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(57) Abstract: The invention relates to a particular substituted heterocycle fused gamma-carboline, in free, or pharmaceutically acceptable salt, and/or substantially pure form as described herein, pharmaceutical compositions thereof, and methods of use in the treatment of diseases involving the 5-HT2A receptor, the serotonin transporter (SERT), and/or pathways involving the dopamine D1 and D2 receptor signaling system.

ORGANIC COMPOUND

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is an international application which claims priority to and the benefit of U.S. Provisional Application No. 62/780,804, filed on December 17, 2018, the contents of which are hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0001] The invention relates to a new compound, a particular substituted heterocycle fused gamma-carboline, and new methods and uses pertaining thereto, and pharmaceutical compositions thereof, such as methods of use in the treatment of diseases involving the 5-HT_{2A} receptor, the serotonin transporter (SERT), and/or pathways involving dopamine D_1 and D_2 receptor signaling systems, e.g., diseases or disorders such as anxiety, psychosis, schizophrenia, sleep disorders, sexual disorders, migraine, conditions associated with cephalic pain, social phobias, gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility and obesity; depression and mood disorders associated with psychosis or Parkinson's disease; psychosis such as schizophrenia associated with depression; bipolar disorder; mood disorders; and other psychiatric and neurological conditions, as well as to combinations with other agents.

BACKGROUND OF THE INVENTION

[0002] Substituted heterocycle fused gamma-carbolines are known to be agonists or antagonists of 5-HT_2 receptors, particularly 5-HT_{2A} and 5-HT_{2C} receptors, in treating central nervous system disorders. These compounds have been disclosed in U.S. Pat. No. 6,548,493; 7,238,690; 6,552,017; 6,713,471; 7,183,282; U.S. RE39680, and U.S. RE39679, as novel compounds useful for the treatment of disorders associated with 5-HT_{2A} receptor modulation such as obesity, anxiety, depression, psychosis, schizophrenia, sleep disorders, sexual disorders migraine, conditions associated with cephalic pain, social phobias, gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility, and obesity. PCT/US08/03340 (WO 2008/112280), and its U.S. equivalent US 2010/113781, and U.S. Application Serial No. 10/786,935 (published as US 2004/209864) also disclose methods of making substituted

heterocycle fused gamma-carbolines and uses of these gamma-carbolines as serotonin agonists and antagonists useful for the control and prevention of central nervous system disorders such as addictive behavior and sleep disorders.

[0003] In addition, WO/2009/145900 (and its equivalent US 2011/071080) discloses use of particular substituted heterocycle fused gamma-carbolines for the treatment of a combination of psychosis and depressive disorders as well as sleep, depressive and/or mood disorders in patients with psychosis or Parkinson's disease. In addition to disorders associated with psychosis and/or depression, this patent application discloses and claims use of these compounds at a low dose to selectively antagonize 5-HT_{2A} receptors without affecting or minimally affecting dopamine D_2 receptors, thereby useful for the treatment of sleep disorders without the side effects associated with high occupancy of the dopamine D_2 pathways or side effects of other pathways (e.g., $GABA_A$ receptors) associated with convention sedative-hypnotic agents (e.g., benzodiazepines) including but not limited to the development of drug dependency, muscle hypotonia, weakness, headache, blurred vision, vertigo, nausea, vomiting, epigastric distress, diarrhea, joint pains, and chest pains. WO 2009/114181 (and its equivalent US 2011/112105) also discloses of methods of preparing toluenesulfonic acid addition salt crystals of these substituted heterocycle fused gamma-carbolines.

[0004] Conventional antidepressants often take weeks or months to achieve their full effects. For example, selective serotonin reuptake inhibitors (SSRIs), such as sertraline (Zoloft, Lustral), escitalopram (Lexapro, Cipralex), fluoxetine (Prozac), paroxetine (Seroxat), and citalopram, are considered first line therapies for depression, including major depressive disorder, due to their relatively mild side effects and broad effect on the symptoms of depression and anxiety. SSRIs, however, are generally not effective right away, and so are not particularly useful for acute treatment of depression. This delayed onset of action increases the risk for suicidal behavior. Benzodiazepines can be used for acute treatment of anxiety but can be addictive and have a high risk of overdose. Ketamine has recently been tested as a rapid-acting antidepressant for treatment-resistant depression, in bipolar disorder and major depressive disorder, but it has significant side effects and risk of overdose, and it is not orally active.

[0005] Over the last twenty years, at least six placebo-controlled clinical trials have studied ketamine as a rapid-acting antidepressant. In one study by Berman et al., involving 23 to 56-year old patients with major depressive episodes, it was found that a 40-minute infusion of ketamine

at a total dose of 0.5 mg/kg resulted in significantly improved ratings on the Hamilton Depression Rating Scale (HDRS) compared to placebo after only 24 hours. Similar results were shown by Zarate et al. in 2006. Ketamine's effects begin as early 4 hours after intravenous infusion and can persist for up to 2 weeks. However, ketamine's approved medical uses are limited because of side effects, including perceptual disturbances, anxiety, dizziness, feelings of depersonalization and even psychosis (and it is a schedule III drug carrying risks of addiction and abuse). Ketamine also produces dissociative effects, such as hallucination and delirium, as well as analgesia and amnesia, none of which are associated with traditional antidepressants. These dissociative and other effects appear to be mediated by distinct cellular pathways from those which mediate the antidepressant effects of ketamine.

[0006] Unlike traditional antidepressants, which predominantly operate within the monoamine neurotransmitter sphere (i.e., serotonin, norepinephrine, and dopamine), ketamine is a selective NMDA receptor antagonist. The most widely prescribed current anti-depressants are SSRIs, monoamine oxidase inhibitors, and tricyclic antidepressants (primarily serotonin uptake, norepinephrine uptake, and/or dopamine uptake inhibitors). Ketamine acts through a separate system unrelated to the monoamines, and this is a major reason for its much more rapid effect. Ketamine directly antagonizes extrasynaptic glutamatergic NMDA receptors, which also indirectly results in activation of AMPA-type glutamate receptors. The downstream effects involve the brain-derived neurotrophic factor (BDNF) and mTOR (e.g., mTORC1) kinase pathways.

[0007] Animal studies of depression have shown a link to reduction of mTOR (e.g., mTORC1) expression. mTOR is a serine/threonine and tyrosine kinase which is a member of the phosphatidyl inositol 3-kinase family (PI3K family). It operates as a major component of the mTOR complex 1 (mTORC1) and the mTOR complex 2 (mTORC2). The mTOR pathways are central regulators of mammalian metabolism and physiology, with impacts on cell growth and survival, cytoskeleton organization, synaptic plasticity, memory retention, neuroendocrine regulation and neuronal recovery from stress (e.g. hypoxic stress). Studies have shown that activation of mTOR signaling reverses some of the synaptic and behavioral deficits caused by stressors, including chronic stress. There is evidence suggesting that ketamine's anti-depressant effects may be mediated through its activation of mTOR signaling (in combination with its promotion of the release of stored BDNF). Research has shown that a single antidepressant-

effective dose of ketamine can induce a rapid-onset (within 30 minutes of administration) induction of phosphor-mTOR, as well as phospho-p70S6 kinase and phospho4EBP176,177, in the prefrontal cortex and hippocampus of mice and rats. This suggests a mechanism whereby ketamine-induced protein translation occurs in an mTOR activation-dependent manner.

[0008] It was recently surprisingly found that certain fused heterocycle gamma-carbolines, such as those disclosed in U.S. 8,309,722 and U.S. 8,598,119, particularly lumateperone (the Compound of Formula B, below), exhibit a fast-acting antidepressant action via indirect dopamine D1 receptor-dependent enhancement of NMDA and AMPA currents coupled with activation of the mTOR (e.g., mTORC1) signaling pathway, and paralleled by anti-inflammatory properties. Such compounds are thus expected to be useful as orally-available, rapid-acting treatments for depression and anxiety, alone or in conjunction with other anti-anxiety or anti-depressant drugs, lacking the adverse side effects of ketamine and other current pharmacological approaches. In contrast to traditional treatments for depression, such as SSRIs, which typically have an onset of action 3-4 weeks after initiation of daily dosing, the unique pharmacological profile of the compounds described herein are predicted to result in immediate onset of action (e.g., hours to days after initial dosing). In addition, unlike benzodiazepine class agents, the compounds described herein appear to be non-addictive. They are therefore particularly suitable for the treatment of acute depressive episodes, including suicidal ideation and severe acute depression and/or severe acute anxiety.

[0009] Other substituted heterocycle fused gamma-carbolines are disclosed in WO 2017/132408 and US 2017/319580, which are incorporated by reference in their entireties.

[00010] The related publications WO 2017/132408 and US 2017/319580 disclose novel heterocycle fused gamma-carbolines with structures somewhat related to those disclosed in the aforementioned patents, e.g., U.S. Patents U.S. 8,309,722 and U.S. 8,598,119. These new compounds retain much of the unique pharmacologic activity of the prior compounds, including serotonin receptor inhibition, SERT inhibition, and dopamine receptor modulation. However, these new compounds were found to unexpectedly also show significant activity at mu-opiate receptors.

[00011] There remains a need for compounds having strong serotonin receptor, serotonin transporter (SERT), and/or dopamine D_1 and D_2 receptor activities but without mu-opiate receptor activity and with improved pharmacokinetic properties.

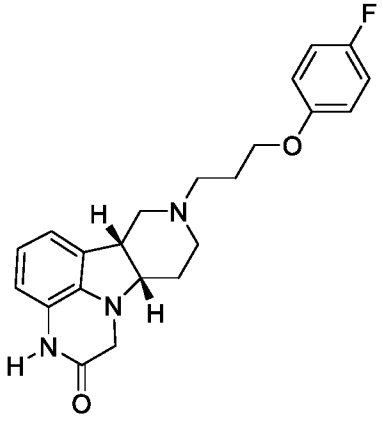
[00011a] The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

[00011b] Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to be interpreted as specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

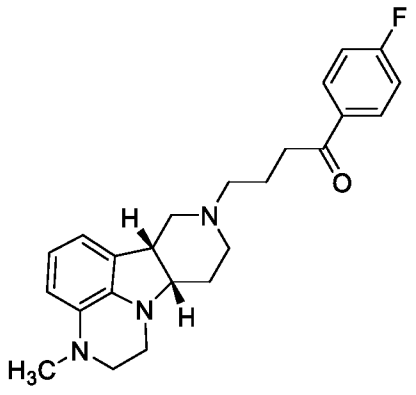
SUMMARY OF THE INVENTION

[00012] The compounds of the present disclosure have been unexpectedly found to have potent activity at serotonin receptors (e.g., 5-HT_{2A}), serotonin transporters (SERT), dopamine receptors (e.g., D1 and/or D2), with significantly improved pharmacokinetic stability compared to prior art compounds, and without mu-opiate receptor activity. It is also believed that the compounds of the present disclosure, via their D1 receptor activity, may also enhance NMDA and AMPA mediated signaling through the mTOR pathway.

[00013] Compounds of Formula A and B, shown below, are both potent serotonin 5-HT_{2A} receptor antagonists, and potent D1/D2 receptor modulators, yet they have widely different activity at SERT and at the mu-opiate receptor.



Formula A



Formula B

[00014] Despite the close similarity in their structures, it was unexpectedly found that the compound of Formula A is a relatively weak SERT antagonist, but a very strong mu-opiate antagonist. In contrast, the compound of Formula B is a very strong SERT antagonist and has

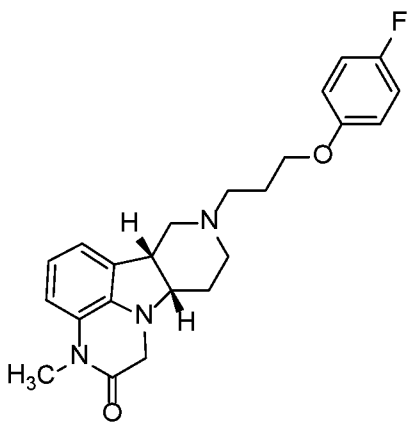
no mu-opiate activity. Both compounds bind well to both the D1 and D2 dopamine receptors, although the compound of Formula B shows approximate parity in binding (D2/D1 ratio 1.20), while the compound of Formula A shows more than three-fold higher D2 binding (D2/D1 ratio 3.20). It is further believed that the Compound of Formula B, via its D1 receptor activity, also enhances NMDA and AMPA mediated signaling through the mTOR pathway.

