(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 March 2010 (11.03.2010)

PCT

(10) International Publication Number
WO 2010/028130 A2

(51) International Patent Classification:
C07C 215/64 (2006.01) *A61P 25/24* (2006.01)
A61K 31/365 (2006.01) *A61P 25/22* (2006.01)
A61K 31/133 (2006.01) *A61P 25/00* (2006.01)

(21) International Application Number:
PCT/US2009/055865

(22) International Filing Date:
3 September 2009 (03.09.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/094,045 3 September 2008 (03.09.2008) US

(71) Applicant *(for all designated States except US)*: **CONCERT PHARMACEUTICALS, INC.** [US/US]; 99 Hayden Avenue, Suite 500, Lexington, MA 02421 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **TUNG, Roger** [US/US]; C/o Concert Pharmaceuticals, Inc., 99 Hayden Avenue, Suite 500, Lexington, MA 02421 (US).

(74) Agents: **HSI, Jeffrey, D.** et al.; Edwards Angell Palmer & Dodge LLP, P.O. Box 55874, Boston, MA 02205 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2010/028130 A2

(54) Title: ANTIDEPRESSANT COMPOUNDS

(57) Abstract: The present invention relates to deuterated forms of desvenlafaxine and the use of such compounds in pharmaceutical composition and for treatment of psychological disorders.

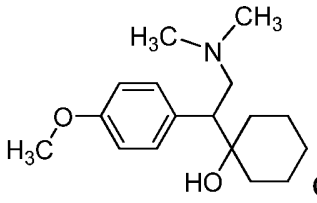
ANTIDEPRESSANT COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of priority to U.S. Provisional Patent Application No. 61/094,045, filed September 3, 2008, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

A number of nontricyclic antidepressants have recently been developed that reduce the cardiovascular and anticholinergic adverse-side effects associated with tricyclic antidepressants. Some of these compounds are also used as anti-obesity agents and have shown promise in the treatment of Parkinson's disease and senile dementia. See, e.g., WO 94/00047 and WO 94/00114. The nontricyclic Compound 1, known as venlafaxine or by its chemical name 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol and as 1-[α-[(dimethyl-amino)methyl]-p-methoxybenzyl] cyclohexanol, is an antidepressant which has been studied extensively and which is described in, for example, U. S. Patent No. 4,761,501 and Pento, J. T. Drugs of the Future 13 (9): 839-840 (1988). Its hydrochloride salt is a clinically and commercially important antidepressant agent with annual sales in 2005 of $3.5B (Wyeth 2005 annual report).



Compound 1

Venlafaxine contains an asymmetric carbon atom and is sold as a racemate. In humans, venlafaxine is transformed by a saturable metabolic pathway into one major O-demethylated metabolite, desvenlafaxine.

In vitro studies suggest that desvenlafaxine is a more potent inhibitor of norepinephrine and dopamine reuptake than venlafaxine (Muth, E. A. et al. Drug Develop. Res. 23: 191-199, 1991). Desvenlafaxine has been reported to have a half-life ($t_{1/2}$) of about 10 hours, which is approximately 2.5 times the half-life of venlafaxine (Klamerus, K. J. et al., *supra*). Desvenlafaxine has been studied

extensively in clinical trials and has also proven to be an effective antidepressive agent. Indeed, desvenlafaxine is now marketed by Wyeth in the United States for the treatment of major depressive disorder under the name Pristiq. Desvenlafaxine is registered for the treatment of postmenopausal syndrome, and is in Phase III for fibromyalgia and neuropathic pain

Despite the beneficial activities of desvenlafaxine, there is a continuing need for new compounds to treat the aforementioned diseases and conditions

Definitions

The term "treat" includes both therapeutic and prophylactic treatment. Both terms mean decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein).

"Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of Compound 3 will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada E et al., Seikagaku 1994, 66:15; Gannes LZ et al., Comp Biochem Physiol Mol Integr Physiol 1998, 119:725.

In a compound of this invention, when a particular position is designated as having deuterium, it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of at least 3000 (45% deuterium incorporation) at each atom designated as deuterium in said compound.

The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000

(75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

The term "isotopologue" refers to a species that differs from a specific compound of this invention only in the isotopic composition thereof.

The term "compound," as used herein, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues *in toto* will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

The invention also provides salts of the compounds of the invention.

A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A "pharmaceutically acceptable counterion" is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

The compounds of the present invention (e.g., compounds of Formula I), may contain an asymmetric carbon atom, for example, as the result of deuterium substitution or otherwise. As such, compounds of this invention can exist as either individual enantiomers, or mixtures of the two enantiomers. Accordingly, a compound of the present invention may exist as either a racemic mixture or a

scalemic mixture, or as individual respective stereoisomers that are substantially free from another possible stereoisomer. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers, or less than "X"% of other stereoisomers (wherein X is a number between 0 and 100, inclusive) are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

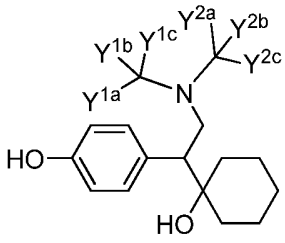
The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

"D" refers to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers. "Tert", "^{t}", and "t-" each refer to tertiary. "US" refers to the United States of America.

Throughout this specification, a variable may be referred to generally (e.g.,"each R") or may be referred to specifically (e.g., R^1, R^2, R^3, etc.). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides deuterium-containing nontricyclic antidepressants having advantageous biopharmaceutical properties for the treatment of psychological disorders, including depressive diseases and anxiety disorders. In particular, the invention provides compounds of Formula I:



(Formula I), or a pharmaceutically acceptable salt thereof, wherein:

each Y is independently selected from deuterium or hydrogen;

each hydrogen is independently optionally replaced with deuterium; with the proviso that at least one Y is deuterium.

