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- (71) **Applicant: INTRA-CELLULAR THERAPIES, INC.** [US/US]; 430 East 29 street, Suite 900, New York, New York 10016 (US).
- (72) **Inventors: MATES, Sharon;** c/o Intra-Cellular Therapies, Inc., 430 East 29 street, Suite 900, New York, New York 10016 (US). **LI, Peng;** c/o Intra-Cellular Therapies, Inc., 430 East 29 street, Suite 900, New York, New York 10016 (US). **WENNOGLE, Lawrence P.;** c/o Intra-Cellular Therapies, Inc., 430 East 29 street, Suite 900, New York, New York 10016 (US). **DAVIS, Robert;** c/o Intra-Cellular Therapies, Inc., 430 East 29 street, Suite 900, New York, New York 10016 (US).
- (74) **Agent: POKER, Cory;** Hoxie & Associates, LLC, 75 Main Street, Suite 203, Millburn, New Jersey 07041 (US).
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(54) **Title:** ORGANIC COMPOUNDS

(57) **Abstract:** The invention relates to particular substituted heterocycle fused gamma-carbolines, their prodrugs, in free, solid, pharmaceutically acceptable salt and/or substantially pure form as described herein, pharmaceutical compositions thereof, and methods of use in the treatment of diseases involving 5-HT_{2A} receptor, serotonin transporter (SERT) and/or pathways involving dopamine D₁/D₂ receptor signaling systems, and/or the treatment of residual symptoms.

ORGANIC COMPOUNDS

This international application claims priority to U.S. Provisional Application No. 61/975,502 filed on April 4, 2014, and U.S. Provisional Application No. 62/015,120, filed on June 20, 2014, the contents of each of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0001] The invention relates to particular substituted heterocycle fused gamma-carbolines, in free, pharmaceutically acceptable salt and/or substantially pure form as described herein, pharmaceutical compositions thereof, and methods of use in the treatment of diseases involving 5-HT_{2A} receptor, serotonin transporter (SERT) and/or pathways involving dopamine D₁/D₂ 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; and other psychiatric and neurological conditions, as well as to combinations with other agents.

[0002] Psychosis, particularly schizophrenia, affects 1.1% of the population worldwide. This illness comprises three phases: prodromal phase, active phase and residual phase. Prodromal phase is an early phase wherein subclinical signs and symptoms are observed. These symptoms may include loss of interest in usual pursuits, withdrawal from friends and family members, confusion, trouble with concentration, feeling of listlessness and apathy. Active phase is characterized by exacerbations of positive symptoms such as delusions, hallucinations and suspiciousness. Residual phase is characterized by negative symptoms such as emotional withdrawal, passive social withdrawal, and stereotyped thinking; and general psychopathology symptoms including active social avoidance, anxiety, tension, and somatic concerns. Residual phase symptoms also are often accompanied by depression, cognitive dysfunction and insomnia. Collectively, these residual phase symptoms are not well-treated by many antipsychotic drugs currently available on the market and therefore are usually observed after the active phase symptoms have subsided after treatment. This phase of the illness is when patients would like to return to more productive and fulfilling lives, but since the residual negative symptoms and cognitive impairment are not properly treated, it

frustrates the return to such a function. There remains an urgent need for anti-psychotic agent, which can treat not just the active or acute phase symptoms, but also the residual phase symptoms of psychosis, e.g., schizophrenia. In addition, there is a need for medications to treat these symptoms that are free from undesirable side effects caused by off-target interactions with histamine H1 and muscarinic acetylcholine receptor systems.

BACKGROUND OF THE INVENTION

[0003] Substituted heterocycle fused gamma-carbolines are known to be agonists or antagonists of 5-HT₂ 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.

[0004] PCT/US08/03340 (WO 2008/112280) and U.S. Application Serial No. 10/786,935 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.

[0005] WO/2009/145900 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 D₂ receptors, thereby useful for the treatment of sleep disorders without the side effects of the dopamine D₂ pathways or side effects of other pathways (e.g., GABA_A receptors) associated with conventional 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.

[0006] Furthermore, it has been discovered that these substituted heterocycle fused gamma-carboline compounds are effective in treating not just acute symptoms, but also residual symptoms of psychosis. Therefore, methods of using these substituted heterocycle

fused gamma-carboline compounds, either alone or as an adjunctive therapy for the treatment of residual symptoms of psychosis, particularly schizophrenia, were disclosed. See for example, application PCT/US2014/68443.

[0007] WO 2009/114181 discloses methods of preparing toluenesulfonic acid addition salt crystals of particular substituted heterocycle fused gamma-carbolines, e.g., toluenesulfonic acid addition salt of 4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrindo[3',4': 4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone.

[0008] WO 2011/133224 discloses prodrugs/metabolites of substituted heterocycle fused gamma-carboline for improved formulation, e.g., extended/controlled release formulation. This application discloses that heterocycle fused gamma-carboline N-substituted with a 4-fluorophenyl(4-hydroxy)butyl moiety are shown to have high selectivity for the serotonin transporter (SERT) relative to the heterocycle fused gamma-carboline containing 4-fluorophenylbutanone. The hydroxy group on these compounds, however, is inter-converted to and from the ketone within the plasma and the brain, allowing it to serve as a reservoir for the 4-fluorophenylbutanone drug. While substituted heterocycle fused gamma-carbolines and their uses are known, our inventors have surprisingly found that particular substituted heterocycle fused gamma-carbolines, while less active in *in-vitro* tests, are inter-converted between these less active compounds and the highly active ketone drug within the plasma and the brain. Our inventors have further provided prodrugs of particular substituted heterocycle fused gamma-carbolines that have altered pharmacokinetic profile, e.g., altered mechanisms and/or rate of absorption and distribution, and therefore may be useful for an improved formulation and/or for controlling the duration of the effect of the drug in the body (e.g., for sustained- or controlled release).

[0009] WO 2013/155505 discloses compounds which block the *in vivo* inter-conversion between the hydroxy and the ketone, by incorporating an alkyl substituent on the carbon bearing the hydroxyl group, thus yielding compounds which antagonize 5-HT_{2A} receptors and also inhibit serotonin re-uptake transporter.

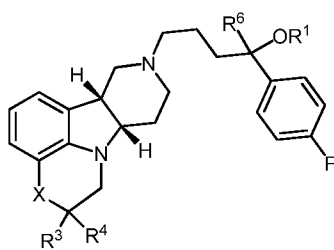
[00010] Some of the major routes of metabolism of the previously disclosed ketone and ether compounds are N-demethylation and O-demethylation catalyzed by cytochrome oxidase enzymes, and ketone reduction catalyzed by ketone reductase.

SUMMARY OF THE INVENTION

[00011] Without being bound by theory, the current invention provides compounds which partially limit metabolism of the N-methyl substituent, by incorporating deuterium atoms in various locations. Drug compounds in which deuterium is substituted for hydrogen are believed to generally have similar biological activity to the non-deuterated analog. Thus, the current invention provides compounds containing a mono-, di- or tri-deuterated N-methyl, or a mono- or di-deuterated methylene adjacent to the N-methyl, or any combination of these deuterium substitutions. The current invention also provides O-deuteroalkyl ether analogs of the previously disclosed alcohols, which will also limit metabolism of the O-alkyl substituent. These novel compounds will antagonize 5-HT_{2A} receptors, inhibit the serotonin re-uptake transporter, and modulate dopamine receptor initiated protein phosphorylation, in a like manner as to their natural hydrogen analogs, but will have an improved metabolic profile. Our inventors have shown that deuterations of some metabolically labile positions improves *in vitro* hepatic microsome stability, whereas deuteration of the 4-fluorophenyl ring (to yield a compound containing a 2,3,5,6-tetradeutero-4-fluoro ring) does not improve microsomal stability.

[00012] The current invention also provides further compounds which partially or fully block the *in vivo* inter-conversion between the hydroxy and the ketone, by way of incorporating a deuterium atom at the carbon bearing the hydroxyl group, yielding new, novel compounds which antagonize 5-HT_{2A} receptors, inhibit the serotonin re-uptake transporter, and modulate dopamine receptor initiated protein phosphorylation.

[00013] In the first aspect, the invention provides a compound of formula I:



Formula I

wherein:

X is N(H), N(R⁵) or O;

R⁵ is C₁₋₆ alkyl, optionally substituted with D (e.g. CH₃, CH₂D, CHD₂ or CD₃);

R³ and R⁴ are each independently H or D;

R⁶ is H or D;

R¹ is H, or

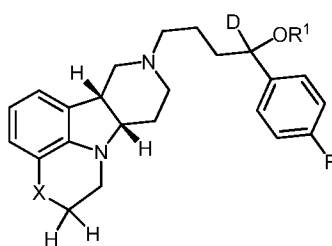
C₁₋₆ alkyl, optionally substituted with D (e.g. CH₃, CH₂D, CHD₂ or CD₃), or a pharmaceutically acceptable and physiologically labile moiety, e.g. a pharmaceutically acceptable and physiologically labile acyl moiety, for example, wherein the labile moiety is -C(O)-R², and R² is a C₁₋₂₁ alkyl, e.g., a linear C₁₋₂₁ alkyl,

wherein D is deuterium,

and provided that at least one of R¹, R², R³, R⁴, R⁵, or R⁶ includes at least one D;

in free or salt form.