[00015] Low doses of an antipsychotic drug (APD) enhance the effectiveness of antidepressants in patients suffering from treatment-resistant depression (TRD) (Tohen et al., 2010). At the molecular level, combined application of low concentrations of antipsychotic drugs

with selective serotonin uptake inhibitors (SSRIs) robustly and synergistically increase the activity of NMDA receptors on pyramidal neurons in the medial prefrontal cortex (mPFC). Further, combined application of an APD with an SSRI enhances AMPA receptor currents in the mPFC– an effect not seen with either treatment alone. Interestingly, this enhancement of glutamatergic neurotransmission in mPFC via both NMDA and AMPA receptors is mimicked by non-anesthetic doses of ketamine, an agent which provides rapid antidepressant efficacy in patients with TRD. Together, this data indicates that a combination of APD and SSRI properties is effective for alleviating TRD.

[00016] It has been found that the Compound of Formula B (lumateperone) possesses the properties an APD and an SSRI and enhances glutamatergic neurotransmission by effects on both NMDA and AMPA receptor conductance in rat mPFC slices. The actions of lumateperone are consistent with the effects of other rapid-acting antidepressant therapies, including the combined use of olanzapine (a D2-receptor antagonist APD) with fluoxetine (an SSRI) and of ketamine, thus supporting a molecular action of lumateperone consistent with an acute therapeutic action on anxiety and treatment-resistant depression.

[00017] The present disclosure provides the Compound of Formula I, which is useful for the treatment or prophylaxis of central nervous system disorders. In a first aspect, the present disclosure relates to a compound (Compound 1) of Formula 1:



Formula I

in free or salt form, for example in an isolated or purified free or salt form.

[00018] The present disclosure provides additional exemplary embodiments of the Compound of Formula I, in free or salt form, for example in an isolated or purified free or salt form, including:

1.1 Compound 1 in free form (i.e., free base form);

1.2 Compound 1 in salt form, e.g., pharmaceutically acceptable salt form;

1.3 Compound 1.2, wherein the salt is an acid addition salt selected from hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like;

1.4 Compound 1, or any of 1.1-1.3, in solid form;

1.5 Compound 1 or any of 1.1-1.4, wherein the carbon atom CH is substantially present in either the *R* configuration or the *S* configuration, e.g., wherein the diastereomer having the *R* configuration or the *S* configuration at this carbon is present in greater than 70% diastereomeric excess, for example, greater than 75%, or greater than 80%, or greater than 85%, or greater than 90%, or greater than 95%, or greater than 97%, or greater than 98% or greater than 99%, diastereomeric excess;

1.6 Compound 1 or any of 1.1-1.5 in isolated or purified form.

[00019] In a second aspect, the present disclosure provides a pharmaceutical composition (Pharmaceutical Composition 2) comprising a Compound 1 or any of 1.1-1.6, e.g., in admixture with a pharmaceutically acceptable diluent or carrier. The present disclosure provides additional exemplary embodiments of Pharmaceutical Composition 2, including:

2.1 Pharmaceutical Composition 2, wherein the Compound of Formula 1 or any of 1.1-1.6 is in solid form;

2.2 Pharmaceutical Composition 2 or 2.1, wherein the compound of Formula 1 is in pharmaceutically acceptable salt form, e.g., a compound selected from Compound 1.3 or 1.4.

[0020] In a preferred embodiment, the Pharmaceutical Composition of the present disclosure comprises a Compound of Formula I or any one of 1.1-1.6, in free or pharmaceutically acceptable salt form, in admixture with a pharmaceutically acceptable diluent or carrier.

[0021] In a further embodiment, the Pharmaceutical Compositions of the present disclosure, are sustained or delayed release formulations, for example, depot formulations. In one

embodiment, the depot formulation (Pharmaceutical Composition 2.3) is the Pharmaceutical Composition 2 or any of 2.1-2.2, preferably in free or pharmaceutically acceptable salt form, and preferably in admixture with a pharmaceutically acceptable diluent or carrier, e.g., providing sustained or delayed release as an injectable depot.

[0022] In a further embodiment, the present disclosure provides Pharmaceutical Composition 2.4, which is Pharmaceutical Composition 2 or any of 2.1-2.3, wherein the Compound of Formula 1 et seq. is in a polymeric matrix. In one embodiment, the Compound of the present disclosure is dispersed or dissolved within the polymeric matrix. In a further embodiment, the polymeric matrix comprises standard polymers used in depot formulations such as polymers selected from a polyester of a hydroxyfatty acid and derivatives thereof, or a polymer of an alkyl alpha-cyanoacrylate, a polyalkylene oxalate, a polyortho ester, a polycarbonate, a polyortho-carbonate, a polyamino acid, a hyaluronic acid ester, and mixtures thereof. In a further embodiment, the polymer is selected from a group consisting of polylactide, poly d,l-lactide, poly glycolide, PLGA 50:50, PLGA 85:15 and PLGA 90:10 polymer. In another embodiment, the polymer is selected form poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxanone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and natural polymers including albumin, casein, and waxes, such as, glycerol mono- and distearate, and the like. In a preferred embodiment, the polymeric matrix comprises poly(d,l-lactide-co-glycolide).

[0023] For example, in one embodiment of Pharmaceutical Composition 2.4, the Compound is the Compound of Formula 1 or 1.1 et seq., in free or pharmaceutically acceptable salt form. In another example of Pharmaceutical Composition 2.4, the Compound is the Compound of Formula 1 or 1.1 et seq. in free or pharmaceutically acceptable salt form, in admixture with a pharmaceutically acceptable diluent or carrier. In another example of Pharmaceutical Composition 2.4, the Compound is the Compound of Formula 1 or 1.1 et seq., in admixture with a pharmaceutically acceptable diluent or carrier, wherein the diluent or carrier comprises a polymeric matrix, optionally wherein the polymeric matrix comprises a poly(d,l-lactide-co-glycolide) copolymer.

[0024] In some embodiments, Pharmaceutical Composition 2.4 is particularly useful for sustained or delayed release, wherein the Compound of the present disclosure is released upon

degradation of the polymeric matrix. These Compositions may be formulated for controlled- and/or sustained-release of the Compounds of the present disclosure (e.g., as a depot composition) over a period of up to 180 days, e.g., from about 14 to about 30 to about 180 days. For example, the polymeric matrix may degrade and release the Compounds of the present disclosure over a period of about 30, about 60 or about 90 days. In another example, the polymeric matrix may degrade and release the Compounds of the present disclosure over a period of about 120, or about 180 days.

[0025] In still another embodiment, the Pharmaceutical Compositions of the present disclosure, for example the depot composition of the present disclosure, e.g., Pharmaceutical Composition 2.3, is formulated for administration by injection.

[0026] In further embodiment, the present disclosure provides the Compounds of Formulas 1 or 1.1 et seq. as hereinbefore described, in an osmotic controlled release oral delivery system (OROS), which is described U.S. Pub. No. 2009/0202631, the contents of which are incorporated by reference in its entirety. Therefore in one embodiment of the seventh aspect, the present disclosure provides a pharmaceutical composition or device comprising (a) a gelatin capsule containing a Compound of any of Formulas 1 or 1.1 et seq. in free or pharmaceutically acceptable salt form or a Pharmaceutical Composition of the Invention, as hereinbefore described; (b) a multilayer wall superposed on the gelatin capsule comprising, in outward order from the capsule: (i) a barrier layer, (ii) an expandable layer, and (iii) a semipermeable layer; and (c) and orifice formed or formable through the wall (Pharmaceutical Composition P.1).

[0027] In another embodiment, the invention provides a pharmaceutical composition comprising a gelatin capsule containing a liquid, the Compound of Formulas 1 or 1.1 et seq. in free or pharmaceutically acceptable salt form or a Pharmaceutical Composition of the Invention, e.g., any of Pharmaceutical Composition 2 or 2.1-2.4, the gelatin capsule being surrounded by a composite wall comprising a barrier layer contacting the external surface of the gelatin capsule, an expandable layer contacting the barrier layer, a semi-permeable layer encompassing the expandable layer, and an exit orifice formed or formable in the wall (Pharmaceutical Composition P.2).

[0028] In still another embodiment, the invention provides a composition comprising a gelatin capsule containing a liquid, the Compound of Formulas 1 or 1.1 et seq. in free or pharmaceutically acceptable salt form or a Pharmaceutical Composition of the Invention, e.g.,

any of Pharmaceutical Composition 2 or 2.1-2.4, the gelatin capsule being surrounded by a composite wall comprising a barrier layer contacting the external surface of the gelatin capsule, an expandable layer contacting the barrier layer, a semipermeable layer encompassing the expandable layer, and an exit orifice formed or formable in the wall, wherein the barrier layer forms a seal between the expandable layer and the environment at the exit orifice (Pharmaceutical Composition P.3).

[0029] In still another embodiment, the invention provides a composition comprising a gelatin capsule containing a liquid, the Compound of Formulas 1 or 1.1 et seq. in free or pharmaceutically acceptable salt form or a Pharmaceutical Composition of the Invention, e.g., any of Pharmaceutical Composition 2 or 2.1-2.4, the gelatin capsule being surrounded by a barrier layer contacting the external surface of the gelatin capsule, an expandable layer contacting a portion of the barrier layer, a semi-permeable layer encompassing at least the expandable layer, and an exit orifice formed or formable in the dosage form extending from the external surface of the gelatin capsule to the environment of use (Pharmaceutical Composition P.4). The expandable layer may be formed in one or more discrete sections, such as for example, two sections located on opposing sides or ends of the gelatin capsule.

[0030] In a particular embodiment, the Compound of the present disclosure in the Osmotic-controlled Release Oral Delivery System (i.e., in Pharmaceutical Composition P.1-P.4) is in a liquid formulation, which formulation may be neat, liquid active agent, liquid active agent in a solution, suspension, emulsion or self-emulsifying composition or the like.

[0031] Further information on Osmotic-controlled Release Oral Delivery System composition including characteristics of the gelatin capsule, barrier layer, an expandable layer, a semi-permeable layer; and orifice may be found in US 2001/0036472, the contents of which are incorporated by reference in its entirety.

[0032] Other Osmotic-controlled Release Oral Delivery System for the Compound of 1 or 1.1 et seq. or the Pharmaceutical Composition of the present disclosure may be found in U.S. Pub. No. 2009/0202631, the contents of which are incorporated by reference in their entirety. Therefore, in another embodiment of the seventh aspect, the invention provides a composition or device comprising (a) two or more layers, said two or more layers comprising a first layer and a second layer, said first layer comprises the Compound of 1 or 1.1 et seq., in free or pharmaceutically acceptable salt form, or a Pharmaceutical Composition as herein before

described said second layer comprises a polymer; (b) an outer wall surrounding said two or more layers; and (c) an orifice in said outer wall (Pharmaceutical Composition P.5).

[0033] Composition P.5 preferably utilizes a semi-permeable membrane surrounding a three-layer-core: in these embodiments the first layer is referred to as a first drug layer and contains low amounts of drug (e.g., the Compound of 1 or 1.1 et seq.) and an osmotic agent such as salt, the middle layer referred to as the second drug layer contains higher amounts of drug, excipients and no salt; and the third layer referred to as the push layer contains osmotic agents and no drug (Pharmaceutical Composition P.6). At least one orifice is drilled through the membrane on the first drug layer end of the capsule-shaped tablet.