In one embodiment, each Y^1 is the same and each Y^2 is the same, e.g. if Y^{1a} is deuterium, then Y^{1b} and Y^{1c} are also deuterium. In one aspect of this embodiment, each Y^1 is deuterium. In another aspect of this embodiment, each Y^1 and each Y^2 is deuterium.

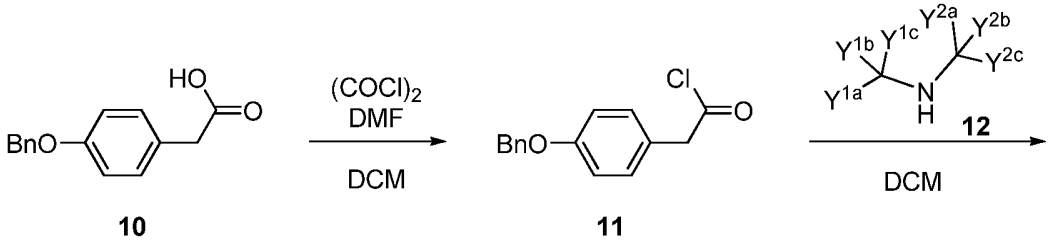
In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

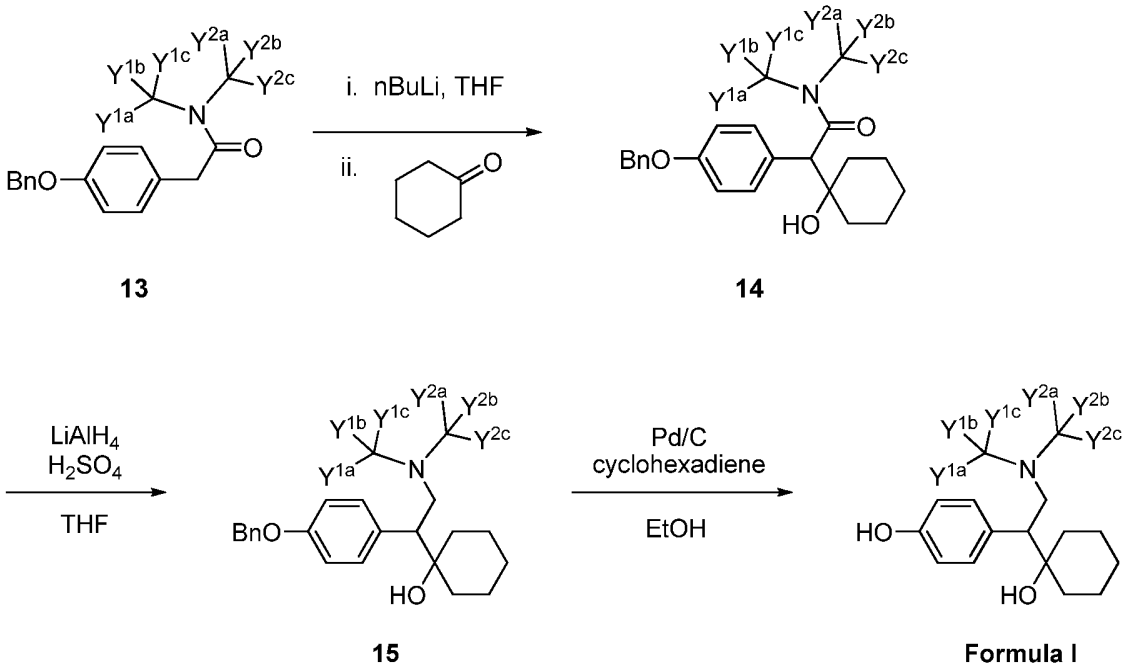
The synthesis of compounds of Formula I can be readily achieved by synthetic chemists of ordinary skill. Relevant procedures and intermediates are disclosed, for instance in PCT patent publication Nos. WO 98/04559 and WO 00/44752 and in European patent publication EP 0112669.

Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure. Certain intermediates can be used with or without purification (e.g., filtration, distillation, sublimation, crystallization, trituration, solid phase extraction, and chromatography).

Compound Synthesis

Scheme 1. Synthesis of a Compound of Formula I.





Scheme 1 depicts a general route to preparing compounds of Formula I. Commercially-available (4-benzyloxyphenyl)acetic acid **10** is treated with oxalyl chloride in dichloromethane in the presence of a catalytic amount of DMF to provide acid chloride **11**, which is condensed with appropriately-deuterated dimethylamine **12** in dichloromethane to produce amide **13**. Treatment of amide **13** with n-butyl lithium in THF, followed by cyclohexanone, affords alcohol **14**. Reduction of **14** with alane, prepared *in situ* from lithium aluminum hydride and sulfuric acid, provides amine **15**. Compound **15** is debenzylated via transfer hydrogenation utilizing Pd/C and cyclohexadiene to yield compounds of Formula I.

One example of an appropriately-deuterated dimethylamine **12** that can be used according to Scheme 1 to provide compounds of Formula I wherein all Y are deuterium is commercially-available dimethyl-d6-amine.

Compounds of Formula 1 can be made by means known in the art of organic synthesis. For instance, relevant routes to the all-hydrogen isotopologues of compounds of this invention are described in US Patent Nos. 4,535,186; 6,197,828; and 6,689,912; Yardley JP et al., J. Med.Chem. 1990 33: 2899; European patent publication EP 0112669; and PCT patent application nos. WO2005049560, WO2006035457, and WO2006067808.

Additional reaction schemes and protocols may be determined by the skilled artisan by use of commercially-available structure-searchable database software, for

instance, SciFinder® (CAS division of the American Chemical Society) and CrossFire Beilstein® (Elsevier MDL), or by appropriate keyword searching using an internet search engine such as Google® or keyword databases such as the US Patent and Trademark Office text database.