[0014] In a second aspect, the invention provides the Compound of Formula I-B:



Formula I-B

wherein:

X is N(H), N(R⁵) or O;

R⁵ is C₁₋₆ alkyl;

R¹ is H, or

C₁₋₆ alkyl, or

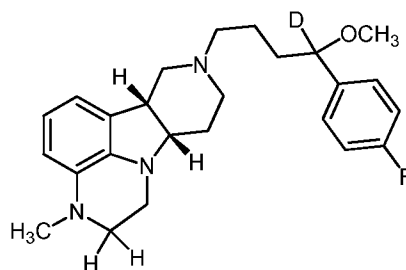
a pharmaceutically acceptable and physiologically labile moiety, e.g. a pharmaceutically acceptable and physiologically labile acyl moiety, for example, wherein the labile moiety is -C(O)-R², and R² is a C₁₋₂₁ alkyl, e.g., a linear C₁₋₂₁ alkyl,

and wherein D is deuterium;

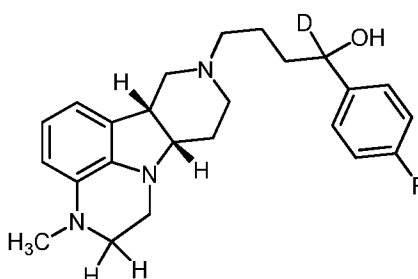
[0015] In a further embodiment, the invention provides the Compound of Formula I or I-B, as described in the following formulae:

- 1.1 the compound of Formula I or I-B, wherein R¹ is H;
- 1.2 the compound of Formula I or I-B, wherein R¹ is C₁₋₆alkyl (e.g., methyl);
- 1.3 the compound of Formula I or I-B, wherein R¹ is C₁₋₆ alkyl optionally substituted with D;
- 1.4 the compound of Formula I or I-B, wherein R¹ is CH₃;
- 1.5 the compound of Formula I or I-B wherein R¹ is CD₃;

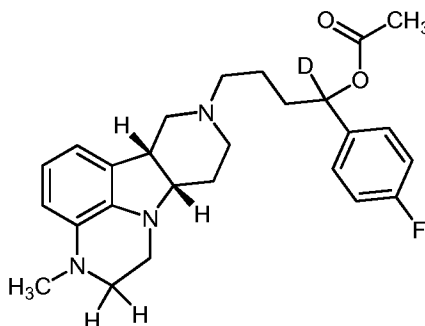
- 1.6 the compound of Formula I or I-B, wherein R¹ is a pharmaceutically acceptable and physiologically labile moiety, e.g. a pharmaceutically acceptable and physiologically labile acyl moiety;
- 1.7 the compound of Formula I or I-B, wherein R¹ is -C(O)-R², and wherein R² is C₁₋₂₁ alkyl;
- 1.8 the compound of Formula I or I-B, wherein R¹ is -C(O)-R², and wherein R² is C₁₋₁₅ alkyl;
- 1.9 the compound of Formula I or I-B, wherein R¹ is -C(O)-R², and wherein R² is C₁₋₉ alkyl;
- 1.10 the compound of Formula I or I-B, wherein R¹ is -C(O)-R², and wherein R² is methyl, ethyl or propyl;
- 1.11 the compound of Formula I or I-B, wherein R¹ is -C(O)-R², and wherein R² is methyl;
- 1.12 the compound of Formula I or I-B or any of formulae 1.1-1.11 wherein X is N(H), N(R⁵) or O;
- 1.13 the compound of Formula I or I-B or any of formulae 1.1-1.11, wherein X is O;
- 1.14 the compound of Formula I or I-B or any of formulae 1.1-1.11, wherein X is N(H);
- 1.15 the compound of Formula I or I-B or any of formulae 1.1-1.11, wherein X is N(R⁵), and wherein R⁵ is C₁₋₄ alkyl;
- 1.16 the compound of Formula I or I-B or any of formulae 1.1-1.11, wherein X is N(R⁵), and wherein R⁵ is CH₃;
- 1.17 the compound of Formula I or I-B or any of formulae 1.1-1.11, wherein X is N(R⁵), and wherein R⁵ is CD₃;
- 1.18 the compound of Formula I or I-B or any of formula 1.1-1.17, wherein R³ is D;
- 1.19 the compound of Formula I or I-B or any of formula 1.1-1.17, wherein R⁴ is D;
- 1.20 the compound of Formula I or I-B or any of formula 1.1-1.17, wherein R³ and R⁴ are D;
- 1.21 the compound of Formula I or I-B or any of formula 1.1-1.20, wherein X is N(R⁵), and R⁵ is CD₃ and R³ and R⁴ are both D;
- 1.22 the Compound of Formula I or I-B or any of formulae 1.1-1.21, wherein the Compound is:



1.23 the Compound of Formula I or I-B or any of 1.1-1.21, wherein the Compound is:



1.24 the Compound of Formula I or I-B or any of 1.1-1.21, wherein the Compound is:



1.25 the Compound of Formula I or I-B or any of 1-1.21, wherein the Compound is in substantially pure diastereomeric form (i.e., substantially free from other diastereomers);

1.26 the Compound of Formula I or I-B or any of 1-1.21, wherein the Compound has a diastereomeric excess of greater than 70%, preferably greater than 80%, more preferably greater than 90% and most preferably greater than 95%;

in free or salt form.

[0016] In a further embodiment of the first or second aspect, the invention provides a compound of Formula I, in free or salt form as described in the following formulae:

- 4.1 the Compound of Formula I or any of 1-1.26, wherein the salt is selected from a group consisting of hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like;
- 4.2 the Compound of Formula I or I-B or formula 4.1, wherein the salt is fumaric acid addition salt;
- 4.3 the Compound of Formula I or I-B or formula 4.1, wherein the salt is phosphoric acid addition salt;
- 4.4 the Compound of Formula I or I-B or formula 4.1, wherein the salt is a toluenesulfonic acid addition salt.

[0017] In a third aspect, the invention provides a pharmaceutical composition comprising the compound of formula I or I-B, or any of 1-1.26 or 4.1-4.4 (the Compounds of the Invention), in free or pharmaceutically acceptable salt form, in admixture with a pharmaceutically acceptable diluent or carrier, e.g. to provide immediate release or to provide sustained or delayed release.

[0018] In a further embodiment of the third aspect, the Pharmaceutical Composition of the Invention is for a sustained or delayed release, e.g., a depot formulation. In one embodiment, the depot formulation comprises the Compounds of the Invention in a polymeric matrix. In another embodiment, the Compounds of the Invention are 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 hydroxy fatty acid and derivatives thereof, or a polymer of an alkyl alpha-cyanoacrylate, a polyalkylene oxalate, a poly(ortho ester), a polycarbonate, a polyortho-carbonate, a poly(amino 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 75:25, PLGA 85:15 and PLGA 90:10 polymer. In another embodiment, the polymer is selected from poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, 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 particular embodiment, the polymeric matrix comprises poly (d,l-lactide-co-glycolide). Any of the Compositions hereinbefore described may be a pharmaceutical composition wherein said composition is in admixture with a pharmaceutically acceptable diluent or carrier.

[0019] The (Pharmaceutical) depot formulations as hereinbefore described are particularly useful for sustained or delayed release, wherein the Compounds of the Invention are released upon degradation of the polymeric matrix. These Compositions may be formulated for controlled- and/or sustained-release of the Compounds of the Invention (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 Invention 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 Invention over a period of about 120, or about 180 days.

[0020] In still another further embodiment, the Pharmaceutical Compositions of the Invention, particularly the depot compositions of the Invention, are formulated for administration by injection.

[0021] In the fourth aspect, the invention provides the Compounds of the Invention as hereinbefore described in an oral sustained or delayed release formulation. For example, the invention provides an osmotic controlled release oral delivery system (OROS) for delivery of the Compounds of the Invention, e.g. analogous to the systems described in WO 2000/35419 and EP 1 539 115 (U.S. Pub. No. 2009/0202631), the contents of each of which applications are incorporated by reference in their entirety. Therefore in one embodiment of this aspect, the invention provides a pharmaceutical composition or device comprising (a) a gelatin capsule containing a Compound of the Invention 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) an orifice formed or formable through the wall. (Composition P.1)

[0022] In another embodiment of this aspect, the invention provides a composition comprising a gelatin capsule containing a liquid, the Compounds of the Invention in free or pharmaceutically acceptable salt form or a Pharmaceutical Composition of the Invention as hereinbefore described, 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. (Composition P.2)

[0023] In still another embodiment of the fourth aspect, the invention provides a composition comprising a gelatin capsule containing a liquid, the Compound of the Invention in free or pharmaceutically acceptable salt form or a Pharmaceutical Composition of the Invention as hereinbefore described, 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. (Composition P.3)

[0024] In still another embodiment of the fourth aspect, the invention provides a composition comprising a gelatin capsule containing a liquid, the Compound of the Invention in free or pharmaceutically acceptable salt form or a Pharmaceutical Composition of the Invention as hereinbefore described, 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. (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.

[0025] In a particular embodiment of the fourth aspect, the Compound of the Inventions in the Osmotic-controlled Release Oral delivery System (i.e., in Composition P.1-P.4) are 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.

[0026] 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 WO 2000/35419, the contents of which are incorporated by reference in their entirety. Other Osmotic-controlled Release Oral delivery System for the Compound or the Pharmaceutical Composition of the Invention may be found in EP 1 539 115 (U.S. Pub. No. 2009/0202631), the contents of which are incorporated by reference in their entirety.

[0027] Therefore, in another embodiment of the fourth 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 the Invention, 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. (Composition P.5)

[0028] 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 Compounds of the Invention) 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. At least one orifice is drilled through the membrane on the first drug layer end of the capsule-shaped tablet. (Composition P.6)

[0029] 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. 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. (Composition P.7)

[0030] In a particular embodiment, the invention provides Composition P.7 wherein the first drug layer comprising salt and the second drug layer containing no salt. Composition P.5-P.7 may optionally comprise a flow-promoting layer between the membrane and the drug layers. Compositions P.1-P.7 will generally be referred to as Osmotic-controlled Release Oral delivery System Composition.