[0034] Composition P.5 or P.6 may comprise a membrane defining a compartment, the membrane surrounding an inner protective subcoat, at least one exit orifice formed or formable therein and at least a portion of the membrane being semi-permeable; an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semi-permeable portion of the membrane; a first drug layer located adjacent the exit orifice; and a second drug layer located within the compartment between the first drug layer and the expandable layer, the drug layers comprising the Compound of the Invention in free or pharmaceutically acceptable salt thereof (Pharmaceutical Composition P.7). Depending upon the relative viscosity of the first drug layer and second drug layer, different release profiles are obtained. It is imperative to identify the optimum viscosity for each layer. In the present invention, viscosity is modulated by addition of salt, sodium chloride. The delivery profile from the core is dependent on the weight, formulation and thickness of each of the drug layers.

[0035] In a particular embodiment, the invention provides Pharmaceutical Composition P.7 wherein the first drug layer comprising salt and the second drug layer containing no salt. Pharmaceutical Composition P.5-P.7 may optionally comprise a flow-promoting layer between the membrane and the drug layers.

[0036] Pharmaceutical Compositions P.1-P.7 may generally be referred to as Osmotic-controlled Release Oral Delivery System Composition.

[0037] In a third aspect, the invention provides a method (Method 3) for the treatment or prophylaxis of a central nervous system disorder, comprising administering to a patient in need thereof a Compound of Formula 1 or 1.1 et seq. or a Pharmaceutical Composition 2 or 2.1-2.4 or P.1-P.7.

[0038] In a further embodiment of the third aspect, the present disclosure provides Method 3, wherein the method is further as described as follows:

3.1 Method 3, wherein the central nervous system disorder is a disorder involving serotonin 5-HT_2A, dopamine D2 and/or D1 receptor system and/or the serotonin reuptake transporter (SERT) pathways as similarly described in US 2011/071080, the contents of which are herein incorporated by reference in its entirety;

3.2 Method 3 or 3.1, wherein the central nervous system disorder is a disorder selected from the group consisting of obesity, anxiety, depression (for example refractory depression and MDD (major depressive disorder)), psychosis (including psychosis associated with dementia, such as hallucinations in advanced Parkinson's disease or paranoid delusions), schizophrenia, sleep disorders (particularly sleep disorders associated with schizophrenia and other psychiatric and neurological diseases), sexual disorders, migraine, conditions associated with cephalic pain, social phobias, agitation in dementia (e.g., agitation in Alzheimer's disease), agitation in autism and related autistic disorders, gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility, and dementia, for example dementia of Alzheimer's disease or of Parkinson's disease; and mood disorders; obsessive-compulsive disorder (OCD), obsessive-compulsive personality disorder (OCPD), general anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, compulsive gambling disorder, compulsive eating disorder, body dysmorphic disorder, hypochondriasis, pathological grooming disorder, kleptomania, pyromania; attention deficit-hyperactivity disorder (ADHD), attention deficit disorder (ADD), impulse control disorder; and related disorders, and combination thereof;

3.3 Method 3 or 3.1, wherein the central nervous system disorder is a disorder selected from the following: (i) psychosis, e.g., schizophrenia, in a patient suffering from depression; (2) depression in a patient suffering from psychosis, e.g., schizophrenia; (3) mood disorders associated with psychosis, e.g., schizophrenia or Parkinson's disease; (4) sleep disorders associated with psychosis, e.g., schizophrenia or Parkinson's disease; ad (5) substance a use

disorders and/or substance-induced disorders, optionally wherein the patient suffers from residual symptoms of anxiety or anxiety disorder;

3.4 Method 3 or 3.1, wherein the central nervous system disorder is psychosis, e.g., schizophrenia and said patient is a patient suffering from depression;

3.5 Method 3 or 3.1, wherein the central nervous system disorder is selected from obsessive-compulsive disorder (OCD), obsessive-compulsive personality disorder (OCPD), social anxiety disorder, panic disorder, agoraphobia, compulsive gambling disorder, compulsive eating disorder, body dysmorphic disorder and impulse control disorder;

3.6 Method 3 or 3.1, wherein the central nervous system disorder is obsessive-compulsive disorder (OCD) or obsessive-compulsive personality disorder (OCPD);

3.7 Method 3 or 3.1, wherein said central nervous system disorder is depression and said patient is a patient suffering from psychosis, e.g., schizophrenia, or Parkinson's disease;

3.8 Method 3 or 3.1, wherein the central nervous system disorder is a sleep disorder;

3.9 Method 3.8, wherein said sleep disorder is sleep maintenance insomnia, frequent awakening, and/or waking up feeling unrefreshed;

3.10 Method 3.7 or 3.8, wherein the patient is also suffering from depression;

3.11 Method 3.7, 3.8 or 3.9, wherein said patient is also suffering from psychosis, e.g., schizophrenia;

3.12 Method 3.7-3.11, wherein said patient is also suffering from Parkinson's disease;

3.13 Method 3 or 3.1, wherein the central nervous system disorder is depression, anxiety or a combination thereof;

3.14 Method 3.13, wherein the depression and/or anxiety is acute depression and/or acute anxiety;

3.15 Method 3.14, wherein the acute depression and/or acute anxiety to be treated is alleviated within one week, e.g., within three days, e.g., within one day;

3.16 Method 3.14 or 3.15, wherein the patient is diagnosed as having suicidal ideation and/or suicidal tendencies;

3.17 Any of methods 3.13-3.16, wherein the condition to be treated is acute anxiety (e.g., a short-duration anxious episode associated with generalized anxiety disorder, panic disorder, specific phobias, or social anxiety disorder, or social avoidance);

3.18 Any of methods 3.13-3.17, wherein the condition to be treated is acute depression (e.g., acute major depressive episode, acute short-duration depressive episode, acute recurrent brief depressive episode);

3.19 Any of methods 3.13-3.18, wherein the condition to be treated is treatment resistant depression (e.g., depression which has not responded to treatment with an antidepressant agent selected from a selective serotonin reuptake inhibitor (SSRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant, a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor (NRI), a dopamine reuptake inhibitor (DRI), an SRI/NRI, an SRI/DRI, an NRI/DRI, an SRI/NRI/DRI (triple reuptake inhibitor), a serotonin receptor antagonist, or any combination thereof);

3.20 Any of Methods 3.13-3.19, wherein the condition to be treated is selected from bipolar depression and major depressive disorder;

3.21 Any of Methods 3.13-3.20, wherein the patient shows an acute response to treatment within less than 3 weeks, for example, less than 2 weeks, or less than 1 week, or from 1 to 7 days, or 1 to 5 days, or 1 to 3 days, or 1 to 2 days, or about 1 day, or less than 2 days, or less than 1 day (e.g., 12-24 hours);

3.22 Method 3 or any of 3.1-3.21, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with selective serotonin reuptake inhibitors (SSRIs), such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline;

3.23 Any foregoing method, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, sibutramine, duloxetine, atomoxetine, desvenlafaxine, milnacipran, and levomilnacipran;

3.24 Any foregoing method, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with antipsychotic agents, such as clomipramine, risperidone, quetiapine and olanzapine;

3.25 Any foregoing method, wherein said patient is unable to tolerate the side effects of conventional antipsychotic drugs, e.g., chlorpromazine, haloperidol, droperidol, fluphenazine, loxapine, mesoridazine molindone, perphenazine, pimozide, prochlorperazine promazine, thioridazine, thiothixene, trifluoperazine, clozapine, aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone;

3.26 Any foregoing method, wherein said patient is unable to tolerate the side effects of conventional antipsychotic drugs, e.g., haloperidol, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone;

3.27 Method 3 or 3.1, wherein the central nervous system disease or disorder is a drug dependency (for example, opiate dependency (i.e., opioid use disorder), cocaine dependency, amphetamine dependency, and/or alcohol dependency), or withdrawal from drug or alcohol dependency (e.g., opiate, cocaine, or amphetamine dependency), and optionally wherein the patient also suffers from a co-morbidity, such as anxiety, depression or psychosis; optionally wherein the patient also suffers from a current or prior opiate overdose;

3.28 Any of the foregoing methods, wherein said patient is suffering from a drug dependency disorder, optionally in conjunction with any preceding disorders, for example, wherein said patient suffers from opiate dependency and/or alcohol dependency, or from withdrawal from drug or alcohol dependency, optionally wherein the patient suffers from residual symptoms of anxiety or anxiety disorder, or depression or psychosis, etc.; further optionally wherein the patient suffers from an opiate overdose;

3.29 Method 3 or 3.1, wherein the central nervous system disorder is a pain disorder, e.g., a condition associated with pain, such as cephalic pain, idiopathic pain, neuropathic pain, chronic pain (e.g., moderate to moderately severe chronic pain, for example, in patients requiring 24-hour extended treatment for other ailments), fibromyalgia, dental pain, traumatic pain, or chronic fatigue;

3.30 Any foregoing method, wherein the patient is not responsive to or cannot tolerate the side effects of non-narcotic analgesics and/or opiate and opioid drugs, or wherein the use of opiate drugs are contraindicated in said patient, for example, due to prior substance abuse or a high potential for substance abuse, such as opiate and opioid drugs including, e.g., morphine, codeine, thebaine, oripavine, morphine dipropionate, morphine dinicotinate, dihydrocodeine, buprenorphine, etorphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, fentanyl, alpha-methylfentantyl, alfentanyl, trefantinil, brifentanil, remifentanil, octfentanil, sufentanil, carfentanyl, meperidine, prodine, promedol, propoxyphene, dextropropoxyphene, methadone, diphenoxylate, dezocine, pentazocine, phenazocine, butorphanol, nalbuphine, levorphanol, levomethorphan, tramadol, tapentadol, and anileridine, or any combinations thereof;

3.31 Any of the foregoing methods, wherein the effective amount is 1 mg-1000mg, preferably 2.5mg-50mg;

3.32 Any of the foregoing methods, wherein the effective amount is 1 mg-100mg per day, preferably 2.5mg-50mg per day;

3.33 Any of the foregoing methods wherein a condition to be treated is dyskinesia, e.g. in a patient receiving dopaminergic medications, e.g., medications selected from levodopa and levodopa adjuncts (carbidopa, COMT inhibitors, MAO-B inhibitors), dopamine agonists, and anticholinergics, e.g., levodopa;

3.34 Any of the foregoing methods wherein the patient suffers from Parkinson's disease;

3.35 Any of the foregoing methods wherein the method comprises administering the Compound of Formula 1 in free form;

3.36 Any of Methods 3.1 to 3.35, wherein the method comprises administering the Compound of Formula 1 in salt form, e.g., pharmaceutically acceptable salt form;

3.37 Any of Methods 3.1 to 3.35, wherein the method comprises administering any Compound of Formula 1 or 1.1 to 1.6;

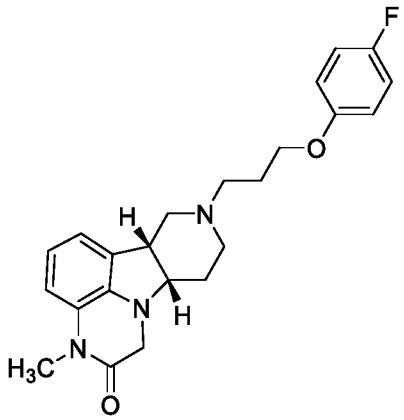
3.38 Any preceding method, wherein the method comprises administering a pharmaceutical composition comprising the Compound of Formula 1 or any of 1.1 to 1.6, in admixture with a pharmaceutically acceptable diluent or carrier;

3.39 Method 3.36, wherein the pharmaceutical Composition is Pharmaceutical Composition 2, or any of 2.1-2.4 or any of P.1 to P.7;

3.40 Any preceding method wherein the method comprises administering the Compound of Formula 1 or any of 1.1-1.6 in a form formulated for controlled- and/or sustained-release of the Compound over a period of from about 14 days, about 30 to about 180 days, preferably over the period of about 30, about 60 or about 90 days;

3.41 Any foregoing method, wherein the method further comprises concurrent administration of one or more additional therapeutic agents, optionally wherein the dose of either the Compound of the present disclosure and/or the one or more additional therapeutic agents is provided at a lower dose compared to when said Compound or agent is used as monotherapy.