The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., R^1, R^2, R^3, etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

Additional methods of synthesizing compounds of Formula I and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene TW et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

Compositions

The invention also provides pyrogen-free compositions comprising an effective amount of a compound of Formula I (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and an acceptable carrier. In one embodiment, a composition of this invention is formulated for pharmaceutical use ("a pharmaceutical composition"), wherein the carrier is a pharmaceutically acceptable carrier. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a

pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this invention optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See United States patent 7,014,866; and United States patent publications 20060094744 and 20060079502.

The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA (17th ed. 1985).

Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz JD and Zaffaroni AC, US Patent 6,803,031, assigned to Alexza Molecular Delivery Corporation.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene

polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention.

Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

Where an organ or tissue is accessible because of removal from the patient, such organ or tissue may be bathed in a medium containing a composition of this invention, a composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as Compound 3.

In one embodiment, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from disorders of the central nervous system, including anxiety and convulsions; and neuropathic, inflammatory and migraine associated pain.

In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing

regimen, is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., (1966) Cancer Chemother. Rep 50: 219. Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

In one embodiment, an effective amount of a compound of this invention can range from about 0.01 to about 5000 mg per treatment. In more specific embodiments the range is from about 0.1 to 2500 mg, or from 0.2 to 1000 mg, or most specifically from about 1 to 500 mg. Treatment typically is administered one to three times daily.

Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for L-838417.

For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. In one embodiment, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. *See*, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the

advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Therapeutic Methods

The present invention also provides compositions comprising a compound of Formula I and related methods for preventing or ameliorating a psychological disorder, such as a depressive disease or anxiety disorder, including, but not limited to, major depressive disorder, generalized anxiety disorder, social anxiety disorder, panic disorder, postmenopausal syndrome and posttraumatic stress disorder or symptoms thereof by administering to a subject a compound of Formula I. Alternatively, compositions comprising Formula I are useful for the treatment of pain including neuropathic pain and fibromyalgia. Compounds of the invention can be employed for the treatment of virtually any disease or disorder where Compound 1 or a metabolite thereof is used, including diseases and disorders disclosed in US Patents 5,506,270; 5,744,474; 5,788,986; 5,788,986; 5,916,923; 5,922,341; 6,001,848; 6,211,171; 6,441,048; 6,552,014; 6,703,044; 6,911,479; and 7,001,920.

The methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of the formulae herein (e.g., Formula I) to a subject (e.g., a mammal such as a human). Thus, one embodiment is a method of treating a subject suffering from or susceptible to a mood or cognitive disease or disorder or symptom thereof. The method includes the step of administering to the mammal a therapeutic amount of an amount of a compound herein sufficient to treat the disease or disorder or symptom thereof, under conditions such that the disease or disorder is treated.

The methods herein include administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method). As used herein, the terms "treat," "treating," "treatment," and the like refer to reducing or ameliorating a disorder and/or symptoms associated therewith. It will be appreciated that, although not precluded, treating a disorder or

condition does not require that the disorder, condition or symptoms associated therewith be completely eliminated. As used herein, the terms "prevent," "preventing," "prevention," "prophylactic treatment" and the like refer to reducing the probability of developing a disorder or condition in a subject, who does not have, but is at risk of or susceptible to developing a disorder or condition.

The therapeutic methods of the invention (which include prophylactic treatment) in general comprise administration of a therapeutically effective amount of the compounds herein, such as a compound of the formulae herein to a subject (e.g., animal, human) in need thereof, including a mammal, particularly a human. Such treatment will be suitably administered to subjects, particularly humans, suffering from, having, susceptible to, or at risk for a mood or cognitive disease, disorder, or symptom thereof. Determination of those subjects "at risk" can be made by any objective or subjective determination by a diagnostic test or opinion of a subject or health care provider (e.g., genetic test, enzyme or protein marker, Marker (as defined herein, such as the level or reuptake of a bioactive amine, such as norepinephrine, serotonin, or dopamine), family history, and the like). The compounds herein may be also used in the treatment of any other disorders in which the reuptake of a bioactive amine, such as norepinephrine, serotonin, or dopamine, may be implicated.

Pharmaceutical Compositions

The invention also provides compositions comprising an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof; and an acceptable carrier. In one embodiment, a composition of the invention is formulated for pharmaceutical use ("a pharmaceutical composition"), wherein the carrier is a pharmaceutically acceptable carrier. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in amounts typically used in medicaments.

For therapeutic uses, the compositions comprising compounds of Formula I are obtained using the methods disclosed herein. Pharmaceutical compositions comprising such compounds may be administered systemically, for example, formulated in a pharmaceutically-acceptable buffer, such as physiological saline. Preferable routes of administration include, for example, subcutaneous, intravenous, interperitoneally, intramuscular, or intradermal injections that provide continuous,

sustained levels of the drug in the patient. Treatment of human patients or other animals will be carried out using a therapeutically effective amount of a compound of Formula 1 in a physiologically-acceptable carrier. Suitable carriers and their formulation are described, for example, in Remington's Pharmaceutical Sciences by E. W. Martin. The amount of the therapeutic agent to be administered varies depending upon the manner of administration, the age and body weight of the patient, and with the clinical symptoms of a depressive disease or anxiety disorder. Generally, amounts will be in the range of those used for other agents used in the treatment of other depressive diseases or anxiety disorders, although in certain instances lower amounts will be needed because of the decreased oxidation and increased half-life of the compound. A compound is administered at a dosage that controls the clinical or physiological symptoms of a depressive disease or anxiety disorder as determined by a diagnostic method known to one skilled in the art.