[0031] In the fifth aspect, the invention provides a method (Method I) for the treatment or prophylaxis of a central nervous system disorder, comprising administering to a patient in

need thereof, a Compound of Formula I or I-B or any of formulae 1-1.26, in free or pharmaceutically acceptable salt form as described in any of 4.1-4.4, or a pharmaceutical composition as hereinbefore described.

[0032] In a further embodiment of the fifth aspect, the invention provides Method I wherein the method is further as described in the following formulae:

- 7.1 Method I, wherein the central nervous system disorder is one or more disorders associated with dementia, e.g., disorders associated with mild cognition impairment and dementing illnesses including senile dementia, Alzheimer's disease, Pick's disease, fronto-temporal dementia, parasupranuclear palsy, dementia with Lewy bodies, vascular dementia, Huntington's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Down syndrome, elderly depression, Wernicke-Korsakoff's syndrome, cortico-basal degenerations and prion disease, autism and attention deficit hyperactivity disorder, as disclosed in WO 2013/155506, the contents of which is incorporated herein by reference in its entirety;
- 7.2 Method I or 7.1, wherein the disorders associated with dementia is selected from the group consisting of (1) behavioral or mood disorders such as agitation/irritation, aggressive/assaultive behavior, anger, physical or emotional outbursts; (2) psychosis; (3) depression; and (4) sleep disorders;
- 7.3 Method I or 7.1, wherein the central nervous system disorder is agitation/irritation, aggressive/assaultive behavior, anger, physical or emotional outbursts as disclosed in WO 2013/155504, the contents of which is incorporated herein by reference in its entirety;
- 7.4 Method I, wherein the central nervous system disorder is a disorder selected from a group consisting of obesity, anxiety, depression (for example refractory depression and major depressive disorder (MDD)), psychosis, 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, and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility;

- 7.5 Method I or any of 7.1-7.4, wherein the central nervous system disorder is a disorder involving serotonin 5-HT_{2A}, dopamine D₁/D₂ receptor system and/or serotonin reuptake transporter (SERT) pathways as similarly described in WO/2009/145900, the contents of which are herein incorporated by reference in their entirety;
- 7.6 Method I or any of Formulae 7.1-7.5, wherein the central nervous system disorder is a disorder involving serotonin reuptake transporter (SERT) pathways;
- 7.7 Method I or any of Formulae 7.1-7.6, wherein the central nervous system disorder is a disorder selected from the following: (1) 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; and (4) sleep disorders associated with psychosis, e.g., schizophrenia or Parkinson's disease; (5) depression; (6) anxiety; (7) post-traumatic stress disorder; or (8) impulse control disorder, e.g., intermittent explosive disorder;
- 7.8 Method I or any of Formulae 7.1-7.7, wherein the central nervous system disorder is psychosis, e.g., schizophrenia and said patient is a patient suffering from depression;
- 7.9 Method I or any of Formulae 7.1-7.8, wherein said patient is unable to tolerate the side effects of convention 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;
- 7.10 Method I or any of Formulae 7.1-7.9, wherein said patient is unable to tolerate the side effects of convention antipsychotic drugs, e.g., haloperidol, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone;
- 7.11 Method I or any of Formulae 7.1-7.10, wherein said disorder is depression and said patient is a patient suffering from psychosis, e.g., schizophrenia, or Parkinson's disease;
- 7.12 Method I or any of Formulae 7.1-7.6, wherein said disorder is sleep disorder and said patient is suffering from depression;

- 7.13 Method I or any of 7.1-7.6, wherein said one or more disorders is sleep disorder and said patient is suffering from psychosis, e.g., schizophrenia;
- 7.14 Method I or any of 7.1-7.6, wherein said one or more disorders is sleep disorder and said patient is suffering from Parkinson's disease;
- 7.15 Method I or any of 7.1-7.6, wherein said one or more disorders is sleep disorder and said patient is suffering from depression and psychosis, e.g., schizophrenia, or Parkinson's disease;
- 7.16 Method I or any of 7.1-7.6, wherein the central nervous system disorder is residual symptoms of psychosis, for example, schizophrenia (e.g., residual sub-type), delusional disorder (e.g., somatic type), major depression with psychosis, bipolar disorder with psychotic symptoms, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder or psychosis caused by a medical condition or substance use. Preferably, the patient is suffering from residual symptoms of schizophrenia;
- 7.17 Method I or any of 7.1-7.6, wherein the residual phase symptoms include: negative symptoms such as blunted affect, emotional withdrawal, poor rapport, passive or apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking; general psychopathology symptoms such as somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation and active social avoidance; cognitive impairment and sleep disorders (e.g., insomnia);
- 7.18 Any of the foregoing methods, wherein the effective amount is 1 mg-1000 mg, preferably 2.5 mg-50 mg, still preferably 1-40 mg, e.g., 1-10 mg, e.g., 10 mg, 20 mg, greater 20 mg, e.g., 30 mg, 40 mg;
- 7.19 Any of the foregoing methods, wherein the effective amount is 1mg-100mg per day, preferably 2.5 mg-50 mg per day, still preferably 1-40 mg/day, e.g., 1-10 mg/day, e.g., 10 mg/day, 20 mg/day, greater 20 mg/day, e.g., 30 mg/day, 40 mg/day;
- 7.20 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;
- 7.21 Any of the foregoing methods wherein the patient suffers from Parkinson's disease;
- 7.22 Any of the foregoing methods wherein the patient does not respond to a selective serotonin re-uptake inhibitor, e.g. selected from one or more of citalopram (Celexa, Cipramil, Cipram, Dalsan, Recital, Emocal, Sepram, Seropram, Citox, Cital); dapoxetine (Priligy); escitalopram (Lexapro, Cipralext, Seroplex, Esertia); fluoxetine (Depex, Prozac, Fontex, Seromex, Seronil, Sarafem, Ladose, Motivest, Flutop, Fluctin (EUR), Fluox (NZ), Depress (UZB), Lovan (AUS), Prodep (IND)); fluvoxamine (Luvox, Fevarin, Faverin, Dumyroxt, Favoxil, Movox); indalpine (Upstene); paroxetine (Paxil, Seroxat, Sereupin, Aropax, Deroxat, Divarius, Rexetin, Xetanor, Paroxat, Loxamine, Deparoc); sertraline (Zoloft, Lustral, Serlain, Asentra); vilazodone (Viibryd); or zimelidine (Zelmid, Normud);
- 7.23 Any of the foregoing methods wherein the patients is also receiving a selective serotonin re-uptake inhibitor, e.g. selected from one or more of citalopram (Celexa, Cipramil, Cipram, Dalsan, Recital, Emocal, Sepram, Seropram, Citox, Cital); dapoxetine (Priligy); escitalopram (Lexapro, Cipralext, Seroplex, Esertia); fluoxetine (Depex, Prozac, Fontex, Seromex, Seronil, Sarafem, Ladose, Motivest, Flutop, Fluctin (EUR), Fluox (NZ), Depress (UZB), Lovan (AUS), Prodep (IND)); fluvoxamine (Luvox, Fevarin, Faverin, Dumyroxt, Favoxil, Movox); indalpine (Upstene); paroxetine (Paxil, Seroxat, Sereupin, Aropax, Deroxat, Divarius, Rexetin, Xetanor, Paroxat, Loxamine, Deparoc); sertraline (Zoloft, Lustral, Serlain, Asentra); vilazodone (Viibryd); or zimelidine (Zelmid, Normud);
- 7.24 Any of the foregoing methods wherein the patients is suffering from autistic spectrum disorder, e.g., autism or Asperger Syndrome;
- 7.25 Any of the foregoing methods wherein the patients is suffering from dementia, e.g., disorders associated with mild cognition impairment and dementing illnesses including senile dementia, Alzheimer's disease, Pick's disease, fronto-temporal dementia, parasupranuclear palsy, dementia with Lewy bodies, vascular dementia, Huntington's disease, Parkinson's disease, multiple

- sclerosis, amyotrophic lateral sclerosis, Down syndrome, elderly depression, Wernicke-Korsakoff's syndrome, cortico-basal degenerations and prion disease, autism and attention deficit hyperactivity disorder;
- 7.26 Any of the foregoing methods wherein the patient is also receiving a cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor) or an N-Methyl D-Aspartate (NMDA) receptor antagonist, in free or pharmaceutically acceptable salt form;
- 7.27 Method 7.26, wherein the cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor) is selected from the group consisting of Tacrine, rivastigmine (Exelon), donepezil (Aricept), and galantamine (Razadyne, formerly called Reminyl) in free or pharmaceutically acceptable salt form;
- 7.28 Method 7.26, wherein the cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor) is donepezil in free or pharmaceutically acceptable salt form;
- 7.29 Method 7.26, wherein the NMDA receptor antagonist is memantine in free or pharmaceutically acceptable salt form;
- 7.30 Any of the foregoing methods further comprising administering one or more other therapeutic agents such as additional antipsychotic agents and/or anti-depressive agents and/or hypnotic agents;
- 7.31 Method 7.30, wherein the one or more other therapeutic agents are selected from anti-depressive agents such as compounds that modulate GABA activity (e.g., enhances the activity and facilitates GABA transmission), a GABA-B agonist, a 5-HT modulator (e.g., a 5-HT_{1A} agonist, a 5-HT_{2A} antagonist, a 5-HT_{2A} inverse agonist, etc.), a melatonin agonist, an ion channel modulator (e.g., blocker), a serotonin-2 antagonist/reuptake inhibitor (SARIs), an orexin receptor antagonist, an H3 agonist, a noradrenergic antagonist, a galanin agonist, a CRH antagonist, human growth hormone, a growth hormone agonist, estrogen, an estrogen agonist, a neurokinin-1 drug; and antipsychotic agents, e.g., atypical antipsychotic agents, in free or pharmaceutically acceptable salt form;
- 7.32 Method 7.30 or 7.31, wherein the one or more other therapeutic agents are antipsychotic agents, e.g., chlorpromazine, haloperidol, droperidol, fluphenazine, loxapine, mesoridazine, molindone, perphenazine, pimozide, prochlorperazine promazine, thioridazine, thiothixene, trifluoperazine,

clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, paliperidone, asenapine, lurasidone, iloperidone, cariprazine, amisulpride, zotepine, sertindole, wherein the one or more other therapeutic agents are administered as an adjunct to the compound of Formula I or the compound of Formula I is an adjunct to the one or more other therapeutic agents.

