venfalaxine (effexor).

34. The method of claim 25, wherein the MAO-I is selected from the group consisting of tranylcypromine (Parnate), phenelzine (Nardil), maprotiline, and isocarboxazid (Marplan).

35. The method of claim 25, wherein the TCA is selected from the group consisting of amitryptiline (Norpramine), amoxapineclomipramine (Anafranil), desipramine, doxepin (Sinequan), imipramine (Tofranil), maprotiline, (Elavil), protryptiline, and trimipramine.

36. The method of claim 25, wherein the antipsychotic agent is selected from the group consisting of a phenothiazine, a phenylbutylpiperadine, a debenzapine, a benzisoxidil, and a salt of lithium.

37. The method of claim 36, wherein the phenothiazine is selected from the group consisting of chlorpromazine (Thorazine®), mesoridazine (Serentil®), prochlorperazine (Compazine®), and thioridazine (Mellaril®).

38. The method of claim 36, wherein the phenylbutylpiperadine is selected from the group consisting of haloperidol (Haldol®) and pimozide (Orap®).

39. The The method of claim 36, wherein the debenzapine is selected from the group consisting of clozapine (Clozaril®), loxapine (Loxitane®), olanzapine (Zyprexa®), and quetiapine (Seroquel®).

40. The method of claim 36, wherein the benzisoxidil is selected from the group consisting of resperidone (Resperidal®) and ziprasidone (Geodon®).

41. The method of claim 36, wherein the salt of lithium is lithium carbonate.

42. The method of claim 25, wherein the antipsychotic agent is selected from the group consisting of Aripiprazole (Abilify), Etrafon Haldol, Inapsine, Mellaril, Moban, Navane, Permitil, Prolixin, Phenergan, Reglan, Risperdal, Stelazine, Taractan, Triavil, and Trilafon.

43. The method of claim 25, wherein the norepinephrine reuptake inhibitor is selected from the group consisting of thionisoxetine and reboxetine.

44. The method of claim 25, wherein the dopamine agonist is selected from the group consisting of sumatriptan, almotriptan, naratriptan, frovatriptan, rizatriptan, zomitriptan, cabergoline, amantadine, lisuride, pergolide, ropinirole, pramipexole, and bromocriptine.

45. The method of claim 25, wherein the anti-insomnia drug is selected from the group consisting of alprazolam (Xanax), chlordiazepoxide (Librium, Limbitrol), clorazepate (Tranxene), estazolam (ProSom), flurazepam (Dalmane), hydroxyzine (Atarax), lorazepam (Ativan), pentobarbital (Nembutal), quazepam (Doral), secobarbital (Seconal), temazepam (Restoril), triazolam (Halcion), valium, zaleplon (Sonata), zolpidem (Ambien), and the benzodiazepine family of drugs.

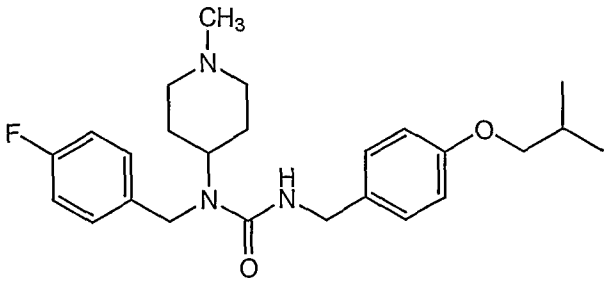
46. The method of claim 25, wherein the anti-insomnia drug is an H1 antagonist or inverse agonist.

47. The method of claim 46, wherein the H1 antagonist or inverse agonistis selected from the group consisting of azatadine, astemizole, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, ktotifen, leocabastine, meclizine, mepramine, manserin, promethazine, tipelennamine, triprolidine, acrivastine, cetrizine, desloratadine, fexofenadine, and loratidine.

48. The method of claim 25, wherein the anti-manic drug is selected from the group consisting of divalproex (Depakote), lithium carbonate (Eskalith), and lithium citrate.

49. The method of claim 25, wherein the anti-phobia drug is D-cycloserine.

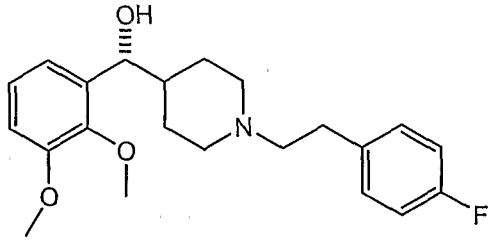
50. The method of claim 25, wherein, the disorder is depression and the first compound is the compound of Formula (I):



(I)

and the second compound is fluoxetine.

51. Use of a first compound and a second compound for the preparation of medicament for treating a disorder in a patient, the disorder selected from the group consisting of depression, mania, social phobia, psychosis, insomnia, and a neuropsychiatric disorder, wherein the first compound is selected from the group consisting of an inverse agonist of a serotonin receptor, an antagonist of a serotonin receptor, and pharmaceutically acceptable salts thereof, and wherein the second compound is selected from the group consisting of a SSRI, a SNRI, a MAO-I, a TCA, an antipsychotic agent, a norepinephrine reuptake inhibitor, a dopamine agonist, an anti-insomnia drug, an anti-manic drug, an anti-phobia drug, the compound of Formula (II)

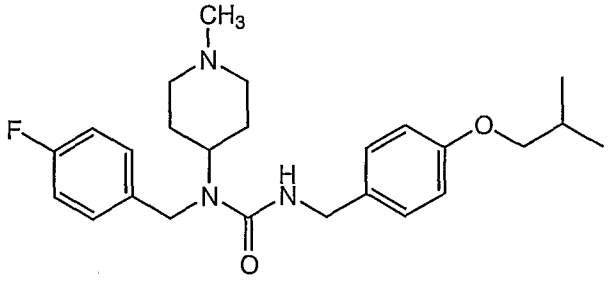


(II)

and pharmaceutically acceptable salts thereof.

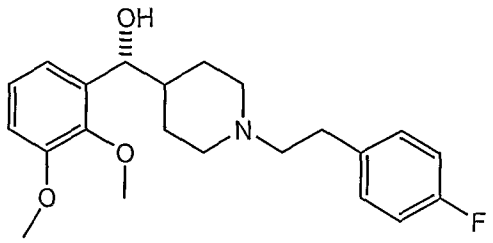
52. The use of claim 51, wherein the serotonin receptor is a 5HT2A receptor.

53. The use of claim 51, wherein the first compound is a compound of Formula (I):



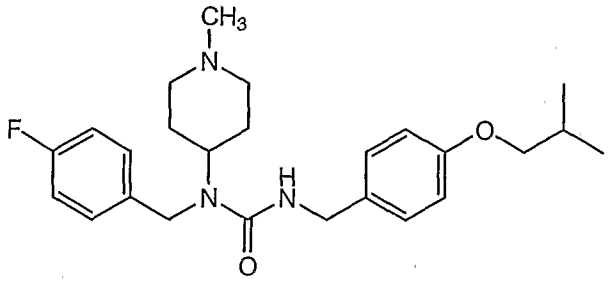
(I)

54. The use of claim 51, wherein the first compound is a compound of Formula (II):



(II)

55. The use of claim 51, wherein, the disorder is depression and the first compound is the compound of Formula (I):



(I)

and the second compound is fluoxetine.