The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including for instance subcutaneous, intramuscular, intravenous, intrathecal and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets and sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA, 18th ed. 1990 (Genaro AE, editor), Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, and US Patent Nos. 6,352,721; 6,589,556; 6,645,528; 6,717,015; and 6,998,140.

Pharmaceutical compositions according to the invention may be formulated to release the active compound substantially immediately upon administration or at any predetermined time or time period after administration. The latter types of compositions are generally known as controlled release formulations, which include (i) formulations that create a substantially constant concentration of the drug within the body over an extended period of time; (ii) formulations that after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period of time; (iii) formulations that sustain action during a predetermined time period by maintaining a relatively, constant, effective level in the

body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active substance (sawtooth kinetic pattern); (iv) formulations that localize action by, e.g., spatial placement of a controlled release composition adjacent to or in the tissue to be treated; (v) formulations that allow for convenient dosing, such that doses are administered, for example, once every day; once every 2 or 3 days, or once per week or per two weeks; and (vi) formulations that target a depressive disease or anxiety disorder by using carriers or chemical derivatives to deliver the therapeutic agent to a particular cell type. For some applications, controlled release formulations can contribute to the reduced rate of metabolism of the therapeutic compound and obviate the need for frequent dosing during the day to sustain the plasma level at a therapeutic level.

Extended release formulations, such as those disclosed in US Patent nos. 6,274,171; 6,403,120; 6,482,440; 6,607,751; 6,706,283; and 6,893,661; and PCT patent application nos. WO2004091580, WO2004096186, WO2005039555, WO2005048923, and WO2006010605 can be valuable to enhance efficacy or reduce adverse effects. Inhaled forms of Compound 1 also comprise useful approaches to delivering the drug; see Rabinowitz JD and Zaffaroni AC, US Patents 6,783,753; 7,029,658; and 7,060,254; each to Alexza.

Any of a number of strategies can be pursued in order to obtain controlled release in which the rate of release outweighs the rate of metabolism of the compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, e.g., various types of controlled release compositions and coatings. Thus, the therapeutic is formulated with appropriate excipients into a pharmaceutical composition that, upon administration, releases the therapeutic in a controlled manner. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, molecular complexes, nanoparticles, patches, and liposomes.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5 mg to 1200 mg, preferably 1 mg to 1000mg, more preferably 5 mg to 400 mg of a compound of Formula I, depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical formulations may be presented in unit dose forms containing a

predetermined amount of active ingredient per unit dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Combination Therapies

Optionally, therapeutics described herein (e.g., compounds of Formula I) are administered in combination with any other standard therapy for the treatment of depression or anxiety; such methods are known to the skilled artisan and described in Remington's Pharmaceutical Sciences by E. W. Martin. In particular, compounds of Formula I may be employed where Compound 1 therapy is used in combination with additional bioactive agents. In particular embodiments, compounds of Formula I are used in combination with any one or more of the following agents that are conventionally used for the treatment of a psychological disorder: 5-HT1A antagonist or ligand; an NK1-receptor antagonist; a serotonin receptor antagonist; 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole (pramipexole), the (+)- or (-)-enantiomer thereof; a sulfamate anticonvulsant agent; a precursor or prodrug of serotonin, or an intermediate in the biosynthesis of serotonin; selective agonists and antagonists of one or both of the 5-HT1A and 5-HT1D receptors; a composition containing dimethylaminoethanol (DMAE), omega 3-fatty acids, betaine, oligomeric proanthocyanidins, folic acid, vitamins C, E, B12, B6, B5 and beta-carotene and minerals (calcium, magnesium, zinc and selenium); naltrexone; cyclobenzaprine, or metabolites thereof; olanzapine; olanazapine-N-oxide; 2-hydroxymethylolanzapine; an atypical antipsychotic; tramadol; an aldose reductase inhibitor, or a prodrug thereof; 1-threo-methylphenidate; a Type III, Type IV, mixed Type III-Type IV, or Type V phosphodiesterase inhibitor, or an ester, amide, prodrug, active metabolite, or combination thereof; a substituted indole estrogenic agent; (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane; folic acid; methyltetrahydrofolate; WAY 100635; betaxolol; (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide hydrogen (2R,3R)-tartrate monohydrate; R-tofisopam; N-acetyl-serotonin; a DRD2-specific dopamine agonist; a 5HT4 receptor antagonist; nalmefene; moxonidine; mirtazapine; paroxetine; chromium; a cyclooxygenase-2 selective inhibitor; a 5HT2A selective receptor antagonist; a CB1 receptor antagonist;

a MCH-1R receptor antagonist; a tetra-substituted pyrimidopyrimidine; a selective dopamine D4 receptor ligand; trimebutine, fedotozine and mixtures thereof; an NMDA partial receptor agonist; an NMDA receptor antagonist; a cholinesterase inhibitor; a GSK-3 inhibitor; an alpha-2-delta ligand or a prodrug thereof; an extract of kava; a norephinephrine reuptake inhibitor; a corticosteroid; a non-steroidal immunophilin-dependent immunosuppressant; N-desmethylclozapine; an (R)-2,3-benzodiazepine as disclosed in US Patent Application 20040224943; a selective neuronal nitric oxide synthase inhibitor; modafinil; a selective oxytocin antagonist; a nicotine receptor antagonist; an adenosine A2a receptor antagonist; a 5-HT2C receptor antagonist; an AMPA receptor potentiator; a nicotine partial agonist; irindalone; a delta opioid receptor ligand; a growth hormone secretagogue; p-chloro-N-(2-morpholinoethyl)-benzamide and its metabolites; and neuroleptics; a pharmaceutically acceptable salt of any of the said additional therapeutic agents; or combinations of two or more of the foregoing.