[0033] In a particular embodiment of the fifth aspect, the invention provides a method (Method I_P) for the treatment or prophylaxis of a central nervous system disorder as hereinbefore described, comprising administering to a patient in need thereof:

- 7.4P a compound of Formula I or I-B or any of formulae 1-1.26, in free or (pharmaceutically acceptable) salt form as described in any of 4.1-4.4;
- 7.8P a Pharmaceutical or Depot Composition as hereinbefore described; or
- 7.11P Osmotic-controlled Release Oral delivery System Composition as hereinbefore described.

[0034] In a further embodiment of the fifth aspect, the invention provides Method I_P, wherein the method is further described in any one of formulae 7.1-7.32.

[0035] In a particular embodiment of the fifth aspect, the invention provides Method I, I_P, or any of 7.1-7.32, wherein the disorder is schizophrenia or sleep disorder.

[0036] In a particular embodiment of the fifth aspect, the invention provides Method I, I_P, or any of 7.1-7.32, wherein the disorder is depression or anxiety.

[0037] In a particular embodiment of the fifth aspect, the invention provides Method I, I_P, or any of 7.1-7.32, wherein the disorder is post-traumatic stress disorder or an impulse control disorder, e.g., intermittent explosive disorder.

[0038] In a particular embodiment of the fifth aspect, the invention provides Method I, I_P, or any of 7.1-7.32, wherein the disorder is post-traumatic stress disorder or an impulse control disorder, e.g., intermittent explosive disorder in a patient suffering from dementia, e.g., senile dementia, Alzheimer's disease, Pick's disease, fronto-temporal dementia, parasupranuclear palsy, dementia with Lewy bodies, vascular dementia, Huntington's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Down syndrome, elderly depression, Wernicke-Korsakoff's syndrome, cortico-basal degenerations, prion disease, autism and/or attention deficit hyperactivity disorder.

[0039] In still another embodiment of the fifth aspect, the invention provides Method I, I_P, or any of 7.1-7.32, wherein the Depot Composition of the Invention is administered for controlled- and/or sustained-release of the Compounds of the Invention 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. Controlled- and/or sustained-release is particularly useful for circumventing premature discontinuation of therapy, particularly for antipsychotic drug therapy where non-compliance or non-adherence to medication regimes is a common occurrence.

[0040] In the sixth aspect, the invention provides a method (Method II) for the prophylaxis or treatment one or more sleep disorders, agitation, aggressive behaviors, post-traumatic stress disorder and/or impulse control disorder, e.g., intermittent explosive disorder, comprising administering to a patient in need thereof a compound as described in the following formulae:

- 8.1 a compound of Formula I or I-B or any of formulae 1-1.26, in free or (pharmaceutically acceptable) salt form as described in any of 4.1-4.4;
- 8.2 a Pharmaceutical or Depot Composition as hereinbefore described;
- 8.3 Osmotic-controlled Release Oral delivery System Composition as hereinbefore described.

[0041] In one embodiment of the sixth aspect, the invention provides Method II or any of 8.1-8.3, wherein the disorder is sleep disorders. In another embodiment of the fifth aspect, the invention provides Method II, wherein the disorder is agitation, aggressive behaviors, post-traumatic stress disorder and/or impulse control disorder, e.g., intermittent explosive disorder.

[0042] In a further embodiment of the sixth aspect, the invention provides Method II, 8.1-8.3, wherein the sleep disorder includes sleep maintenance insomnia, frequent awakenings, and waking up feeling unrefreshed;

- 8.11 Any of the foregoing methods, wherein the sleep disorder is sleep maintenance insomnia;
- 8.12 Any of the foregoing methods, wherein the effective amount is 1 mg-10 mg per day, e.g., 1-5 mg, preferably 2.5-5 mg, per day, still preferably 10 mg per day;
- 8.13 Any of the foregoing methods, wherein the effective amount is 2.5 mg or 5 mg, per day or 10 mg per day;
- 8.14 Any of the foregoing methods wherein the sleep disorder is in a patient suffering from or at risk of dyskinesia, e.g., 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., receiving levodopa;

8.15 Any of the foregoing methods wherein the patient suffers from Parkinson's disease.

[0043] The Compounds of the Invention provide effective treatment of 5-HT_{2A}, SERT and/or D₂ receptor related disorders without or with minimal extrapyramidal side effects as similarly disclosed and claimed in WO 2009/145900, the contents of which are incorporated by reference in their entirety. Therefore, the Compounds of the Invention, the Pharmaceutical Compositions of the Invention or the Depot Compositions of the Invention 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. Therefore, the Compounds of the Invention 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 or dementia. In another example, side effects may be reduced or minimized by administering a Compound of the Invention 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 Invention and the second therapeutic agent, are lower than if the agent/compound are administered as a monotherapy. In a particular embodiment, the Compounds of the Invention 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.

[0044] Therefore, in the seventh aspect, the current invention provides Method I or I_p, e.g., or any of formulae 7.1-7.32, or Method II or any of 8.1-8.15, further comprises one or more therapeutic agents selected from compounds that modulate GABA activity (e.g., enhances the activity and facilitates GABA transmission), a GABA-B agonist, a 5-HT modulator (e.g., a 5-HT_{1A} agonist, a 5-HT_{2A} antagonist, a 5-HT_{2A} inverse agonist, etc.), a melatonin 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, and an antipsychotic agent, e.g., an atypical antipsychotic agent, in free or pharmaceutically acceptable salt form (Method I-A and II-A respectively).

[0045] In another embodiment of the seventh aspect, Method I-A and II-A, Method I, Method I_P, e.g., or any of formulae 7.1-7.32, or Method II or any of 8.1-8.15, further comprises one or more therapeutic agents selected from a cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor) or an N-Methyl D-Aspartate (NMDA) receptor antagonist, in free or pharmaceutically acceptable salt form. In a specific embodiment, the cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor) is selected from the group consisting of Tacrine, rivastigmine (Exelon), donepezil (Aricept), and galantamine (Razadyne, formerly called Reminyl)) in free or pharmaceutically acceptable salt form. In a further embodiment, the cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor) is donepezil in free or pharmaceutically acceptable salt form. In another embodiment, the NMDA receptor antagonist is memantine in free or pharmaceutically acceptable salt form.

[0046] In a further embodiment of the seventh aspect, the invention provides Method I-A or II-A as follows, further comprising one or more therapeutic agents.

- 9.1 Method I-A or II-A, wherein the therapeutic agent(s) is compounds that modulate GABA activity (e.g., enhances the activity and facilitates GABA transmission);
- 9.2 Method I-A or II-A or 9.1, 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, gabaxadol, vigabatrin, tiagabine, EVT 201 (Evotec Pharmaceuticals) and estazolam;
- 9.3 Method I-A or II-A, wherein the therapeutic agent is an additional 5HT_{2A} antagonist;
- 9.4 Method I-A or II-A or 9.3, wherein said additional 5HT_{2A} 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); Method I-A or II-A, 9.3 or 9.4 additionally selected from pimavanserin (ACP-103) and pizotifen;
- 9.5 Method I-A or II-A, wherein the therapeutic agent is a melatonin agonist;

- 9.6 Method I-A or II-A or 9.5, wherein the melatonin 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;
- 9.7 Method I-A or II-A, wherein the therapeutic agent is an ion channel blocker;
- 9.8 Method I-A or II-A or 9.7, wherein said ion channel blocker is one or more of lamotrigine, gabapentin and pregabalin.
- 9.9 Method I-A or II-A, wherein the therapeutic agent is an orexin receptor antagonist;
- 9.10 Method I-A or II-A or 9.9, wherein the orexin receptor antagonist is selected from a group consisting of orexin, a 1,3-biaryurea, SB-334867-a (GlaxoSmithKline, UK), GW649868 (GlaxoSmithKline) and a benzamide derivative;
- 9.11 Method I-A or II-A, wherein the therapeutic agent is the serotonin-2 antagonist/reuptake inhibitor (SARI);
- 9.12 Method I-A or II-A or 9.11, 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;
- 9.13 Method I-A or II-A, wherein the therapeutic agent is the 5HT_{1a} agonist;
- 9.14 Method I-A or II-A or 9.13, wherein the 5HT_{1a} agonist is selected from a group consisting of one or more of repinotan, sarizotan, eptapirone, buspirone and MN-305 (MediciNova, San Diego, CA);
- 9.15 Method I-A or II-A, wherein the therapeutic agent is the neurokinin-1 drug;
- 9.16 Method I-A or II-A or 9.15, wherein the neurokinin-1 drug is Casopitant (GlaxoSmithKline);
- 9.17 Method I-A or II-A, wherein the therapeutic agent is an antipsychotic agent;
- 9.18 Method I-A or II-A or 9.17, 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;
- 9.19 Method I-A or II-A, wherein the therapeutic agent is an anti-depressant;