[0038a] In a further embodiment of the third aspect, the present disclosure provides a method for the treatment of a central nervous system disorder, wherein the central nervous system disorder is acute anxiety, acute depression, or the acute treatment of treatment-resistant depression, the method comprising administering to a patient in need thereof a compound of Formula I:



Formula I

in free or pharmaceutically acceptable salt form or a pharmaceutical composition comprising the compound of Formula I in admixture with a pharmaceutically acceptable diluent or carrier.

[0039] The Compounds of the present disclosure, the Pharmaceutical Compositions of the present disclosure or the Depot Compositions of the present disclosure may be used in combination with a second therapeutic agent, particularly at lower dosages than when the individual agents are used as a monotherapy so as to enhance the therapeutic activities of the combined agents without causing the undesirable side effects commonly occur in conventional monotherapy. For example, the Compounds of the present disclosure may be simultaneously, sequentially, or contemporaneously administered with other anti-depressant, anti-psychotic, other hypnotic agents, and/or agents use to treat Parkinson's disease or mood disorders. In another example, side effects may be reduced or minimized by administering a Compound of the present disclosure in combination with one or more second therapeutic agents in free or salt form, wherein the dosages of (i) the second therapeutic agent(s) or (ii) both Compound of the present disclosure and the second therapeutic agents, are lower than if the agents/compounds are administered as a monotherapy. In a particular embodiment, the Compounds of the present disclosure are useful to treat dyskinesia in a patient receiving dopaminergic medications, e.g., selected from levodopa and levodopa adjuncts (carbidopa, COMT inhibitors, MAO-B

inhibitors), dopamine agonists, and anticholinergics, e.g., such as are used in the treatment of Parkinson's disease.

[0040] Substance-use disorders and substance-induced disorders are the two categories of substance-related disorders defined by the Fifth Edition of the DSM (the Diagnostic and Statistical Manual of Mental Disorders, or DSM-V). A substance-use disorder is a pattern of symptoms resulting from use of a substance which the individual continues to take, despite experiencing problems as a result. A substance-induced disorder is a disorder induced by use if the substance. Substance-induced disorders include intoxication, withdrawal, substance induced mental disorders, including substance induced psychosis, substance induced bipolar and related disorders, substance induced depressive disorders, substance induced anxiety disorders, substance induced obsessive-compulsive and related disorders, substance induced sleep disorders, substance induced sexual dysfunctions, substance induced delirium and substance induced neurocognitive disorders.

[0041] The DSM-V includes criteria for classifying a substance use disorder as mild, moderate or severe. In some embodiments of the methods disclosed herein, the substance use disorder is selected from a mild substance use disorder, a moderate substance use disorder or a severe substance use disorder. In some embodiments, the substance use disorder is a mild substance use disorder. In some embodiments, the substance use disorder is a moderate substance use disorder. In some embodiments, the substance use disorder is a severe substance use disorder.

[0042] Anxiety is a highly prevalent co-morbid disorder in patients undergoing treatment of substance use or substance abuse. A common treatment for substance abuse disorder is the combination of the partial opioid agonist buprenorphine with the opioid antagonist naloxone, but neither of these drugs has any significant effect on anxiety, thus leading to the common result that a third drug, such as a benzodiazepine-class anxiolytic agent. This makes treatment regimens and patient compliance more difficult. In contrast, the Compounds of the present disclosure provide opiate antagonism along with serotonin antagonism and dopamine modulation. This may result in significant enhancement of treatment of patients with substance use or abuse disorder concomitant with anxiety. Depression is also a highly prevalent disorder in patients undergoing substance use or substance abuse treatment. Thus, antidepressants, such as SSRIs, are also often used concomitantly in patients undergoing substance abuse treatment. Compounds of the present disclosure may also enhance treatment in such patients by providing treatment for substance use or substance abuse as well as both anxiety and depression.

[0043] The compounds of the present disclosure may have anxiolytic properties ameliorating the need for treatment of a patient with an anxiolytic agent where said patients suffers from co-morbid anxiety. Thus, in some embodiments, the present disclosure provides a method according to Method 3, or any of Methods 3.1-3.41, wherein the central nervous system disorder is a substance addiction, substance use disorders and/or substance-induced disorders, or a substance abuse disorder, for example, in a patient suffering from symptoms of anxiety or who is diagnosed with anxiety as a co-morbid disorder, or as a residual disorder, wherein the method does not comprise the further administration of an anxiolytic agent, such as a benzodiazepine.

[0044] In some further embodiments of the present disclosure, the Pharmaceutical Compositions of the present disclosure or the Depot Compositions of the present disclosure may be used in combination with a second therapeutic agent, particularly at lower dosages than when the individual agents are used as a monotherapy so as to enhance the therapeutic activities of the combined agents without causing the undesirable side effects.

[0045] The Compounds of the present disclosure may be simultaneously, sequentially, or contemporaneously administered with any such additional therapeutic agents.

[0046] In further embodiments of the third aspect, the invention provides:

3.42 Method 3.41, wherein the one or more therapeutic agents are selected from compounds that modulate GABA activity (e.g., enhances the activity and facilitates GABA transmission), a GABA-B agonist, a 5-HT receptor modulator (e.g., a 5 -HT_{1A} agonist, a 5- HT_{2A} antagonist, a 5-HT_{2A} inverse agonist, etc.), a melatonin receptor agonist, an ion channel modulator (e.g., blocker), a serotonin-2 antagonist/reuptake inhibitor (SARIs), an orexin receptor antagonist, an H3 agonist or antagonist, a noradrenergic agonist or antagonist, a galanin agonist, a CRH antagonist, human growth hormone, a growth hormone agonist, estrogen, an estrogen agonist, a neurokinin-1 drug, an anti-depressant, an opiate agonist and/or partial opiate agonist, an opiate antagonist and/or opiate inverse agonist, and an antipsychotic agent, e.g., an atypical antipsychotic agent, in free or pharmaceutically acceptable salt form;

3.43 Method 3.42, wherein the therapeutic agent(s) is compounds that modulate GABA activity (e.g., enhances the activity and facilitates GABA transmission);

3.44 Method 3.43, wherein the GABA compound is selected from a group consisting of one or more of doxepin, alprazolam, bromazepam, clobazam, clonazepam, clorazepate, diazepam, flunitrazepam, flurazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam, triazolam, indiplon, zopiclone, eszopiclone, zaleplon, Zolpidem, gaboxadol, vigabatrin, tiagabine, EVT 201 (Evotec Pharmaceuticals) and estazolam;

3.45 Method 3.42, wherein the therapeutic agent is an additional 5HT2a antagonist;

3.46 Method 3.42, wherein said additional 5HT2a antagonist is selected from one or more of ketanserin, risperidone, eplivanserin, volinanserin (Sanofi-Aventis, France), pruvanserin, MDL 100907 (Sanofi-Aventis, France), HY 10275 (Eli Lilly), APD 125 (Arena Pharmaceuticals, San Diego, CA), and AVE8488 (Sanofi-Aventis, France);

3.47 Method 3.42, wherein the therapeutic agent is a melatonin receptor agonist;

3.48 Method 3.47, wherein the melatonin receptor agonist is selected from a group consisting of one or more of melatonin, ramelteon (ROZEREM®, Takeda Pharmaceuticals, Japan), VEC- 162 (Vanda Pharmaceuticals, Rockville, MD), PD-6735 (Phase II Discovery) and agomelatine;

3.49 Method 3.42, wherein the therapeutic agent is an ion channel blocker;

3.50 Method 3.49, wherein said ion channel blocker is one or more of lamotrigine, gabapentin and pregabalin;

3.51 Method 3.42, wherein the therapeutic agent is an orexin receptor antagonist;

3.52 Method 3.42, wherein the orexin receptor antagonist is selected from a group consisting of orexin, a 1,3-biarylurea, SB-334867-a (GlaxoSmithKline, UK), GW649868 (GlaxoSmithKline) and a benzamide derivative;

3.53 Method 3.42, wherein the therapeutic agent is the serotonin-2 antagonist/reuptake inhibitor (SARI);

3.54 Method 3.53, wherein the serotonin-2 antagonist/reuptake inhibitor (SARI) is selected from a group consisting of one or more Org 50081 (Organon - Netherlands), ritanserin, nefazodone, serzone and trazodone;

3.55 Method 3.42, wherein the therapeutic agent is the 5HTIa agonist;

3.56 Method 3.55, wherein the 5HTIa agonist is selected from a group consisting of one or more of repinotan, sarizotan, eptapirone, buspirone and MN-305 (MediciNova, San Diego, CA);

3.57 Method 3.42, wherein the therapeutic agent is the neurokinin-1 drug;

3.58 Method 3.57, wherein the neurokinin-1 drug is Casopitant (GlaxoSmithKline);

3.59 Method 3.42, wherein the therapeutic agent is an antipsychotic agent;

3.60 Method 3.59, wherein the antipsychotic agent is selected from a group consisting of chlorpromazine, haloperidol, droperidol, fluphenazine, loxapine, mesoridazine, molindone, perphenazine, pimozide, prochlorperazine promazine, thioridazine, thiothixene, trifluoperazine, clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone and paliperidone;

3.61 Method 3.42, wherein the therapeutic agent is an anti-depressant;

3.62 Method 3.61, wherein the anti-depressant is selected from amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine sulfate, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine;

3.63 Method 3.42, wherein the antipsychotic agent is an atypical antipsychotic agent;

3.64 Method 3.63, wherein the atypical antipsychotic agent is selected from a group consisting of clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, and paliperidone;

3.65 Method 3.42, wherein the therapeutic agent is selected from the group consisting of modafinil, armodafinil, doxepin, alprazolam, bromazepam, clobazam, clonazepam, clorazepate, diazepam, flunitrazepam, flurazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam, triazolam, indiplon, zopiclone, eszopiclone, zaleplon, Zolpidem, gaboxadol, vigabatrin, tiagabine, EVT 201 (Evotec Pharmaceuticals), estazolam, ketanserin, risperidone, eplivanserin, volinanserin (Sanofi-Aventis, France), pruvanserin, MDL 100907 (Sanofi-Aventis, France), HY 10275 (Eli Lilly), APD 125 (Arena Pharmaceuticals, San Diego, CA), AVE8488 (Sanofi-Aventis, France), repinotan, sarizotan, eptapirone,

buspirone, MN-305 (MediciNova, San Diego, CA), melatonin, ramelteon (ROZEREM®, Takeda Pharmaceuticals, Japan), VEC- 162 (Vanda Pharmaceuticals, Rockville, MD), PD-6735 (Phase II Discovery), agomelatine, lamotrigine, gabapentin, pregabalin, orexin, a 1,3-biarylurea, SB-334867-a (GlaxoSmithKline, UK), GW649868 (GlaxoSmithKline), a benzamide derivative, Org 50081 (Organon -Netherlands), ritanserin, nefazodone, serzone, trazodone, Casopitant (GlaxoSmithKline), amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine sulfate, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, venlafaxine, chlorpromazine, haloperidol, droperidol, fluphenazine, loxapine, mesoridazine, molindone, perphenazine, pimozide, prochlorperazine promazine, thioridazine, thiothixene, trifluoperazine, clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone and paliperidone;

3.66 Method 3.42, wherein the therapeutic agent is an H3 agonist;

3.67 Method 3.42, wherein the therapeutic agent is an H3 antagonist;

3.68 Method 3.42, wherein the therapeutic agent is a noradrenergic agonist or antagonist;

3.69 Method 3.42, wherein the therapeutic agent is a galanin agonist;

3.70 Method 3.42, wherein the therapeutic agent is a CRH antagonist;

3.71 Method 3.42, wherein the therapeutic agent is a human growth hormone;

3.72 Method 3.42, wherein the therapeutic agent is a growth hormone agonist;

3.73 Method 3.42, wherein the therapeutic agent is estrogen;

3.74 Method 3.42, wherein the therapeutic agent is an estrogen agonist;

3.75 Method 3.42, wherein the therapeutic agent is a neurokinin-1 drug;

3.76 Method 3.42, wherein the therapeutic agent is an anti-Parkinson agent such as L-dopa, co-careldopa, duodopa, stalevo, Symmetrel, benztropine, biperiden, bromocriptine, entacapone, pergolide, pramipexole, procyclidine, ropinirole, selegiline and tolcapone;

3.77 Method 3.42, wherein the therapeutic agent is an opiate agonist or partial opiate agonist, for example, a mu-agonist or partial agonist, or a kappa-agonist or partial agonist, including mixed agonist/antagonists (e.g., an agent with partial mu-agonist activity and kappa-antagonist activity);

3.78 Method 3.77, wherein the therapeutic agent is buprenorphine, optionally, wherein said method does not include co-treatment with an anxiolytic agent, e.g., a GABA compound or benzodiazepine;

3.79 Method 3.42, wherein the therapeutic agent(s) is an opiate receptor antagonist or inverse agonist, e.g., a full opiate antagonist, for example, selected from naloxone, naltrexone, nalmefene, methadone, nalorphine, levallorphan, samidorphan, nalodeine, cyprodime, or norbinaltorphimine.