Examples of 5-HT1A antagonists and ligands include, but are not limited to, alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol; (R)-5-carbamoyl-8-fluoro-3-N,N-disubstituted-amino-3,4-dihydro-2H-1-benzopyran; and those disclosed in US Patents 5,776,969; 5,958,429; 6,136,861; 6,656,951; 6,780,860; 6,815,448; 6,821,981; 6,861,427; 6,894,053; and US Patent Application 20050085475.

Examples of NK1-receptor antagonists include, but are not limited to, those disclosed in US Patents 6,162,805; 6,878,732; US Patent Application 20050137208; as well as CNS-penetrant agents capable of inhibiting NK-1 receptor agonist-induced foot tapping in the gerbil, or attenuating separation-induced vocalizations by guinea-pig pups.

Examples of sulfamate anticonvulsant agents include, but are not limited to, topiramate and those disclosed in and referenced by US Patent 5,384,327.

Examples of precursors or prodrugs of serotonin, and intermediates in the biosynthesis of serotonin, include but are not limited to, L-tryptophan, L-5-hydroxytryptophan, diethyl N-benzyloxycarbonyl-5-benzyloxycarbonyloxy-L-tryptophyl-L-aspartate, dibenzyl N-benzyloxycarbonyl-5-hydroxy-L-tryptophanylaspartate, 5-Hydroxy-L-tryptophyl-L-aspartic acid trihydrate, diethyl N-benzyloxycarbonyl-5-hydroxy-L-tryptophyl-L-glutamate, diethyl 5-hydroxy-L-tryptophyl-L-glutamate hydrochloride, dibenzyl L-benzyloxycarbonyl-5-

hydroxytryptophyl-L-glutamate, 5-hydroxy-L-tryptophyl-L-glutamic acid, pentachlorophenyl ester of N-benzyloxycarbonyl-5-hydroxy-L-tryptophan, methyl ester of N-benzyloxycarbonyl-5-hydroxy-L-tryptophyl-L-tyrosine, N-Acetyl-5-hydroxy-L-tryptophan, methyl ester of N-acetyl-5-hydroxy-L-tryptophyl-L-tyrosine, methyl ester of n-acetyl-5-hydroxy-L-tryptophyl-5-hydroxy-L-tryptophan, 5-hydroxy-L-tryptophyl-L-alanine hydrate, 5-hydroxy-L-tryptophan-L-valine, 5-hydroxy-L-tryptophyl-L-leucine, 5-hydroxy-L-tryptophyl-L-proline, 5-hydroxy-L-tryptophyl-L-phenylalanine, 5-hydroxy-L-tryptophyl-5-hydroxy-L-tryptophan, 5-hydroxy-L-tryptophyl-L-tryptophan, 1-5-hydroxytryptophyl-L-serine, 5-hydroxy-L-tryptophyl-L-arginine, 5-hydroxy-L-tryptophylglycine, 5-hydroxy 1-tryptophyl-gamma-aminobutyric acid, 5-hydroxy-L-tryptophanamide hydrate, methyl ester of 5-hydroxy-L-tryptophyl-L-histidine, benzyl ester of L-5-hydroxytryptophan, benzyl ester of N-benzyloxycarbonyl-5-hydroxy-L-tryptophyl-5-hydroxy-L-tryptophan, 5-Hydroxy-L-tryptophyl-5-hydroxy-L-tryptophan hemihydrate, 5-hydroxytryptophan inosinate, theophylline salt of (DL) 5-hydroxytryptophan, and combinations thereof.

Examples of an atypical antipsychotic agent include, but are not limited to, risperidone, clozapine, seroquel, sertindole, ziprasidone, zotepine, olanzapine, iloperidone, Org 5222, melperone, amperozide, SM-9018, JL-13, and pharmaceutically acceptable salts thereof.

Examples of neuroleptic agents include, but are not limited to, quetiapine, aripiprazole, ziprasidone, risperidone, olanzapine, clozapine, desmethyclozapine, and iloperidone.

Examples of aldose reductase inhibitors include, but are not limited to, fidarestat, epalrestat, minalrestat, SPR-210, and zenarestat or zopolrestat, or a prodrug thereof.

Examples of selective agonists and antagonists of one or both of the 5-HT1A and 5-HT1D receptors include, but are not limited to, those disclosed in US Patent 6,562,813.

Examples of Type III phosphodiesterase inhibitors include, but are not limited to, bipyridines such as amrinone, milrinone and olprinone; anagrelide, bemoradan, ibudilast, isomazole, lixazinone, motapizone, olprinone, phthalazinol, pimobendan, quazinone, siguazodan and trequinsin

Examples of calcium channel blockers include, but are not limited to, amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, and verapamil.

Examples of mixed type III-type IV phosphodiesterase inhibitors include, but are not limited to, anagrelide, bemoradan, ibudilast, isomazole, lixazinone, motapizone, olprinone, phthalazinol, pimobendan, quazinone, siguazodan and trequinsin.

Examples of type IV phosphodiesterase inhibitors include, but are not limited to, pyrrolidinones, in particular rolipram; quinazolinediones, xanthine derivatives, phenyl ethyl pyridines, tetrahydropyrimidones, diazepine derivatives, oxime carbamates, naphthyridinones, benzofurans, naphthalene derivatives, purine derivatives, imidazolidinones, cyclohexane carboxylic acids, benzamidespyridopyridazinones, benzothiophenes, etazolate, S-(+)-glaucine, substituted phenyl compounds and substituted biphenyl compounds as further disclosed in US Patent 6,403,597.

Examples of type V phosphodiesterase inhibitors include, but are not limited to, sildenafil, vardenafil, tadalafil, zaprinast, dipyridamole, 3-isobutyl-8-(6-methoxy-isoquinolin-4-ylmethyl)-1-methyl-3,7-dihydro-purine-2,6-dione; and those disclosed in US Patent Applications 20030055070; 20040044005; 20030139429.