- 9.20 Method I-A or II-A or 9.19, 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, phenelazine sulfate, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine;
- 9.21 Method I-A or II-A, 9.17 or 9.18, wherein the antipsychotic agent is an atypical antipsychotic agent;
- 9.22 Method I-A or II-A, or any of 9.17-9.21, wherein the atypical antipsychotic agent is selected from a group consisting of clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, and paliperidone;
- 9.23 Method I-A or II-A, wherein the therapeutic agent is selected from any of methods 9.1-9.22, e.g., selected from a 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, gabaxadol, 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, phenelazine 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; In addition to the therapeutic agents listed herewith, Method I-A or II-A, is further selected from pimavanserin (ACP-103) and pizotifen;

- 9.24 Method I-A or II-A wherein the therapeutic agent is an H3 agonist;
- 9.25 Method I-A or II-A, wherein the therapeutic agent is an H3 antagonist;
- 9.26 Method I-A or II-A, wherein the therapeutic agent is a noradrenergic agonist or antagonist;
- 9.27 Method I-A or II-A, wherein the therapeutic agent is a galanin agonist;
- 9.28 Method I-A or II-A, wherein the therapeutic agent is a CRH antagonist;
- 9.29 Method I-A or II-A, wherein the therapeutic agent is a human growth hormone;
- 9.30 Method I-A or II-A, wherein the therapeutic agent is a growth hormone agonist;
- 9.31 Method I-A or II-A, wherein the therapeutic agent is estrogen;
- 9.32 Method I-A or II-A, wherein the therapeutic agent is an estrogen agonist;
- 9.33 Method I-A or II-A, wherein the therapeutic agent is a neurokinin-1 drug;
- 9.34 Method I-A or II-A, wherein a therapeutic agent is combined with compounds of Formula (I) and the therapeutic agent is an anti-Parkinson agent such as L-dopa, co-careldopa, duodopa, stalova, Symmetrel, benzotropine, biperiden, bromocriptine, entacapone, pergolide, pramipexole, procyclidine, ropinirole, selegiline and tolcapone;
- 9.35 Method I-A or II-A, wherein compounds of Formula I or I-B may be used to treat sleep disorders, depression, psychosis, or any combinations thereof, in patients suffering from the listed diseases and/or Parkinson's disease;
- 9.36 Method I-A or II-A, wherein the disorder is selected from at least one or more of psychosis, e.g., schizophrenia, depression, mood disorders, sleep disorders (e.g., sleep maintenance and/or sleep onset) or any combination of disorders thereof;
- 9.37 Any of the foregoing methods wherein the disorder is sleep disorder;

9.38 Any of the foregoing methods, wherein the disorder is sleep disorder associated with psychosis, e.g., schizophrenia or Parkinson's disease; in free or pharmaceutically acceptable salt form.

[0047] In another embodiment of the seventh aspect, the current invention provides Method I_P or Method II as hereinbefore described, further comprises one or more therapeutic agents selected from compounds that modulate GABA activity (e.g., enhances the activity and facilitates GABA transmission), a GABA-B agonist, a 5-HT modulator (e.g., a 5HT_{1A} agonist, a 5-HT_{2A} antagonist, a 5-HT_{2A} inverse agonist, etc.), a melatonin 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, and an antipsychotic agent, e.g., an atypical antipsychotic agent, in free or pharmaceutically acceptable salt form (Method I_P-A and II-A respectively). In a further embodiment of this aspect, the invention provides Method I_P-A or II-A as similarly described in any one of formulae 9.1-9.38.

[0048] In still another embodiment of the seventh aspect, Method I_P or Method II as hereinbefore described further comprises one or more therapeutic agents selected from a cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor) or an N-Methyl D-Aspartate (NMDA) receptor antagonist, in free or pharmaceutically acceptable salt form. In a specific embodiment, the cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor) is selected from the group consisting of Tacrine, rivastigmine (Exelon), donepezil (Aricept), and galantamine (Razadyne, formerly called Reminyl) in free or pharmaceutically acceptable salt form. In a further embodiment, the cholinesterase inhibitor (e.g., acetylcholinesterase inhibitor) is donepezil in free or pharmaceutically acceptable salt form. In another embodiment, the NMDA receptor antagonist is memantine in free or pharmaceutically acceptable salt form.

[0049] In the eighth aspect of the invention, the combination of a Compound of the Invention and one or more second therapeutic agents as described in Methods I-A, II-A or any of 9.1-9.38, may be administered as a Pharmaceutical Composition or a depot Composition as hereinbefore described. Similarly, the combination of a Compound of the Invention and one or more second therapeutic agents as described in Methods I_P-A, II-A or any of 9.1-9.38, may be administered 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.

[0050] In a particular embodiment, Methods I-A, II-A, I_p-A, II-A or any of 9.1-9.38 comprises administering to a patient in need thereof, a Compound of the Invention in combination with an atypical antipsychotic agent, e.g., a compound selected from clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, or paliperidone, in free or pharmaceutically acceptable salt form, for example wherein the dosage of the atypical antipsychotic agent is reduced and/or side effects are reduced.

[0051] In another embodiment, Methods I-A, II-A, Methods I_p-A, II-A or any of 9.1-9.38 comprises administering to a patient in need thereof, a Compound of the Invention in combination with an anti-depressant, e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelazine sulfate, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, or venlafaxine, in free or pharmaceutically acceptable salt form. Alternatively, the anti-depressant may be used as an adjunct medication in addition to the compounds of the Invention.

[0052] In still another embodiment, Methods I-A, II-A, I_p-A, II-A or any of 9.1-9.38 comprises administering to a patient in need thereof, a Compound of the Invention in combination with a compound that modulates GABA activity, e.g., a compound selected from doxepin, alprazolam, bromazepam, clobazam, clonazepam, clorazepate, diazepam, flunitrazepam, flurazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam, triazolam, indiplon, zopiclone, eszopiclone, zaleplon, Zolpidem, gabaxadol, vigabatrin, tiagabine, EVT 201 (Evotec Pharmaceuticals), estazolam or any combinations thereof, in free or pharmaceutically acceptable salt form.

[0053] In another particular embodiment, Methods I-A, II-A, I_p-A, II-A or any of 9.1-9.38 comprises administering to a patient in need thereof, a Compound of the Invention in combination with doxepin in free or pharmaceutically acceptable salt form. Dosages of doxepin can vary in any range known to a person of ordinary skill in the art. In one example, a 10 mg dose of doxepin may be combined with any dosage of a compound of the Invention.

[0054] In another embodiment, Methods I-A, II-A, I_p-A, II-A or any of 9.1-9.38 comprises administering to a patient in need thereof, a Compound of the Invention in combination (including as part of a daily dosage regimen) with an atypical stimulant, e.g., a

modafinil, adrafinil, or armodafinil. A regimen incorporating a Compound of the Invention with such drugs promotes more regular sleep, and avoids side effects such as psychosis or mania associated with higher levels of such drugs, e.g., in the treatment of bipolar depression, cognition associated with schizophrenia, and excessive sleepiness and fatigue in conditions such as Parkinson's disease and cancer.

[0055] In the ninth aspect, the invention provides use of a compound as described in the following formulae:

- 11.1 Compound of Formula I or I-B or any of formulae 1-1.26, in free or pharmaceutically acceptable salt form;
- 11.2 a Pharmaceutical Composition as hereinbefore described;
- 11.3 Depot Composition as hereinbefore described; or
- 11.4 Osmotic-controlled Release Oral delivery System Composition as hereinbefore described,

(in the manufacture of a medicament) for the treatment or prophylaxis of one or more disorders as disclosed hereinbefore, e.g., in any of Method I, any of 7.1-7.32, Method II, any of 8.1-8.15, Methods I-A, II-A, any of 9.1-9.38, Method I_P, Methods I_P-A, or any methods described in the sixth or seventh aspect of the invention.

[0056] In the tenth aspect, the invention provides a pharmaceutical composition as hereinbefore described, e.g., in the following formulae:

- 12.1 a Pharmaceutical Composition as hereinbefore described;
- 12.2 Depot Composition as hereinbefore described; or
- 12.3 Osmotic-controlled Release Oral delivery System Composition as hereinbefore described,

for use in the treatment or prophylaxis of one or more disorders as disclosed hereinbefore, e.g., in any of Method I, any of 7.1-7.32, Method II, any of 8.1-8.15, Methods I-A, II-A, any of 9.1-9.38, Method I_P, Methods I_P-A, or any methods described in the sixth or seventh aspect of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0057] If not otherwise specified or clear from context, the following terms as used herein have the following meanings:

- a. "Alkyl" as used herein is a saturated or unsaturated hydrocarbon moiety, e.g., one to 21 carbon atoms, e.g., one to 6 carbon atoms in length, which may be linear or branched (e.g., n-butyl or tert-butyl), unless otherwise specified.

- b. “Residual symptoms” as used herein include negative symptoms and general psychopathology symptoms as described in the Positive and Negative Symptom Scale (PANSS) for Schizophrenia described in Kay et al., *Schizophr. Bull.* (1987) 13(2):261-276, the contents of which are incorporated by reference in their entirety. Negative symptoms include: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking. General psychopathology symptoms include: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation and active social avoidance. Residual symptoms may also include depression, cognitive impairment and sleep disorders (e.g., insomnia). Of these residual symptoms, the compounds of the invention are particularly useful for the treatment of passive social withdrawal, stereotyped thinking, somatic concerns, anxiety, tension, active social avoidance and depression. Therefore, the compounds of the present invention are particularly useful in improving social integration and social function in patients suffering from schizophrenia. Treatment of these residual symptoms is also particularly effective in schizophrenic patients also suffering from depression.
- c. As used herein, the term “deuterated” refers to a compound containing at least one C-D, N-D or O-D bond, wherein D is the heavy hydrogen element deuterium, also known as ^2H .