[0047] In another aspect of the invention, the combination of a Compound of the present disclosure (e.g., Compound 1 or any of 1.1-1.6) and one or more second therapeutic agents as described in Methods 3.28 to 3.79 may be administered to the patient as a Pharmaceutical Composition or a depot Composition as hereinbefore described. The combination compositions can include mixtures of the combined drugs, as well as two or more separate compositions of the drugs, which individual compositions can be, for example, co-administered together to a patient.

[0048] In a fourth aspect, the present disclosure provides for use of the Compound 1, or any of 1.1-1.6, or Pharmaceutical Composition 2, or any of 2.1-2.4, in Method 3 or any of Methods 3.1-3.79.

[0049] In a fifth aspect, the present disclosure provides for use of the Compound 1, or any of 1.1-1.6, or Pharmaceutical Composition 2, or any of 2.1-2.4, in the manufacture of a medicament for the treatment or prophylaxis of one or more central nervous system disorders as provided in any of Method 3 or 3.1-3.79.

[0050] In a sixth aspect, the present disclosure provides present disclosure Compound 1, or any of 1.1-1.6, or Pharmaceutical Composition 2, or any of 2.1-2.4, for use in Method 3 or any of 3.1-3.79.

DETAILED DESCRIPTION OF THE INVENTION

[0051] The words "treatment" and "treating" are to be understood accordingly as embracing prophylaxis and treatment or amelioration of symptoms of disease and/or treatment of the cause

of the disease. In particular embodiments, the words “treatment” and “treating” refer to prophylaxis or amelioration of symptoms of the disease.

[0052] The term "patient" may include a human or non-human patient.

[0053] The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (“DSM-5”), defines “major depressive disorder” (MDD) as having five or more of a set of symptoms during the same two-week period of time, which symptoms represent a change from the patient’s previous functioning. The five symptoms are selected from depressed mood, markedly diminished interest or pleasure in almost all activities, significant weight changes, insomnia or hyposomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive guilt, diminished ability to think or indecisiveness, and recurrent thoughts of death or suicidal ideation, wherein each of such symptoms is present nearly every day. At a minimum, MDD diagnosis requires at least depressed mood or loss of interest or pleasure as one of the five symptoms. MDD may consist of one or more “major depressive episodes” which can be spaced many weeks or months apart (more than 2 weeks apart to qualify as separate episodes). The DSM-5 notes that there is a risk of suicidal behavior at all time during a major depressive episode.

[0054] By its nature, MDD is an acute disorder in so far as the DSM-5 distinguishes it from “persistent depressive disorder”, in which a patient has many of the same symptoms as for MDD, but which persists for at least a 2-year period. In addition to MDD, the DSM-5 also defines a “short-duration depressive episode” as having a depressed affect and at least four of the other symptoms which define MDD for at least 4 days, but less than 14 days. The DSM further defines “recurrent brief depression” as the concurrent presence of depressed mood and at least four other symptoms of depression for 2 to 13 days at least once per month, and persisting for at least 12 consecutive months. Thus, recurrent brief depression similarly consists of brief episodes of depression which recur regularly.

[0055] The DSM-5 also includes major depressive episodes as one of the diagnostic criteria for a patient suffering from bipolar disorder. Thus, a patient presenting a major depressive episode may be suffering from either major depressive disorder or bipolar disorder.

[0056] It is apparent that there are is a particular need for effective treatment of depression during the earliest stages of a major depressive episode, since each day of such episode can have profound consequences for a patient, yet typical SSRI anti-depressive agents take up to 2-4

weeks for beneficial effects to appear. The same is true for treatment of short duration depressive episodes as well as individual episodes of recurrent brief depression.

[0057] Thus, as used herein, the term "acute depression" refers to the initial period of what may be a brief or a chronic episode of depression (e.g., lasting 2 days to 2 weeks, or 2 weeks to 2 months, or 2 months to 2 years, or more). "Acute depression" may thus refer to the initial period of a major depressive episode, a short-duration depressive episode, or a recurrent brief depressive episode. There is a particular need in the art for the treatment of such acute stages of depressive episodes. A treatment initiated during this acute phase of depression may be continued indefinitely in those patients which respond thereto.

[0058] The DSM-5 defines a variety of anxiety disorders, including generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobias. Like the depressive disorders discussed above, anxiety disorders can be marked by recurrent episodes of short duration, such as panic attacks, which may persist over the course of a chronic disorder. For example, generalized anxiety disorder is defined by the DSM-5 to require excessive anxiety and worry occurring more days that not for at least 6 months, about a number of events or activities. A panic attack is defined as an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, but it can repeatedly recur in response to either expected stimuli or unexpected stimuli. Thus, as for the depressive disorders described above, there is a need for rapidly-acting anxiolytic agents that can treat the symptoms of anxiety or panic, yet some of the most common treatments for anxiety disorders are the SSRIs and other antidepressant agents which take 2-4 weeks to provide relief.

[0059] As used herein, "acute anxiety" refers to any short-duration episode of anxiety, e.g., lasting from one day or less to one week, which may be part of a chronic course of anxiety (e.g., lasting 2 days to 2 weeks, or 2 weeks to 2 months, or 2 months to 2 years, or more). "Acute anxiety" may thus include a panic attack or any specific instance of an anxious response to triggering stimuli or events (e.g., to the stimuli which trigger a specific phobia, the events which trigger social anxiety or generalized anxiety). There is a particular need in the art for the treatment of such acute stages of anxious episodes. A treatment initiated during this acute phase of anxiety may be continued indefinitely in those patients which respond thereto.

[0060] Social avoidance can be a critical and debilitating symptom in patients suffering from anxiety disorders, especially social anxiety disorder, as well as in patients suffering from

traumatic anxiety disorders. Social avoidance is often one of the key determinants of whether a person with a severe anxiety disorder is capable of maintaining familial relationships or employment relationships. It has been unexpectedly found that certain substituted fused gamma carbolines having 5-HT_{2A} and dopamine receptor activity, such as lumateperone, are effective in treating the emotional experience symptoms of psychiatric disorders (e.g., the emotional experience negative symptoms of schizophrenics). Negative symptoms of schizophrenia can be divided into two categories: emotional experience (e.g., emotional withdrawal, passive social withdrawal, active social avoidance) and emotional expression (e.g., blunted effect, poor rapport, lack of spontaneity, and motor retardation). In two clinical studies of patients with acute exacerbated schizophrenia, administration of lumateperone once daily (60 mg P.O.), for up to 28 days, resulted in a significant and unexpected improvement in symptoms of emotional experience compared to placebo. These are the symptoms that are most highly correlated with interpersonal functioning. As such, such compounds, including the compounds of Formula I, may be highly effective in treating the emotional experience symptoms of other psychiatric disorders, such as social anxiety disorders, or any other psychiatric disorders in which social withdrawal and social avoidance are symptoms.

[0061] If not otherwise specified or clear from context, the following terms as used herein have the following meetings:

[0062] The term "pharmaceutically acceptable diluent or carrier" is intended to mean diluents and carriers that are useful in pharmaceutical preparations, and that are free of substances that are allergenic, pyrogenic or pathogenic, and that are known to potentially cause or promote illness. Pharmaceutically acceptable diluents or carriers thus exclude bodily fluids such as example blood, urine, spinal fluid, saliva, and the like, as well as their constituent components such as blood cells and circulating proteins. Suitable pharmaceutically acceptable diluents and carriers can be found in any of several well-known treatises on pharmaceutical formulations, for example Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., Basic and Clinical Pharmacology, Ninth Edition, McGraw Hill, 20037ybg; Goodman and Gilman, eds., The Pharmacological Basis of Therapeutics, Tenth Edition, McGraw Hill, 2001; Remington's Pharmaceutical Sciences, 20th Ed., Lippincott Williams & Wilkins., 2000; and

Martindale, The Extra Pharmacopoeia, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference herein in their entirety.

[0063] The terms "purified," "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g., from a reaction mixture), or natural source or combination thereof. Thus, the term "purified," "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization, LC-MS and LC-MS/MS techniques and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

[0064] The term “concurrently” when referring to a therapeutic use means administration of two or more active ingredients to a patient as part of a regimen for the treatment of a disease or disorder, whether the two or more active agents are given at the same or different times or whether given by the same or different routes of administrations. Concurrent administration of the two or more active ingredients may be at different times on the same day, or on different dates or at different frequencies.

[0065] The term “simultaneously” when referring to a therapeutic use means administration of two or more active ingredients at or about the same time by the same route of administration.

[0066] The term “separately” when referring to a therapeutic use means administration of two or more active ingredients at or about the same time by different route of administration.

[0067] The Compounds of the present disclosure are intended for use as pharmaceuticals, therefore pharmaceutically acceptable salts are preferred. Salts which are unsuitable for pharmaceutical uses may be useful, for example, for the isolation or purification of free Compounds of the Invention and are therefore also included within the scope of the compounds of the present disclosure.

[0068] The Compounds of the present disclosure may comprise one or more chiral carbon atoms. The compounds thus exist in individual isomeric, e.g., enantiomeric or diastereomeric form or as mixtures of individual forms, e.g., racemic/diastereomeric mixtures. Any isomer may be present in which the asymmetric center is in the (*R*)-, (*S*)-, or (*R,S*)- configuration. The invention is to be understood as embracing both individual optically active isomers as well as mixtures (e.g., racemic/diastereomeric mixtures) thereof. Accordingly, the Compounds of the

Invention may be a racemic mixture or it may be predominantly, e.g., in pure, or substantially pure, isomeric form, e.g., greater than 70% enantiomeric/diastereomeric excess ("ee"), preferably greater than 80% ee, more preferably greater than 90% ee, most preferably greater than 95% ee. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art (e.g., column chromatography, preparative TLC, preparative HPLC, simulated moving bed and the like).

[0069] Geometric isomers by nature of substituents about a double bond or a ring may be present in cis (*Z*) or trans (*E*) form, and both isomeric forms are encompassed within the scope of this invention.