Examples of substituted indole estrogenic agents include, but are not limited to, those disclosed in and referenced by US Patent 6,369,051.

An example of a DRD2-specific dopamine agonist includes, but is not limited to, bromocriptine.

Examples of 5HT4 receptor antagonists include, but are not limited to, A-85380, SB 204070, SB 207226, SB 207058, SB 207710, SB 205800, SB 203186, SDZ 205557, N 3389, FK 1052, SC 56184, SC 53606, DAU 6285, GR 125487, GR 113808, RS 23597, RS 39604, LY-353433 and R 50595.

Examples of cyclooxygenase-2 selective inhibitors include, but are not limited to, celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, tilmacoxib, cimicoxib, and those disclosed in and referenced by US Patent Applications 20050080084 and 20050085477.

Examples of 5-HT2a receptor antagonists include, but are not limited to, those disclosed and referenced by US Patent application 20050070577.

Examples of CB1 receptor antagonists include, but are not limited to, rimonabant and those disclosed in and referenced by US Patent applications 20040248956, 20050009870, 20050014786, 20050054659, 20050080087, and 20050143381.

Examples of selective MCH-1R receptor antagonists include, but are not limited to, those disclosed in and referenced by US Patent applications 20050009815 and 20050026915.

Examples of tetra-substituted pyrimidopyrimidines include, but are not limited to, dipyridamole, mopidamole, dipyridamole monoacetate, 2,6-di-(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy-4,8-di-piperidinopyrimido- pyrimidine; 2,6-bis-(2,3-dimethyoxypropoxy)-4,8-di-piperidinopyrimidopyrimidine; 2,6-bis[N,N-di(2-methoxy)ethyl]-4,6-di-piperidinopyrimidopyrimidine-; and 2,6-bis(diethanolamino)-4,8-di-4-methoxybenzylaminopyrimidopyrimidine-.

Examples of selective dopamine D4 receptor ligands include, but are not limited to, pipamperone, fananserin, L-745,870, PNU-101387G and U-101387.

An example of a NMDA partial receptor agonist includes, but is not limited to, D-cycloserine. Examples of NMDA receptor antagonists include, but are not limited to, dextromethorphan, dextrorphan, amantadine, and memantine.

Examples of cholinesterase inhibitors include, but are not limited to, tacrine, donepezil, edrophonium, galantamine, physostigmine, eptastigmine, pyridostigmine, neostigmine, ganstigmine, rivastigmine, demecarium, ambenonium, sarin, metrifonate, soman, tabun, and diisopropyl fluorophosphates.

Examples of GSK-3 inhibitors include, but are not limited to, those disclosed and referenced in US Patent Application 20050026946.

Examples of alpha-2-delta ligands include, but are not limited to, gabapentin, pregabalin, [(1R,5R,6S)-6-(aminomethyl)bicyclo[-3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethylcyclohexylmethyl)-4H-[1,2,4]-oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethylcyclopentyl)-acetic acid, (1a,3a,5a)(3-aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyloctanoic acid, (3S,5R)-3-amino-5-methylheptanoic acid, (3S,5R)-3-amino-5-methylnonanoic acid, and (3S,5R)-3-amino-5-methyloctanoic acid.

Examples of norephinephrine reuptake inhibitors include, but are not limited to, bupropion, desipramine, imipramine, amoxapine, nortriptyline, protriptyline, atomoxetine, oxaprotiline, maprotiline, reboxetine, 1-[1-(3-chlorophenyl)-2-(4-methyl-1-piperazinyl)ethyl]cyclohexanol; and those disclosed in US Patent Application 20050014848.

Examples of corticosteroids include, but are not limited to, prednisolone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, fluticasone, prednisone, triamcinolone, and diflorasone.

Examples of non-steroidal immunophilin-dependent immunosuppressants include, but are not limited to, cyclosporine, tacrolimus, ISAtx247, ascomycin, pimecrolimus, rapamycin, and everolimus.

Examples of selective neuronal nitric oxide synthase inhibitors include, but are not limited to, those disclosed in US Patent Application 20040229911.

An example of a selective oxytocin antagonist includes, but is not limited to, L-368,899.

Examples of nicotine receptor antagonists include, but are not limited to, mecamylamine, amantadine, pempidine, dihydro-beta-erythroidine, hexamethonium, erysodine, chlorisondamine, trimethaphan camsylate, tubocurarine chloride, d-tubocurarine, and their optical isomers.

Examples of adenosine A2a receptor antagonists include, but are not limited to, those disclosed in US Patent Application 20030139395.

Examples of 5-HT2C receptor antagonists, inverse agonists and partial agonists include, but are not limited to, ketanserin, SB 242084, SB 206553, SB 243213, SB 228356, ritanserin, deramciclane, mirtazepine, mianserine, sertindole, YM 35 992, Ro 60-0795, Org 38457, Org 12962, EGIS 8465 and RS 102221.

Examples of AMPA receptor potentiators include, but are not limited to, [(methylethyl)sulfonyl]{2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}amine, {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine, N-2-(4-(3-thienyl)phenylpropyl-2-propanesulfonamide, [2-fluoro-2-(4-{3-[(methylsulfonyl)amino]phenyl}phenyl)propyl][(methylethyl)sulfonyl]amine, and, separately, each enantiomer of [2-fluoro-2-(4-{3-[(methylsulfonyl)amino]phenyl}phenyl)propyl][(methylethyl)sulfonyl]amine.

Examples of nicotine receptor partial agonists include, but are not limited to, those disclosed in US Patent Applications 20010036943 and 20030109544.

Examples delta opioid receptor ligands include, but are not limited to, those disclosed in and referenced by US Patent Application 20020077323.