[0058] Unless otherwise indicated, the Compounds of the Invention, e.g., Compounds of Formula I or I-B or any of 1-1.26, or any of formulae 4.1-4.4 may exist in free or salt, e.g., as acid addition salts, form. An acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic, citric, maleic acid, toluene sulfonic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmoic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isoethionic acid, and the like. In addition a salt of a compound of

the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)-amine. In a particular embodiment, the salt of the Compounds of the Invention is a toluenesulfonic acid addition salt. In another particular embodiment, the salt of the Compounds of the Invention is a fumaric acid addition salt. In a particular embodiment, the salt of the Compounds of the Invention is a phosphoric acid addition salt.

[0059] The Compounds of the Invention 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.

[0060] In some embodiments of the invention, Compounds of the Invention are not themselves active moieties, but are rather pro-drugs of active moieties. The term "pro-drug" is a term recognized in the art, and it refers to a drug precursor prior to administration that generates or releases the active metabolite *in vivo* following administration, via some chemical or physiological process. In particular, Compounds of Formula I or I-B, wherein R^1 is H, or C_{1-6} alkyl, or C_{1-6} alkyl optionally substituted with D, are active moieties. In contrast, Compounds of Formula I or I-B, wherein R^1 is a pharmaceutically acceptable and physiologically labile moiety, for example wherein R^1 is $-C(O)-R^2$ and wherein such group $-C(O)-R^2$ is a physiologically labile moiety, will have weak activity or no activity, but under physiological conditions will undergo hydrolysis to produce the Compounds of Formula I or I-B, wherein R^1 is H, and the other hydrolysis product which is not toxic at relevant concentrations (concentrations which would be provided by *in vivo* hydrolysis of a dosage of the prodrug compound). For example, for a Compound of Formula I or I-B wherein R^1 is $-C(O)R^2$, the hydrolysis products would be a Compound of Formula I wherein R^1 is H, and the other hydrolysis product would be a carboxylic acid of formula $R^2-C(O)-OH$. Such physiologically labile moieties include, but are not limited to, carboxylic esters, for example wherein R^2 is a C_{1-21} alkyl group. Under some physiological conditions, Compounds of Formula I or I-B, wherein R^1 is C_{1-6} alkyl (e.g., CH_3 or CD_3), may also under go *in vivo* conversion to the more active compound wherein R^1 is H, and therefore these compounds may be considered to be both active moieties and pro-drugs.

[0061] In a preferred embodiment of the invention, such pro-drug embodiments are selected from the group in which R^2 is chosen to result in a compound that undergoes physiologic hydrolysis at a therapeutically effective rate. One skilled in the art, will be able to select these groups to give Compounds of the Invention with a variety of physiologic rates of hydrolysis, solubility and membrane permeability characteristics, in order to achieve particular desired pharmacokinetic or pharmacodynamics properties.

[0062] In another preferred embodiment, the groups from which R^2 may be chosen may be based on the chemical, physical or toxicological properties of the by-product acids, of the formula $R^2-C(O)-OH$, which results from hydrolysis of the pro-drug compounds. In some embodiments, the groups may be chosen so that hydrolysis of the pro-drug produces a pharmacologically acceptable pro-moiety, e.g. one that is non-toxic and rapidly excreted and for the quantities generated in the course of therapeutic treatment. Such commonly used pro-moieties include acetic acid, butyric acid, isobutyric acid, pivalic acid, and such naturally occurring fatty acids as stearic acid, lauric acid, palmitic acid, arachidonic acid, linoleic acid, linolenic acid and oleic acid.

[0063] The Compounds of the Invention 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).

[0064] 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.

[0065] Wherein X is $-N(R^5)-$, and wherein R^5 is CH_3 or CD_3 , the Compounds of the Invention may further be metabolized *in vivo* to form the des-methyl derivative (i.e., wherein X is $-N(H)$).

[0066] Alternatively and/or additionally, the Compounds of the Invention 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 in the second and third aspect, 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.

[0067] 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 hydroxy-fatty 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-polyethylene glycol copolymer or polyglycolic acid-polyethylene glycol 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.

[0068] 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.

[0069] 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, polydioxonone, 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.

[0070] 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.

[0071] 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).

[0072] 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.

[0073] 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.

[0074] 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.

[0075] The depot composition of the invention 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.

[0076] In a particular embodiment, the Compound of the Invention is formulated into microparticles of an appropriate size to allow slow release kinetics after intramuscular injection.

[0077] 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.

[0078] 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, the contents of which are incorporated by reference.

[0079] 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.

[0080] 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 Publication Number 2008/0069885, the contents of which are incorporated herein by reference in their entirety.

[0081] The amount of the Compounds of the Invention 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 Invention per total weight of microparticle.

[0082] The pharmaceutical depot may comprise a pharmaceutically-acceptable diluent or carrier, such as a water miscible diluent or carrier.

[0083] Details of Osmotic-controlled Release Oral delivery System composition may be found in EP 1 539 115 (U.S. Pub. No. 2009/0202631) and WO 2000/35419, the contents of each of which are incorporated by reference in their entirety.

[0084] 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.

[0085] 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 Compounds of the Invention used, the mode of administration, and the therapy desired.

[0086] 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, is preferably administered parenterally, e.g., by injection.

[0087] In general, satisfactory results for Method I or any of formulae 7.1-7.32 or Method I_P or use of the Compounds of the Invention as hereinbefore described, e.g. for the treatment of a combination of diseases such as a combination of at least depression, psychosis, e.g., (1) 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; and (4) sleep disorders associated with psychosis, e.g., schizophrenia, or Parkinson's disease, 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 about 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.

[0088] Satisfactory results for Method II or any of 8.1-8.15, Method II or use of the Compounds of the Invention as hereinbefore described, e.g. for the treatment of sleep

disorder alone or agitation, aggressive behaviors, post-traumatic stress disorder or impulse control disorder alone, e.g., intermittent explosive disorder alone are indicated to be obtained on oral administration at dosages of the order from about 1 mg-10 mg once daily, e.g., about 2.5 mg-5 mg, e.g., 2.5 mg, 3 mg, 4 mg, 5 mg or 10 mg, of a Compound of the Invention, in free or pharmaceutically acceptable salt form, once daily, preferably via oral administration.

[0089] Satisfactory results for Method I-A or any of 9.1-9.38 or Method I_P-A are indicated to be obtained at less than 100mg, preferably less than 50 mg, e.g., less than 40 mg, less than 30 mg, less than 20 mg, less than 10 mg, less than 5 mg, less than 2.5 mg, once daily. Satisfactory results for Method II-A or any of 9.1-9.38 are indicated to be obtained at less than 10 mg, e.g., less than 5 mg or, preferably less than 2.5 mg.

[0090] 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 1-100 mg, e.g., 25 mg, 50 mg, 100 mg, 500 mg, 1,000 mg, or greater than 1000 mg. In a particular embodiment, the dosage regimen for depot composition includes an initial oral immediate dose along with depot release so as to provide a steady-state blood level of the drug. Duration of action of the Compounds of the Invention 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.

[0091] The pharmaceutically acceptable salts of the Compounds of the Invention 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. Further details for the preparation of these salts, e.g., toluenesulfonic salt in amorphous or crystal form, may be found in PCT/US08/03340 and/or U.S. Provisional Appl. No. 61/036,069.

[0092] Pharmaceutical compositions comprising Compounds of the Invention 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.

[0093] All references herein to dosage, dosage rate or therapeutically effect amount of a Compound or Composition of the Invention refers to the equivalent free-base or

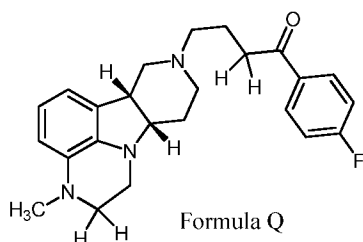
pharmaceutically acceptable salt form of the non-pro-drug moiety or the in the dosage, or in other words, the active-moiety (the Compound of the Invention, wherein R¹ is H or C₁₋₆ alkyl), of the compound or composition described.

Methods of Making the Compounds of the Invention:

[0094] The intermediates of the Compounds of the Invention may be prepared as described in WO PCT/US08/03340 (WO 2008/112280); U.S. Application Serial No. 10/786,935; 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, the contents of which are incorporated by reference in their entirety. Salts of the Compounds of the Invention may also be prepared as similarly described in U.S. Pat. No. 6,548,493; 7,238,690; 6,552,017; 6,713,471; 7,183,282; U.S. RE39680; U.S. RE39679; and WO 2009/114181, the contents of each of which are incorporated by reference in their entirety. All substituents X, R¹, R², R³, R⁴, R⁵ and R⁶ appearing in the structures and formulas of the Examples below are as defined for Formula I and I-B hereinbefore.

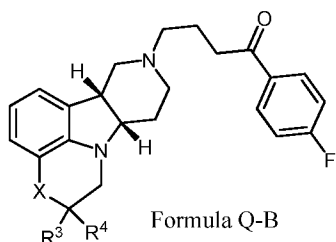
[0095] Isolation or purification of the diastereomers of the Compounds of the Invention may be achieved by conventional methods known in the art, e.g., column purification, preparative thin layer chromatography, preparative HPLC, crystallization, trituration, simulated moving beds and the like.