[0070] It is also intended that the compounds of the present disclosure encompass their stable and unstable isotopes. Stable isotopes are nonradioactive isotopes which contain one additional neutron compared to the abundant nuclides of the same species (i.e., element). It is expected that the activity of compounds comprising such isotopes would be retained, and such compound would also have utility for measuring pharmacokinetics of the non-isotopic analogs. For example, the hydrogen atom at a certain position on the compounds of the disclosure may be replaced with deuterium (a stable isotope which is non-radioactive). Examples of known stable isotopes include, but not limited to, deuterium, ^{13}C, ^{15}N, ^{18}O. Alternatively, unstable isotopes, which are radioactive isotopes which contain additional neutrons compared to the abundant nuclides of the same species (i.e., element), e.g., ^{123}I, ^{131}I, ^{125}I, ^{11}C, ^{18}F, may replace the corresponding abundant species of I, C and F. Another example of useful isotope of the compound of the invention is the ^{11}C isotope. These radio isotopes are useful for radio-imaging and/or pharmacokinetic studies of the compounds of the invention. In addition, the substitution of atoms of having the natural isotopic distributing with heavier isotopes can result in desirable change in pharmacokinetic rates when these substitutions are made at metabolically liable sites. For example, the incorporation of deuterium (^{2}H) in place of hydrogen can slow metabolic degradation when the position of the hydrogen is a site of enzymatic or metabolic activity.

[0071] The Compounds of the present disclosure may be included as a depot formulation, e.g., by dispersing, dissolving or encapsulating the Compounds of the Invention in a polymeric matrix as described herein, such that the Compound is continually released as the polymer degrades over time. The release of the Compounds of the Invention from the polymeric matrix provides for the controlled- and/or delayed- and/or sustained-release of the Compounds, e.g.,

from the pharmaceutical depot composition, into a subject, for example a warm-blooded animal such as man, to which the pharmaceutical depot is administered. Thus, the pharmaceutical depot delivers the Compounds of the Invention to the subject at concentrations effective for treatment of the particular disease or medical condition over a sustained period of time, e.g., 14-180 days, preferably about 30, about 60 or about 90 days.

[0072] Polymers useful for the polymeric matrix in the Composition of the Invention (e.g., Depot composition of the Invention) may include a polyester of a hydroxyfatty acid and derivatives thereof or other agents such as polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly-beta.-hydroxybutyric acid, epsilon.-capro-lactone ring opening polymer, lactic acid-glycolic acid copolymer, 2-hydroxybutyric acid-glycolic acid copolymer, polylactic acid-polyethyleneglycol copolymer or polyglycolic acid-polyethyleneglycol copolymer), a polymer of an alkyl alpha-cyanoacrylate (for example poly(butyl 2-cyanoacrylate)), a polyalkylene oxalate (for example polytrimethylene oxalate or polytetramethylene oxalate), a polyortho ester, a polycarbonate (for example polyethylene carbonate or polyethylenepropylene carbonate), a polyortho-carbonate, a polyamino acid (for example poly-gamma.-L-alanine, poly-.gamma.-benzyl-L-glutamic acid or poly-y-methyl-L-glutamic acid), a hyaluronic acid ester, and the like, and one or more of these polymers can be used.

[0073] If the polymers are copolymers, they may be any of random, block and/or graft copolymers. When the above alpha-hydroxycarboxylic acids, hydroxydicarboxylic acids and hydroxytricarboxylic acids have optical activity in their molecules, any one of D-isomers, L-isomers and/or DL-isomers may be used. Among others, alpha-hydroxycarboxylic acid polymer (preferably lactic acid-glycolic acid polymer), its ester, poly-alpha-cyanoacrylic acid esters, etc. may be used, and lactic acid-glycolic acid copolymer (also referred to as poly(lactide-alpha-glycolide) or poly(lactic-co-glycolic acid), and hereinafter referred to as PLGA) are preferred. Thus, in one aspect the polymer useful for the polymeric matrix is PLGA. As used herein, the term PLGA includes polymers of lactic acid (also referred to as polylactide, poly(lactic acid), or PLA). Most preferably, the polymer is the biodegradable poly(d,l-lactide-co-glycolide) polymer.

[0074] In a preferred embodiment, the polymeric matrix of the invention is a biocompatible and biodegradable polymeric material. The term “biocompatible” is defined as a polymeric material that is not toxic, is not carcinogenic, and does not significantly induce inflammation in body tissues. The matrix material should be biodegradable wherein the polymeric material

should degrade by bodily processes to products readily disposable by the body and should not accumulate in the body. The products of the biodegradation should also be biocompatible with the body in that the polymeric matrix is biocompatible with the body. Particular useful examples of polymeric matrix materials include poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxanone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and natural polymers including albumin, casein, and waxes, such as, glycerol mono- and distearate, and the like. The preferred polymer for use in the practice of this invention is dl(polylactide-co-glycolide). It is preferred that the molar ratio of lactide to glycolide in such a copolymer be in the range of from about 75:25 to 50:50.

[0075] Useful PLGA polymers may have a weight-average molecular weight of from about 5,000 to 500,000 Daltons, preferably about 150,000 Daltons. Dependent on the rate of degradation to be achieved, different molecular weight of polymers may be used. For a diffusional mechanism of drug release, the polymer should remain intact until all of the drug is released from the polymeric matrix and then degrade. The drug can also be released from the polymeric matrix as the polymeric excipient bioerodes.

[0076] The PLGA may be prepared by any conventional method, or may be commercially available. For example, PLGA can be produced by ring-opening polymerization with a suitable catalyst from cyclic lactide, glycolide, etc. (see EP-0058481B2; Effects of polymerization variables on PLGA properties: molecular weight, composition and chain structure).

[0077] It is believed that PLGA is biodegradable by means of the degradation of the entire solid polymer composition, due to the break-down of hydrolysable and enzymatically cleavable ester linkages under biological conditions (for example in the presence of water and biological enzymes found in tissues of warm-blooded animals such as humans) to form lactic acid and glycolic acid. Both lactic acid and glycolic acid are water-soluble, non-toxic products of normal metabolism, which may further biodegrade to form carbon dioxide and water. In other words, PLGA is believed to degrade by means of hydrolysis of its ester groups in the presence of water, for example in the body of a warm-blooded animal such as man, to produce lactic acid and glycolic acid and create the acidic microclimate. Lactic and glycolic acid are by-products of

various metabolic pathways in the body of a warm-blooded animal such as man under normal physiological conditions and therefore are well tolerated and produce minimal systemic toxicity.

[0078] In another embodiment, the polymeric matrix useful for the invention may comprise a star polymer wherein the structure of the polyester is star-shaped. These polyesters have a single polyol residue as a central moiety surrounded by acid residue chains. The polyol moiety may be, e. g., glucose or, e. g., mannitol. These esters are known and described in GB 2,145,422 and in U. S. Patent No. 5,538,739, the contents of which are incorporated by reference.

[0079] The star polymers may be prepared using polyhydroxy compounds, e. g., polyol, e.g., glucose or mannitol as the initiator. The polyol contains at least 3 hydroxy groups and has a molecular weight of up to about 20,000 Daltons, with at least 1, preferably at least 2, e.g., as a mean 3 of the hydroxy groups of the polyol being in the form of ester groups, which contain polylactide or co-polylactide chains. The branched polyesters, e.g., poly (d, l-lactide-co-glycolide) have a central glucose moiety having rays of linear polylactide chains.

[0080] The depot compositions of the invention (e.g., Compositions 6 and 6.1-6.10, in a polymer matrix) as hereinbefore described may comprise the polymer in the form of microparticles or nanoparticles, or in a liquid form, with the Compounds of the Invention dispersed or encapsulated therein. "Microparticles" is meant solid particles that contain the Compounds of the Invention either in solution or in solid form wherein such compound is dispersed or dissolved within the polymer that serves as the matrix of the particle. By an appropriate selection of polymeric materials, a microparticle formulation can be made in which the resulting microparticles exhibit both diffusional release and biodegradation release properties.

[0081] When the polymer is in the form of microparticles, the microparticles may be prepared using any appropriate method, such as by a solvent evaporation or solvent extraction method. For example, in the solvent evaporation method, the Compounds of the Invention and the polymer may be dissolved in a volatile organic solvent (for example a ketone such as acetone, a halogenated hydrocarbon such as chloroform or methylene chloride, a halogenated aromatic hydrocarbon, a cyclic ether such as dioxane, an ester such as ethyl acetate, a nitrile such as acetonitrile, or an alcohol such as ethanol) and dispersed in an aqueous phase containing a suitable emulsion stabilizer (for example polyvinyl alcohol, PVA). The organic solvent is then evaporated to provide microparticles with the Compounds of the Invention encapsulated therein.

In the solvent extraction method, the Compounds of the Invention and polymer may be dissolved in a polar solvent (such as acetonitrile, dichloromethane, methanol, ethyl acetate or methyl formate) and then dispersed in an aqueous phase (such as a water/PVA solution). An emulsion is produced to provide microparticles with the Compounds of the Invention encapsulated therein. Spray drying is an alternative manufacturing technique for preparing the microparticles.

[0082] Another method for preparing the microparticles of the invention is also described in both U.S. Pat. No. 4,389,330 and U.S. Pat. No. 4,530,840.

[0083] The microparticle of the present invention can be prepared by any method capable of producing microparticles in a size range acceptable for use in an injectable composition. One preferred method of preparation is that described in U.S. Pat. No. 4,389,330. In this method the active agent is dissolved or dispersed in an appropriate solvent. To the agent-containing medium is added the polymeric matrix material in an amount relative to the active ingredient that provides a product having the desired loading of active agent. Optionally, all of the ingredients of the microparticle product can be blended in the solvent medium together.

[0084] Solvents for the Compounds of the Invention and the polymeric matrix material that can be employed in the practice of the present invention include organic solvents, such as acetone; halogenated hydrocarbons, such as chloroform, methylene chloride, and the like; aromatic hydrocarbon compounds; halogenated aromatic hydrocarbon compounds; cyclic ethers; alcohols, such as, benzyl alcohol; ethyl acetate; and the like. In one embodiment, the solvent for use in the practice of the present invention may be a mixture of benzyl alcohol and ethyl acetate. Further information for the preparation of microparticles useful for the invention can be found in U.S. Patent Pub. No. 2008/0069885, the contents of which are incorporated herein by reference in their entirety.

[0085] The amount of the Compounds of the present disclosure incorporated in the microparticles usually ranges from about 1 wt % to about 90 wt. %, preferably 30 to 50 wt. %, more preferably 35 to 40 wt. %. By weight % is meant parts of the Compounds of the present disclosure per total weight of microparticle.

[0086] The pharmaceutical depot compositions may comprise a pharmaceutically-acceptable diluent or carrier, such as a water miscible diluent or carrier.

[0087] Details of Osmotic-controlled Release Oral Delivery System composition may be found in U.S. Pub. No. 2009/0202631, the contents of which are incorporated by reference in its entirety.

[0088] A "therapeutically effective amount" is any amount of the Compounds of the invention (for example as contained in the pharmaceutical depot) which, when administered to a subject suffering from a disease or disorder, is effective to cause a reduction, remission, or regression of the disease or disorder over the period of time as intended for the treatment.

[0089] Dosages employed in practicing the present invention will of course vary depending, e.g. on the particular disease or condition to be treated, the particular Compound of the Invention used, the mode of administration, and the therapy desired. Unless otherwise indicated, an amount of the Compound of the Invention for administration (whether administered as a free base or as a salt form) refers to or is based on the amount of the Compound of the Invention in free base form (i.e., the calculation of the amount is based on the free base amount).

[0090] Compounds of the Invention may be administered by any satisfactory route, including orally, parenterally (intravenously, intramuscular or subcutaneous) or transdermally, but are preferably administered orally. In certain embodiments, the Compounds of the Invention, e.g., in depot formulation, are preferably administered parenterally, e.g., by injection.

[0091] In general, satisfactory results for Method 3 et seq., as set forth above, are indicated to be obtained on oral administration at dosages of the order from about 1 mg to 100 mg once daily, preferably 2.5 mg-50 mg, e.g., 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg or 50 mg, once daily, preferably via oral administration. In some embodiments, particularly related to sleep disorders, satisfactory results are obtained on oral administration of dosages of the order from about 2.5mg-5mg, e.g., 2.5mg, 3mg, 4mg or 5mg, of a Compound of the Invention, in free or pharmaceutically acceptable salt form, once daily, preferably via oral administration.