Examples of growth hormone secretagogues include, but are not limited to, MK-0677 (Merck); NN703 (Novo Nordisk); L-162752 and L-163022 (Merck);

hexarelin (Pharmacia & Upjohn); GPA-748 (KP102, GHRP-2) (American Home Products); ipamorelin (Novo Nordisk); and LY444711 (Eli Lilly). The following agents that stimulate GH release via GHRH/GRF receptor (including GHRH/GRF derivatives, analogs and mimetics) are known in the art: Geref (Ares/Serono); GHRH (1-44) (BioNebraska); Somatorelin (GRF 1-44) (Fujisawa/ICN); and ThGRF (Theratechnologies).

See United States Patents Nos. 5,532,244; 5,532,250; 5,532,264; 5,532,268; 5,532,292; 5,552,429; 5,776,969; 5,945,416; 5,958,429; 5,990,159; 6,001,848; 6,066,643; 6,080,736; 6,121,259; 6,127,385; 6,147,072; 6,174,882; 6,191,133; 6,197,828; 6,218,395; 6,239,126; 6,242,448; 6,348,455; 6,352,984; 6,369,051; 6,372,919; 6,395,752; 6,395,788; 6,403,645; 6,420,351; 6,441,038; 6,458,384; 6,468,997; 6,489,341; 6,541,523; 6,572,890; 6,579,899; 6,627,653; 6,649,605; 6,649,614; 6,656,951; 6,667,297; 6,683,114; 6,780,860; 6,815,448; 6,821,981; 6,846,823; 6,861,427; 6,878,732; 6,894,053; 6,936,601; 7,008,641; 7,041,704; and PCT patent application nos. WO2004035036, WO2005049041, and WO2005051297.

Combination therapies according to the present invention thus include the administration of at least one compound of Formula I as well as optional use of other therapeutic agents including other anti-depressive or anti-anxiolytic agents. Such combination of agents may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order, both close and remote in time. The amounts of the compound of Formula I and the other pharmaceutically active agent (s) the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Assays for compounds that inhibit amine reuptake

Optionally, compounds described herein are tested *in vivo* or *in vitro* for their ability to ameliorate a depressive disease or anxiety disorder; or for their ability to inhibit the reuptake of a bioactive amine (e.g., norepinephrine, dopamine, serotonin). Such methods include, but are not limited to, assaying compounds of the invention for the inhibition of bioactive amine reuptake. Accordingly, compounds of the invention are assayed *in vitro* for binding to rat cortical membranes as described by Habert E et. al., Eur. J. Pharmacol. 1985 118: 107. Radiolabeled Compound 1 was found to bind to a single, high affinity, saturable site; compounds that have a similar binding profile in such assays are identified as useful in the methods of the invention.

Compounds that are therapeutically efficacious against a psychological disease described herein (e.g., a depressive disease or anxiety disorder) are those that reduce the reuptake of a bioactive amine (e.g., serotonin, dopamine, norepinephrine). Bioactive amines are stored in a pre-synaptic cell and upon release into the synapse the amines act on a post-synaptic cell to induce a physiological response. The actions of bioactive amines are terminated either by re-uptake into cells from which they have been released (e.g., pre-synaptic neurons) or by enzymatic degradation. Compounds of the invention that reduce the reuptake of bioactive amines can acutely increase extracellular amine concentrations, leading to an increase in negative feedback mediated by inhibitory presynaptic and somatodendritic receptors. As a result, action potential firing frequency and amounts of bioactive amines released from presynaptic button can decrease. On chronic administration, downregulation and/or desensitization of inhibitory receptors can occur, resulting in increased action potential firing frequency and higher bioactive amines concentrations in the synaptic cleft. Other methods for evaluating the effect of compounds of Formula I include, metabolic or pharmacological studies using radiolabeled tracers or precursor loading, microdialysis, assaying bioactive amines or their metabolites in cerebrospinal fluid (CSF), blood or urine, imaging studies that may or may not rely on radiolabeled tracers (e.g., PET and functional magnetic resonance imaging or fMRI).

If desired, compounds selected using any of the screening methods described herein are tested for their efficacy in animal models of depression, neuropathic pain, fibromyalgia, and postmenopausal syndrome. The use of Compound 1 in such models accurately produced results that are correlated with human clinical effects. See, e.g. Akegawa Y et. al. Methods Find Exp Clin Pharmacol 1999 21: 599; Lassen JB, US Patent 4,745,122 to Ferrosan; and Hascoet M et. al., Pharmacol. Biochem. Behav. 2000 65: 339.

In other embodiments, the efficacy of a compound of the invention is evaluated in a human subject using, for example, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety (HAM-A), Clinical Global Impression-Severity of Illness (CGI-S), Panic and Anticipatory Anxiety Scale (PAAS), Panic Disorder Severity Scale, Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I). Compounds that reduce the symptoms of depression or anxiety in a subject, such as where the symptoms are improved, very much improved,

much improved, or in remission (CGI-S rating of not at all ill or borderline ill) are identified as useful in the methods of the invention.