[0096] The Compounds of Formula I or I-B can be prepared by standard methods known to those skilled in the art. US Patent 8,309,722, which is incorporated by reference in its entirety, discloses the synthesis of the Compound of Formula Q, and all of the intermediates therefor:

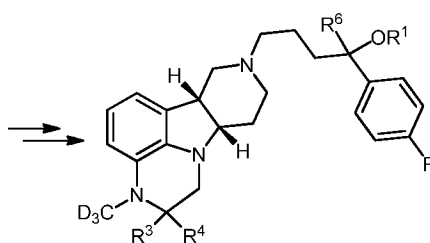
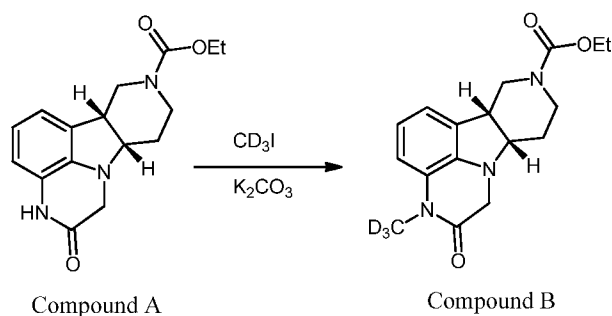


[0097] The Compounds of the Invention are synthesized from the related Compounds of the Formula Q-B, wherein in X, R³ and R⁴ are as defined for Formula I or I-B, which are

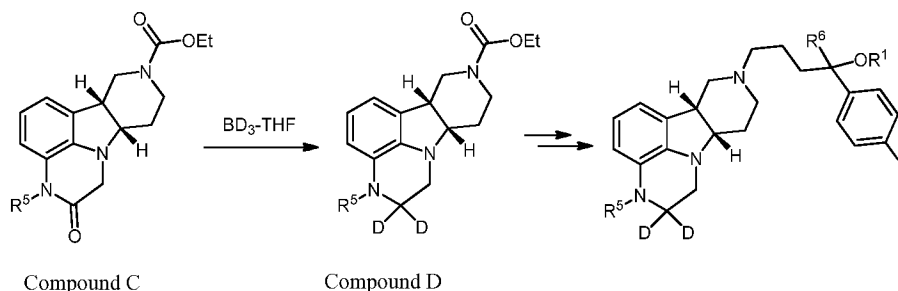
prepared in like manner to the Compounds of Formula Q, using, for example, the intermediate Compounds B and D, as shown in the examples below.



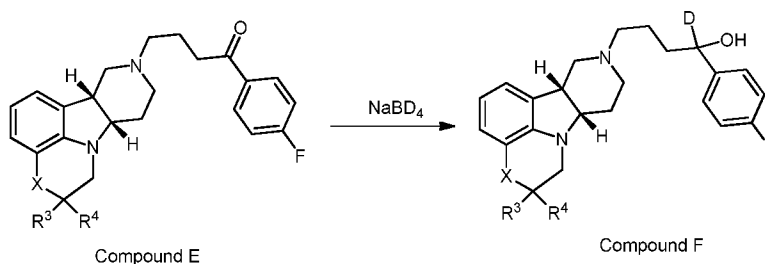
[0098] For example, Compound B may be prepared from Compound A (disclosed in the US Patent 8,309,722) by reacting with d3-iodomethane in the presence of a base, such as potassium carbonate or sodium hydride, in a suitable solvent, such as acetone or dimethylformamide. Following the procedures of US Patent 8,309,722 and those herein, Compound B can then be converted to a Compound of Formula I or I-B, wherein X is N(R⁵) and R⁵ is CD₃. The reaction may be summarized in the reaction scheme below:



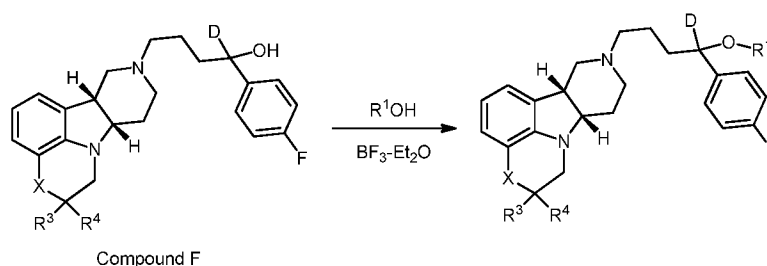
[0099] For example, Compound D may be prepared from a Compound of Formula C (disclosed in the US Patent 8,309,722, and herein) by reacting with d3-borane THF complex, in a suitable solvent, such as tetrahydrofuran. Following the procedures of US Patent 8,309,722 and those herein, Compound D can then be converted a Compound of Formula I or I-B, wherein R³ and R⁴ are D. The reaction may be summarized in the reaction scheme below:



[00100] The Compounds of Formula I can be prepared by standard methods known to those skilled in the art. For example, the Compound of Formula I or I-B, wherein R¹ is H, and wherein X is as defined in Formula I or I-B, e.g. X is, for example, N(CH₃), may be prepared by reacting Compound E with either sodium borodeuteride or lithium aluminum deuteride in an ethereal solvent such as tetrahydrofuran, optionally containing a deuterated protic co-solvent such as methyl alcohol-d (CH₃OD). The reaction may be summarized in the reaction scheme below:

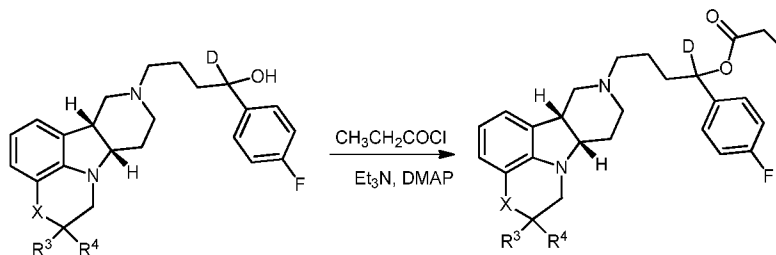


[00101] A Compound of Formula I or I-B, wherein R¹ is C₁₋₆ alkyl may be prepared by reacting Compound F with R¹-OH and BF₃-OEt₂. The reaction may be summarized in the reaction scheme below:



[00102] A Compound of Formula I or I-B wherein R¹ is -C(O)-R², and wherein R² is, e.g. ethyl, may be prepared by reacting Compound F with, e.g. propanoyl chloride in a solvent

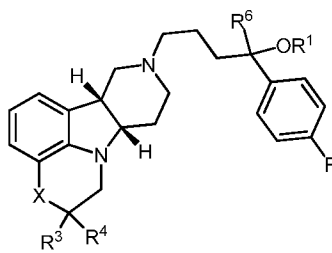
such as dichloromethane, in the presence of a base such as triethylamine and N,N-dimethyl-4-aminopyridine (DMAP). The reaction may be summarized in the reaction scheme below:



Similar compounds of Formula I or I-B wherein R^1 is $-\text{C}(\text{O})-\text{R}^2$, and wherein R^2 is C_{1-21} alkyl, optionally substituted with D, may be prepared in an analogous manner.

Claims:

1. A compound of formula I:



Formula I

wherein:

X is N(H), N(R⁵) or O;

R⁵ is C₁₋₆ alkyl, optionally substituted with D (e.g. CH₃, CH₂D, CHD₂ or CD₃);

R³ and R⁴ are each independently H or D;

R⁶ is H or D;

R¹ is H, or

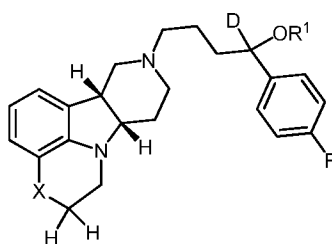
C₁₋₆ alkyl, optionally substituted with D (e.g. CH₃, CH₂D, CHD₂ or CD₃), or a pharmaceutically acceptable and physiologically labile moiety, e.g. a pharmaceutically acceptable and physiologically labile acyl moiety, for example, wherein the labile moiety is -C(O)-R², and R² is a C₁₋₂₁ alkyl, e.g., a linear C₁₋₂₁ alkyl,

wherein D is deuterium,

and provided that at least one of R¹, R², R³, R⁴, R⁵, or R⁶ includes at least one D;

in free or salt form.

2. The compound according to claim 1, wherein said compound is a compound of Formula I-B:



Formula I-B

wherein:

X is N(H), N(R⁵) or O;

R⁵ is C₁₋₆ alkyl;

R¹ is H, or

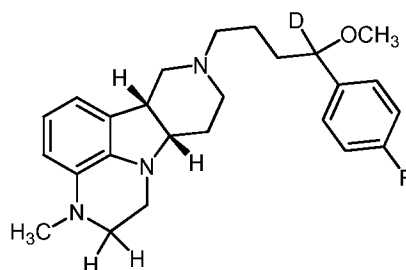
C₁₋₆ alkyl, or

a pharmaceutically acceptable and physiologically labile moiety, e.g. a pharmaceutically acceptable and physiologically labile acyl moiety, for example, wherein the labile moiety is -C(O)-R², and R² is a C₁₋₂₁ alkyl, e.g., a linear C₁₋₂₁ alkyl,

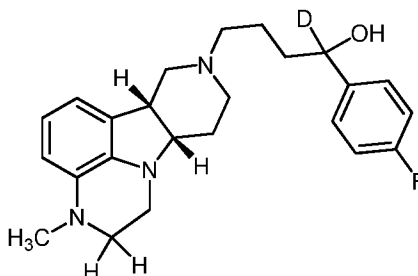
and wherein D is deuterium;