[0092] For treatment of the disorders disclosed herein wherein the depot composition is used to achieve longer duration of action, the dosages will be higher relative to the shorter action composition, e.g., higher than 1-100mg, e.g., 25mg, 50mg, 100mg, 500mg, 1,000mg, or greater than 1000mg. Duration of action of the Compounds of the present disclosure may be controlled by manipulation of the polymer composition, i.e., the polymer:drug ratio and microparticle size. Wherein the composition of the invention is a depot composition, administration by injection is preferred.

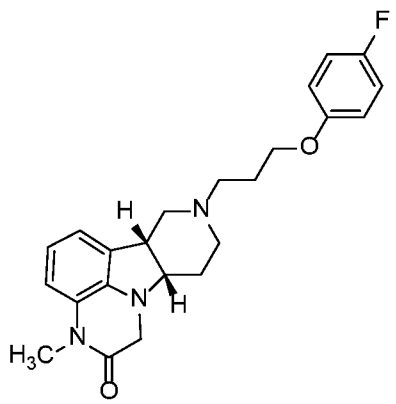
[0093] The pharmaceutically acceptable salts of the Compounds of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free base forms of these compounds with a stoichiometric amount of the appropriate acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

[0094] Pharmaceutical compositions comprising Compounds of the present disclosure may be prepared using conventional diluents or excipients (an example include, but is not limited to sesame oil) and techniques known in the galenic art. Thus, oral dosage forms may include tablets, capsules, solutions, suspensions and the like.

[0095] The prior art discloses numerous synthetic methods applicable generally to fused heterocycle gamma-carbolines related to the compounds disclosed herein. The skilled artisan may follow or adapt procedures as variously described in U.S. Patents RE39,680; U.S. 7,183,282; U.S. 8,309,722; U.S. 9,751,883; and U.S. Patent Pub. 2017/0319580.

[0096] Diastereomers of prepared compounds can be separated by, for example, HPLC using CHIRALPAK® AY-H, 5μ, 30x250mm at room temperature and eluted with 10% ethanol / 90% hexane / 0.1% dimethylethylamine. Peaks can be detected at 230 nm to produce 98-99.9%ee of the diastereomer.

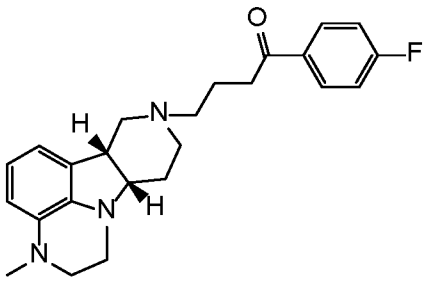
Example 1: Synthesis of (6bR,10aS)-8-(3-(4-fluorophenoxy)propyl)-3-methyl-6b,7,8,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-2(3H)-one



[097] Sodium hydride (60% in mineral oil, 32 mg, 0.786 mmol) is added to a solution of (6bR,10aS)-8-(3-(4-fluorophenoxy)propyl)-6b,7,8,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]

pyrrolo[1,2,3-de]quinoxalin-2(3H)-one (0.1 g, 0.262 mmol) in DMF (1 mL) at 0 °C. The mixture is stirred at 0 °C for 30 mins and iodomethane (19.6 μL, 0.315 mmol) is added. The reaction mixture is stirred at 0 °C for 1 h and water (4mL) is added. The mixture is extracted with ethyl acetate (3 × 4 ml) and the combined organic phase is dried over anhydrous Na_2SO_4. The mixture is filtered, and the filtrate is evaporated to dryness. The residue is purified by column chromatography with 0 – 100% mixed solvents [ethyl acetate/methanol/7N NH_3 (10: 1: 0.1 v/v)] in ethyl acetate. The title compound is obtained as an off-white solid (110 g, yield 99%). MS (ESI) m/z 396.2 $[M+H]^+$.^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.02 – 6.95 (m, 2H), 6.95 – 6.85 (m, 2H), 6.85 – 6.76 (m, 3H), 4.09 – 3.99 (m, 3H), 3.93 (m, 1H), 3.44 (m, 2H), 3.36 (s, 3H), 3.16 – 2.65 (m, 4H), 2.29 (m, 3H), 2.13 (m, 1H), 1.73 (m, 2H).

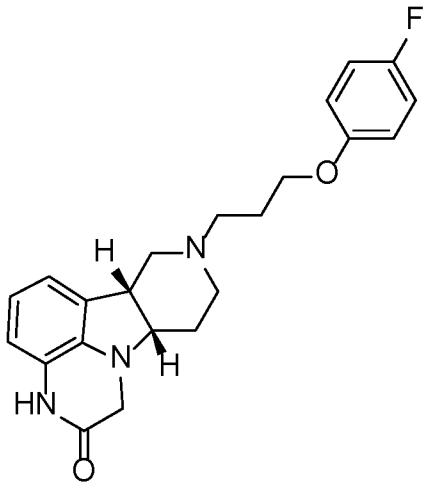
[098] Example 2: Synthesis of 4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido-[3',4':4,5]-pyrrolo[1,2,3-de]quinoxalin-8-(7H)-yl)-1-(4-fluorophenyl)-1-butanone



[099] A suspension of (6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido-[3',4':4,5]-pyrrolo[1,2,3-de]quinoxaline (ca. 11.8g, ca.50mmol), 4-chloro-4'-flurobutyrophenone (15.0g, 74.8mmol), triethylamine (30mL, 214mmol), and potassium iodide (12.6g, 76mmol) in dioxane (65 ml) and toluene (65 ml) is heated to reflux for 7 hours. After filtration and evaporation of the solvent, 200 ml of DCM is added. The DCM solution is washed with brine, dried (Na2SO4) and concentrated to approximately 55 ml. The concentrated solution is added dropwise to 600 ml of 0.5N HCl ether solution. The solid is filtered off and washed with ether and then dissolved in water. The resulting aqueous solution is basified with 2N NaOH and extracted with DCM. The DCM layers are combined, washed with brine (2x200mL) and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue over silica gel gives 4-((6bR,10aS)-3-methyl-

2,3,6b,9,10,10a-hexahydro-1H-pyrido-[3',4':4,5]-pyrrolo[1,2,3-de]quinoxalin-8-(7H)-yl)-1-(4-fluorophenyl)-1-butanone.

Example 3: Synthesis of (6bR,10aS)-8-(3-(4-fluorophenoxy)propyl)-6b,7,8,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-2(3H)-one



[0100] A mixture of (6bR,10aS)-6b,7,8,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo [1,2,3-de]quinoxalin-2(3H)-one (100mg, 0.436 mmol), 1-(3-chloroproxy)-4-fluorobenzene (100µL, 0.65 mmol) and KI (144mg, 0.87 mmol) in DMF (2 mL) is degassed with argon for 3 minutes and DIPEA (150 µL, 0.87 mmol) is added. The resulting mixture is heated to 78 °C and stirred at this temperature for 2 h. The mixture is cooled to room temperature and then filtered. The filter cake is purified by silica gel column chromatography using a gradient of 0 – 100% ethyl acetate in a mixture of methanol/7N NH_3 in methanol (1 : 0.1 v/v) as an eluent to produce partially purified product, which is further purified with a semi-preparative HPLC system using a gradient of 0 – 60% acetonitrile in water containing 0.1% formic acid over 16 min to obtain the title product as a solid (50mg, yield 30%). MS (ESI) m/z 406.2 $[M+1]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 10.3 (s, 1H), 7.2 – 7.1 (m, 2H), 7.0 – 6.9 (m, 2H), 6.8 (dd, J = 1.03, 7.25 Hz, 1H), 6.6 (t, J = 7.55 Hz, 1H), 6.6 (dd, J = 1.07, 7.79 Hz, 1H), 4.0 (t, J = 6.35 Hz, 2H), 3.8 (d, J = 14.74 Hz, 1H), 3.3 – 3.2 (m, 3H), 2.9 (dd, J = 6.35, 11.13 Hz, 1H), 2.7 – 2.6 (m, 1H), 2.5 – 2.3 (m, 2H), 2.1 (t, J = 11.66 Hz, 1H), 2.0 (d, J = 14.50 Hz, 1H), 1.9 – 1.8 (m, 3H), 1.7 (t, J = 11.04 Hz, 1H).

Example 4: Receptor Binding Profile of Compound of Examples 1, 2 and 3

[0101] Receptor binding is determined for the Compounds of Examples 1, 2 and 3 (corresponding to Formula 1, Formula B and Formula A, respectively). The following literature procedures are used, each of which reference is incorporated herein by reference in their entireties: 5-HT_{2A}: Bryant, H.U. et al. (1996), *Life Sci.*, 15:1259-1268; D2: Hall, D.A. and Strange, P.G. (1997), *Brit. J. Pharmacol.*, 121:731-736; D1: Zhou, Q.Y. et al. (1990), *Nature*, 347:76-80; SERT: Park, Y.M. et al. (1999), *Anal. Biochem.*, 269:94-104; Mu opiate receptor: Wang, J.B. et al. (1994), *FEBS Lett.*, 338:217-222.

[0102] In general, the results are expressed as a percent of control specific binding:

$$\frac{\text{measured specific binding}}{\text{control specific binding}} \times 100$$

and as a percent inhibition of control specific binding:

$$100 - \left(\frac{\text{measured specific binding}}{\text{control specific binding}} \times 100 \right)$$

obtained in the presence of the test compounds.

[0103] The IC_{50} values (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficients (nH) are determined by non-linear regression analysis of the competition curves generated with mean replicate values using Hill equation curve fitting:

$$Y = D + \left[\frac{A-D}{1 + (C/C_{50})^{nH}} \right]$$

where Y = specific binding, A = left asymptote of the curve, D = right asymptote of the curve, C = compound concentration, C_{50} = IC_{50}, and nH = slope factor. This analysis was performed using in –house software and validated by comparison with data generated by the commercial software SigmaPlot® 4.0 for Windows® (© 1997 by SPSS Inc.). The inhibition constants (Ki) were calculated using the Cheng Prusoff equation:

$$Ki = \frac{IC_{50}}{(1 + L/K_D)}$$

where L = concentration of radioligand in the assay, and K_D = affinity of the radioligand for the receptor. A Scatchard plot is used to determine the K_D.

[0104] The following receptor affinity results are obtained:

Receptor	Compound 1 (Ex. 1)	Formula B (Ex. 2)	Formula A (Ex. 3)
	Ki (nM) or maximum inhibition		
5-HT_{2A}	3.0	10	8.3
D2	114	49	160
D1	40	41	50
SERT	10.2	16	590
Mu opiate receptor	> 10,000	> 10,000	11

[0105] The Compound of Example 1 is further studied in a cell-based functional assay using Chinese hamster ovary (CHO) cells expressing the human D2S receptor, in both an agonist signaling assay, and in an antagonist signaling assay. To evaluate the agonist or antagonist activity of compounds, the ability of these compounds to either inhibit forskolin-stimulated cAMP accumulation or reverse the inhibition produced by 30 nM of quinpirole is determined.

[0106] CHO-K1 cells expressing human recombinant (hD2S) receptor (FAST-0102C) are grown prior to the test in media without antibiotic, and are then detached by gentle flushing with PBS-EDTA (5 mM EDTA), recovered by centrifugation and resuspended in assay buffer (5 mM KCl, 1.25 mM MgSO4, 124 mM NaCl, 25 mM HEPES, 13.3 mM Glucose, 1.25 mM KH2PO4, 1.45 mM CaCl2, 0.5 g/L protease-free BSA, supplemented with 1 mM IBMX).