While compounds of Formula I are specifically described as useful for the treatment of depressive diseases or anxiety disorders, the invention is not so limited. Compounds of Formula I may be used for the treatment of a variety of diseases and disorders, including without limitation, depression, hypertension, generalized anxiety disorder, phobias, posttraumatic stress syndrome, avoidant personality disorder, and sexual dysfunction; eating disorders including bulimia, anorexia nervosa, and binge eating; obesity, chemical dependencies, cluster headache, migraine; pain, including neuropathic pain, diabetic nephropathy, post-operative pain, psychogenic pain disorders, and chronic pain syndrome; Alzheimer's disease, obsessive-compulsive disorder, panic disorder with or without agoraphobia, memory disorders, Parkinson's diseases, endocrine disorders, vasospasm, cerebellar ataxia, gastrointestinal tract disorders, negative symptoms of schizophrenia, premenstrual syndrome, postmenopausal syndrome, neuropathic pain, fibromyalgia, urinary incontinence, including stress incontinence; Tourette's syndrome, trichotillomania, kleptomania, male impotence, cancer, chronic paroxysmal hemicrania and headache in a mammal, sleep-related breathing disorders, cognitive deficits due to aging, stroke, head trauma, neurodegenerative diseases, schizophrenia, anxiety, aggression and stress, disorders of thermoregulation, respiratory disease, bipolar disorder, psychosis, sleep disorder, mania, acute mania, bladder disorder, genitourinary disorder, cough, emesis, nausea, and psychotic disorders such as paranoia and manic-depressive illness, tic disorder, diabetic cardiomyopathy, diabetic retinopathy, cataracts, myocardial infarction, prolonged fatigue, chronic fatigue, chronic fatigue syndrome, premature ejaculation, dysphoria, post partum depression, social phobia, disruptive behavior disorders, impulse control disorders, borderline personality disorder, attention deficit disorders without hyperactivity, Shy-Drager Syndrome, cerebral ischemia, spinal cord trauma, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, convulsions, perinatal hypoxia, hypoxia, cardiac arrest, hypoglycemic neuronal damage, ocular damage and retinopathy, brain edema, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting, affective disorders, mood disorders agoraphobia without history of panic disorder, an acute stress disorder, autism, dyskinesia, disthymic disorder; obesity due to genetic or environmental causes, polycycstic ovary disease, craniopharyngeoma, Prader-Willi

Syndrome, Frohlich's Syndrome, Type II diabetes, growth hormone deficiency, and Turner's Syndrome; excessive or undesired proinflammatory cytokine secretion or production, jet lag, insomnia, hypersomnia, nocturnal enuresis, restless-legs syndrome, vaso-occlusive events, hyperglycemia, hyperinsulinaemia, hyperlipidaemia, hypertriglyceridemia, diabetes, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, glomerulosclerosis, syndrome X, coronary heart disease, angina pectoris, vascular restenosis, endothelial dysfunction, impaired vascular compliance, and congestive heart failure.

Pharmaceutical Kits

The present invention also provides kits for use to treat depressive diseases and anxiety disorders. These kits comprise (a) a pharmaceutical composition comprising a compound of Formula I or a salt thereof, wherein said pharmaceutical composition is in a container; and (b) instructions describing a method of using the pharmaceutical composition to treat depressive diseases or anxiety disorders.

The container may be any vessel or other sealed or sealable apparatus that can hold said pharmaceutical composition. Examples include bottles, ampules, divided or multi-chambered holders bottles, wherein each division or chamber comprises a single dose of said composition, a divided foil packet wherein each division comprises a single dose of said composition, or a dispenser that dispenses single doses of said composition. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box. In one embodiment, the container is a blister pack.

The kits of this invention may also comprise a device to administer or to measure out a unit dose of the pharmaceutical composition. Such device may include

an inhaler if said composition is an inhalable composition; a syringe and needle if said composition is an injectable composition; a syringe, spoon, pump, or a vessel with or without volume markings if said composition is an oral liquid composition; or any other measuring or delivery device appropriate to the dosage formulation of the composition present in the kit.

In certain embodiments, the kits of this invention may comprise in a separate vessel of container a pharmaceutical composition comprising a second therapeutic agent, such as one of those listed above for use for co-administration with a compound of this invention.

Example 1. Evaluation of Metabolic Stability

Microsomal Assay: Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, KS). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

Determination of Metabolic Stability: 7.5 mM stock solutions of test compounds are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5-50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes are added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 12.5-50 μM test compound is added to the microsomes and the mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25-1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM $MgCl_2$. The reaction mixtures are incubated at 37 °C, and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4 °C for 20 minutes after which 100 μL of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for desvenlafaxine and the positive control, 7-ethoxycoumarin (1 μM). Testing is done in triplicate.

Data analysis: The *in vitro* $t_{1/2}$s for test compounds are calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.

in vitro $t_{½}$ = 0.693/k

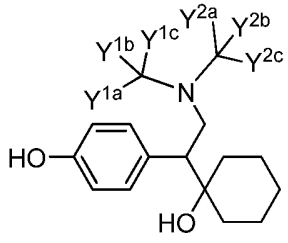
k = -[slope of linear regression of % parent remaining(ln) vs incubation time]

Data analysis is performed using Microsoft Excel Software.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

What is claimed is:

1. A compound of Formula I:



Formula I

or a salt thereof wherein:

each Y is independently selected from deuterium or hydrogen;

each hydrogen is independently optionally replaced with deuterium; and

wherein at least one Y group is deuterium.

2. The compound of claim 1, wherein each Y^1 is the same, and each Y^2 is the same.

3. The compound of claim 2, wherein each of Y^{1a}, Y^{1b} and Y^{1c} is deuterium.

4. The compound of claim 3, wherein each of Y^{1a}, Y^{1b}, Y^{1c} Y^{2a}, Y^{2b} and Y^{2c} is deuterium.

5. The compound of any one of claims 1 to 4, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

6. A pharmaceutical composition comprising an effective amount of the compound of claim 1, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

7. The composition of claim 6 for use in ameliorating a psychological disorder in a subject in need thereof.

8. The composition of claim 7, wherein the psychological disorder is selected from major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder.

9. The composition of claim 6, for use in reducing bioactive amine reuptake in a patient in need thereof.

10. The composition of claim 9, wherein the compound is capable of reducing the activity of a bioactive amine transporter.

11. The composition of claim 10, wherein the bioactive amine transporter is a serotonin or norepinephrine transporter.