3. The compound according to Claim 1 or 2, wherein R¹ is H;
4. The compound according to Claim 1 or 2, wherein R¹ is C₁₋₆alkyl (e.g., methyl);
5. The compound according to Claim 1, wherein R¹ is C₁₋₆ alkyl optionally substituted with D;
6. The compound according to Claim 1 or 2, wherein R¹ is CH₃;
7. The compound according to Claim 1 wherein R¹ is CD₃;
8. The compound according to Claim 1 or 2, wherein R¹ is a pharmaceutically acceptable and physiologically labile moiety, e.g. a pharmaceutically acceptable and physiologically labile acyl moiety;
9. The compound according to Claim 1 or 2, wherein R¹ is -C(O)-R², and wherein R² is C₁₋₂₁ alkyl;
10. The compound according to Claim 1 or 2, wherein R¹ is -C(O)-R², and wherein R² is C₁₋₁₅ alkyl;
11. The compound according to Claim 1 or 2, wherein R¹ is -C(O)-R², and wherein R² is C₁₋₉ alkyl;
12. The compound according to Claim 1 or 2, wherein R¹ is -C(O)-R², and wherein R² is methyl, ethyl or propyl;
13. The compound according to Claim 1 or 2, wherein R¹ is -C(O)-R², and wherein R² is methyl;
14. The compound according to any of Claims 1-13, wherein X is N(H), N(R⁵) or O;
15. The compound according to any of Claims 1-13, wherein X is O;
16. The compound according to any of Claims 1-13, wherein X is N(H);
17. The compound according to any of Claims 1-13, wherein X is N(R⁵), and wherein R⁵ is C₁₋₄ alkyl;

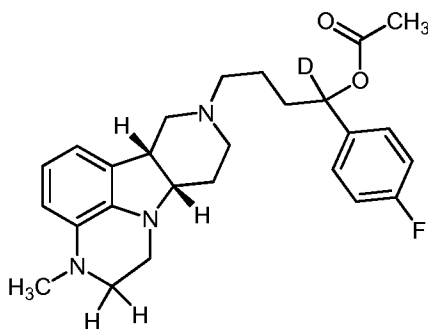
18. The compound according to any of Claims 1-13, wherein X is N(R⁵), and wherein R⁵ is CH₃;
19. The compound according to any of Claims 1-13, wherein X is N(R⁵), and wherein R⁵ is CD₃;
20. The compound according to any of Claims 1-19, wherein R³ is D;
21. The compound according to any of Claims 1-19, wherein R⁴ is D;
22. The compound according to any of Claims 1-19, wherein R³ and R⁴ are D;
23. The compound according to any of Claims 1-22, wherein X is N(R⁵), and R⁵ is CD₃ and R³ and R⁴ are both D;
24. The compound according to any of Claims 1-23, wherein the Compound is:



25. The compound according to any of Claims 1-23, wherein the Compound is:



26. The compound according to any of Claims 1-23, wherein the Compound is:



27. The compound according to any one of claims 1-26, wherein said compound is in salt form.
28. The compound according to claim 27, wherein the salt is selected from a group consisting of toluenesulfonic, fumaric and phosphoric acid addition salt.
29. A pharmaceutical composition comprising a compound according to any one of claims 1-28, in free or pharmaceutically acceptable salt form, in combination or association with a pharmaceutically acceptable diluent or carrier.
30. A method for the treatment or prophylaxis of a central nervous system disorder comprising administering to a patient in need thereof a therapeutically effective amount of the compound according to any one of claims 1-28, in free or pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 29.
31. The method according to claim 30, wherein said disorder is selected from a group consisting of obesity, anxiety, depression (for example refractory depression and MDD), psychosis, 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, 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, post-traumatic stress disorder, impulse control disorders, intermittent explosive disorder.
32. The method according to claim 30, wherein said disorder is one or more disorders associated with dementia, e.g., disorders associated with mild cognition impairment and dementing illnesses including senile dementia, Alzheimer's disease, Pick's disease, fronto-temporal dementia, parasupranuclear palsy, dementia with Lewy bodies, vascular dementia, Huntington's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Down syndrome, elderly depression, Wernicke-Korsakoff's syndrome, cortico-basal degenerations and prion disease, autism an attention deficit hyperactivity disorder.
33. The method according to claim 30, wherein said disorder is a disorder involving one of the serotonin 5-HT_{2A}, dopamine D2 and/or serotonin reuptake transporter (SERT) pathways.

34. The method according to any one of claims 30 to 32, wherein the central nervous system disorder is residual symptoms of psychosis, e.g., schizophrenia, delusional disorder, major depression with psychosis, bipolar disorder with psychotic symptoms, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder or psychosis caused by a medical condition or substance use, preferably, the patient is suffering from residual symptoms of schizophrenia.
35. The method according to claim 34, wherein said residual phase symptoms are selected from negative symptoms such as blunted affect, emotional withdrawal, poor rapport, passive or apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking; general psychopathology symptoms such as somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation and active social avoidance; cognitive impairment and sleep disorders (e.g., insomnia).
36. The method according to any one of claims 30-35, further comprising the administration of one or more other therapeutic agents such as an additional antipsychotic agents and/or anti-depressive agents and/or hypnotic agents.
37. The method of claim 36, wherein the one or more other therapeutic agents are selected from anti-depressive agents such as compounds that modulate GABA activity (e.g., enhances the activity and facilitates GABA transmission), a GABA-B agonist, a 5-HT modulator (e.g., a 5-HT_{1A} agonist, a 5-HT_{2A} antagonist, a 5-HT_{2A} inverse agonist, etc.), a melatonin agonist, an ion channel modulator (e.g., blocker) a serotonin-2 antagonist/reuptake inhibitor (SARIs), an orexin receptor antagonist, an H3 agonist, a noradrenergic antagonist, a galanin agonist, a CRH antagonist, human growth hormone, a growth hormone agonist, estrogen, an estrogen agonist, a neurokinin-1 drug; and antipsychotic agents, e.g., atypical antipsychotic agents, in free or pharmaceutically acceptable salt form.
38. The method of any of claims 36-37, wherein the one or more other therapeutic agents are antipsychotic agents selected from chlorpromazine, haloperidol, droperidol, fluphenazine, loxapine, mesoridazine molindone, perphenazine, pimozide, prochlorperazine promazine, thioridazine, thiothixene, trifluoperazine, clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, paliperidone, asenapine,

lurasidone, iloperidone, cariprazine, amisulpride, zotepine, sertindole, in free or pharmaceutically acceptable salt form.

39. The method of any one of claims 36-38, wherein the one or more other therapeutic agents are anti-depressive agents selected from one or more of amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelazine sulfate, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine.
40. The method of any one of claims 36-39 wherein the one or more other therapeutic agents are anti-depressive agent selected from selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants.
41. The method of claim 40, wherein the anti-depressive agent is a SSRI.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/24345

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 31/4985; C07D 471/14 (2015.01) CPC - A61K 31/4985, 31/5383; C07D 471/14 According to International Patent Classification (IPC) or to both national classification and IPC</p>														
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC(8): A61K 31/4985; C07D 471/14 (2015.01) CPC: A61K 31/4985, 31/5383; C07D 471/14 USPC: 514/229.5, 250</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PATSEER (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Google Scholar; IP.com; EBSCO; KEYWORDS: fused gamma carboline*, 5 HT2A, treat*, sleep disorder*, antagoni* 5 HT2A, dopamine D2, SERT, combination therap*, antipsychotic*, chlorpromazine, 5 HT2A receptor, isotope*, deuterium, 2H, metabolic stabilit*, half life, substitut* carboline*, dementia</p>														
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>WO 2013/155505 A1 (INTRA-CELLULAR THERAPIES) 17 October 2013; paragraphs [0007]-[0008], [0010]-[0011]</td> <td>1-2, 3/1-2, 4/1-2, 5, 6/1-2, 7, 8/1-2, 9/1-2, 10/1-2, 11/1-2, 12/1-2, 13/1-2</td> </tr> <tr> <td>A</td> <td>US 2011/0263592 A1 (XIONG, Y et al.) 27 October 2011; paragraphs [0001], [0132], [0372], [0374], [0409]</td> <td>1-2, 3/1-2, 4/1-2, 5, 6/1-2, 7, 8/1-2, 9/1-2, 10/1-2, 11/1-2, 12/1-2, 13/1-2</td> </tr> <tr> <td>A</td> <td>US 2012/0157469 A1 (SURMAN, MD et al.) 21 June 2012; paragraphs [0002], [0068], [0195]</td> <td>1-2, 3/1-2, 4/1-2, 5, 6/1-2, 7, 8/1-2, 9/1-2, 10/1-2, 11/1-2, 12/1-2, 13/1-2</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	WO 2013/155505 A1 (INTRA-CELLULAR THERAPIES) 17 October 2013; paragraphs [0007]-[0008], [0010]-[0011]	1-2, 3/1-2, 4/1-2, 5, 6/1-2, 7, 8/1-2, 9/1-2, 10/1-2, 11/1-2, 12/1-2, 13/1-2	A	US 2011/0263592 A1 (XIONG, Y et al.) 27 October 2011; paragraphs [0001], [0132], [0372], [0374], [0409]	1-2, 3/1-2, 4/1-2, 5, 6/1-2, 7, 8/1-2, 9/1-2, 10/1-2, 11/1-2, 12/1-2, 13/1-2	A	US 2012/0157469 A1 (SURMAN, MD et al.) 21 June 2012; paragraphs [0002], [0068], [0195]	1-2, 3/1-2, 4/1-2, 5, 6/1-2, 7, 8/1-2, 9/1-2, 10/1-2, 11/1-2, 12/1-2, 13/1-2
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A	US 2012/0157469 A1 (SURMAN, MD et al.) 21 June 2012; paragraphs [0002], [0068], [0195]	1-2, 3/1-2, 4/1-2, 5, 6/1-2, 7, 8/1-2, 9/1-2, 10/1-2, 11/1-2, 12/1-2, 13/1-2												
<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.</p>														
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="vertical-align: top;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>										
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<p>Date of the actual completion of the international search</p> <p>30 May 2015 (30.05.2015)</p>		<p>Date of mailing of the international search report</p> <p>25 JUN 2015</p>												
<p>Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300</p>		<p>Authorized officer</p> <p>Shane Thomas</p> <p>PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>												

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/24345

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

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

3. Claims Nos.: 14-41
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.