[0107] For the agonist test, 12 µL of cells (2,500 cells/well) are mixed with 6 µL forskolin (10 µM final assay concentration) and 6 µL of the test compound at increasing concentrations in the wells of a 384-well plate, and then incubated for 30 minutes at room temperature. After addition of lysis buffer and 1 hour of incubation, cAMP concentrations are measured using the Cisbio "cAMP Dynamic2 Assay Kit" (Cisbio, 62AM4PEB). All assay points are determined in triplicate and data is presented as average values with standard deviation. Curve fitting is performed using XLfit software (IDBS), and affinity constants are determined using a 4-parameter logistic fit.

[0108] For the antagonist test, 12 µL of cells (2,500 cells/well) are mixed with 6 µL of the test compound at increasing concentrations in the wells of a 384-well plate, and then incubated 10 minutes at room temperature. Then 6 µL of a mix of quinpirole (final assay concentration 30 nM, corresponding to its measured EC80) and forskolin (10 µM final assay concentration) is added and

the plates are incubated for 30 minutes at room temperature. After addition of lysis buffer and 1 hour of incubation, cAMP concentrations are measured with the Cisbio "cAMP Dynamic2 Assay Kit". All assay points are determined in triplicate and data is presented as average values with standard deviation. Curve fitting is performed using XLfit software (IDBS), and affinity constants are determined using a 4-parameter logistic fit. For the antagonists, the apparent dissociation constants (K_B) are calculated using the modified Cheng Prusoff equation $K_B=IC_{50}/(1+(A/EC_{50A}))$, where A = concentration of reference agonist (30 nM of quinpirole) in the assay, and $EC_{50A}=EC_{50}$ value of the reference agonist (EC_{50} of 3.2 nM for quinpirole).

[0109] The results are shown in the table below.

Compound	Antagonist IC_{50} (nM)	Agonist EC_{50} (nM)	Apparent Dissociation Constants, K_B (nM)
IC201376	907	no activity (> 3 μM)	87.42

[0110] The results show that the Compound of Example 1 has antagonist activity at the D2S receptor, but no detectable agonist activity.

Example 5: Animal Pharmacokinetic Data

[0111] Using standard procedures, the pharmacokinetic profile of the compound of Examples 1, 2 and 3 are studied in rats.

Example 5a: Rat PK Study of the Compound of Example 1

[0112] Surgically modified rats are housed one per cage, and supplied with water and a commercial rodent diet *ad libitum* prior to study initiation. Food is withheld from the animals for a minimum of twelve hours before and during the study, until four hours post-dose, at which time food is returned. Animals are dosed IV, SC and PO, and blood samples are collected following the study design in the following table. Blood samples (~0.25 mL) are collected via JVC or tail vein, placed into chilled blood collection tubes containing sodium heparin as the anticoagulant, and kept on ice until centrifugation. Blood samples are then centrifuged at a temperature of 2 to 8 °C, at 3,000 g, for 5 minutes. Drug levels in the plasma samples are quantified via HPLC with MS/MS detection. Pharmacokinetic parameters based on the group geomean concentration versus time data, are calculated using a noncompartmental pharmaceutical data analysis software PK Solutions 2.0 (Summit Research Services, Montrose, CO).

Group #	Dosing Route	Total Animals N=	Dose (mg/kg)	Dosing Solution Conc.(mg/mL)	Dosing Volume (mL/kg)	Dose Vehicle	Sampling Time Points
1	IV	5	1	0.5	2	10% Trapposol/ 1% Tween 80 in water	0.03, 0.08, 0.25, 0.5, 1, 2, 6, 8, 24, and 48 hr
2	SC	5	1	0.5	2	PEG 400	0.03, 0.08, 0.25, 0.5, 1, 2, 6, 8, 24, and 48 hr
3	PO	5	1	0.5	2	PEG 400	0.03, 0.08, 0.25, 0.5, 1, 2, 6, 8, 24, and 48 hr

[0113] The results are summarized in the table below.

	IV (1 mg/kg)	PO (1 mg/kg)	SC (1 mg/kg)
30 min (ng/mL)	116	4.2	23.6
1 hour (ng/mL)	70	2.9	28.1
6 hours (ng/mL)	1.6	1.4	12.8
24 hours (ng/mL)	--	--	1.3
48 hours (ng/mL)	--	--	--
Cmax (ng/mL)	505	5.0	34.0
AUC (ng-hr/mL)	270	22.6	246.8
Bioavailability	100%	10%	90%
t-1/2 (hr)	1.0	--	--

Example 5b: Rat PK Study of the Compound of Example 2

[0114] This study is performed according to the same procedure as outlined in Example 5a, with the blood samples collected as shown in the table below.

Group #	Dosing Route	Total Animals N=	Dose (mg/ kg)	Dosing Solution Conc. (mg/mL)	Dosing Volume (mL/kg)	Dose Vehicle	Sampling Time Points
1	IV	6	1	0.2	5	50 mM citrate/ phosphate buffer pH 3.1	0.03, 0.08, 0.25, 0.5, 2, 4, 6, 8, and 12 hr
2	PO	6	10	2	5	0.02N HCl	0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hr
3	SC	5	45	12	3	20% (w/w) Trapposol/ 0.05%EDTA/ 0.5% Sodium meta-bisulfite in saline	0.083, 0.25, 0.5, 1, 2, 6, 12, 24, and 48 hr

[0115] Representative results are tabulated below (* indicates plasma concentration below measurable level of quantitation):

	Study 1		Study 2
	IV (1 mg/kg)	PO (10 mg/kg)	SC (45 mg/kg)
30 min (ng/mL)	92.5	12.2	704.7
1 hour (ng/mL)	--	13.8	699.7
6 hours (ng/mL)	3.1	1.5	498.4
12 hours (ng/mL)	0.5	0.3	168.3
24 hours (ng/mL)	--	*	12.3
Cmax (ng/mL)		13.8	746.8
AUC (ng-hr/mL)	230.6	56	7627
Bioavailability	100%	2%	73%
t-1/2 (hr)	1.4	--	--

Example 5c: Rat PK Studies of the Compound of Example 3

[0116] In a first study, rats are administered the compound of Example 3 either by intravenous bolus (IV) at 1 mg/kg in 45% Trapposol vehicle, or orally (PO) at 10 mg/kg in 0.5% CMC vehicle (N=3 each group). In a second study, rats are administered the compound of Example 2 at 10mg/kg PO or 3 mg/kg subcutaneously (SC), each in 45% Trapposol vehicle (N=6 for each group). Plasma concentrations of the drug are measured at time points from 0 to 48 hours post dose. Representative results are tabulated below (* indicates plasma concentration below measurable level of quantitation):

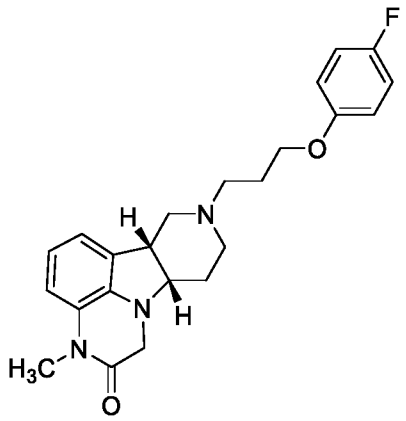
	Study One		Study Two	
	IV (1 mg/kg)	PO (10 mg/kg)	PO (10 mg/kg)	SC (3 mg/kg)
30 min (ng/mL)	99.0	30.7	54.9	134.4
1 hour (ng/mL)	47.3	37.2	60.6	140.9
6 hours (ng/mL)	1.1	9.4	21.0	18.2
24 hours (ng/mL)	*	0.1	0.4	1.9
48 hours(ng/mL)	*	*	ND	ND
Cmax (ng/mL)	314.8	37.2	60.6	140.9
AUC (ng-hr/mL)	182	215	409	676
Bioavailability	100%	12%	22%	123%
t-1/2 (hr)	1.1		-	

[0117] Together these results show that the compounds of the present disclosure are well-absorbed and distributed to the brain and tissues and are retained with a reasonably long half-life to enable once-daily administration of therapeutic doses.

2019403150 27 Mar 2025

The claims defining the invention are as follows:

1. A method for the treatment of a central nervous system disorder, wherein the central nervous system disorder is acute anxiety, acute depression, or the acute treatment of treatment-resistant depression, the method comprising administering to a patient in need thereof a compound of Formula I:



Formula I

in free or pharmaceutically acceptable salt form or a pharmaceutical composition comprising the compound of Formula I in admixture with a pharmaceutically acceptable diluent or carrier.

2. The method according to claim 1, wherein the central nervous system disorder is acute anxiety (e.g., a short-duration anxious episode associated with generalized anxiety disorder, panic disorder, specific phobias, or social anxiety disorder, or social avoidance).

3. The method according to claim 1, wherein the central nervous system disorder is acute depression (e.g., acute major depressive episode, acute short-duration depressive episode, acute recurrent brief depressive episode).

4. The method according to claim 1, wherein the central nervous system disorder is treatment resistant depression (e.g., depression which has not responded to treatment with an antidepressant agent selected from a selective serotonin reuptake inhibitor (SSRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant, a monoamine

oxidase inhibitor, a norepinephrine reuptake inhibitor (NRI), a dopamine reuptake inhibitor (DRI), an SRI/NRI, an SRI/DRI, an NRI/DRI, an SRI/NRI/DRI (triple reuptake inhibitor), a serotonin receptor antagonist, or any combination thereof).

5. The method according to claim 1, wherein the central nervous system disorder is an acute major depressive episode, acute short-duration depressive episode, or acute recurrent brief depressive episode (e.g., associated with major depressive disorder, bipolar disorder, or treatment resistant depression).

6. The method according to claim 1, wherein the central nervous system disorder is an acute major depressive episode.

7. The method according to claim 6, wherein the acute major depressive episode is associated with major depressive disorder.

8. The method according to claim 6, wherein the acute major depressive episode is associated with bipolar disorder.

9. The method according to claim 6, wherein the acute major depressive episode is associated with treatment resistant depression.

10. The method according to any one of claims 1 to 9, wherein the treatment has immediate onset of action.

11. The method according to claim 10, wherein said onset of action is within hours after initial dosing of the compound or composition.

12. The method according to claim 10, wherein said onset of action is within days after initial dosing of the compound or composition.

13. The method according to any one of claims 1 to 12, wherein the treatment provides an acute response within less than 1 week or from 1 to 7 days, or from 1 to 5 days, or from 1 to 3 days, after initial dosing of the compound or composition.

14. The method according to any one of claims 1 to 13, wherein the patient is diagnosed as having suicidal ideation and/or suicidal tendencies.

15. The method according to any one of claims 1 to 14, wherein the compound is in toluenesulfonic acid addition salt form.

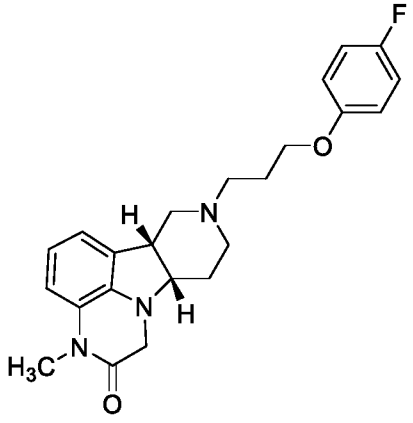
16. The method according to any one of claims 1 to 15, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with selective serotonin reuptake inhibitors (SSRIs), such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

17. The method according to any one of claims 1 to 15, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, sibutramine, duloxetine, atomoxetine, desvenlafaxine, milnacipran, and levomilnacipran.

18. The method according to any one of claims 1 to 15, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with antipsychotic agents, such as clomipramine, risperidone, quetiapine and olanzapine.

19. The method according to any one of claims 1 to 15, wherein the compound is administered as a sustained or delayed release composition, optionally as an injectable depot (e.g., comprising a polymeric matrix comprising poly(d,l-lactide-co-glycolide)).

20. Use of a compound of Formula I:



Formula I

in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for the treatment of a central nervous system disorder, wherein the central nervous system disorder is acute anxiety, acute depression, or the acute treatment of treatment-resistant depression.