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(54) Title: QUATERNARY PIPERIDINE COMPOUNDS AND USES THEREOF

(57) Abstract: This invention generally relates to quaternary piperidine compounds, particularly (S)-N-(2-(3-(4-chlorophenyl)piperidin-3-yl)etriyl)- 1,1,1-trifluoro-2-methylpropan-2- amine and salts thereof. This invention also relates to pharmaceutical compositions comprising such a compound, uses of such a compound (including, for example, treatment methods and medicament preparations), and processes for making such a compound.

QUATERNARY PIPERIDINE COMPOUNDS AND USES THEREOF

FIELD OF THE INVENTION

[0001] This invention generally relates to quaternary piperidine compounds, particularly (S)-N-(2-(3-(4-chlorophenyl)piperidin-3-yl)ethyl)- 1,1,1-trifluoro-2-methylpropan-2-amine and salts thereof. This invention also relates to pharmaceutical compositions comprising such a compound, uses of such a compound (including, for example, treatment methods and medicament preparations), and processes for making such a compound.

BACKGROUND

[0002] The brain contains neurons that communicate with each other through chemical messengers called neurotransmitters. Neurotransmitters are produced by neurons. The cellular membrane of a neuron contains receptors with which the neurotransmitters may interact. Serotonin (SERT), dopamine (DAT), and norepinephrine (NET) neurotransmitters belong to a group of neurotransmitters called the monoamine neurotransmitters.

[0003] Monoamine neurotransmitters are released into the synaptic cleft between neurons and act by stimulating postsynaptic receptors. Monoamine neurotransmitters are removed (or inactivated) primarily by reuptake into presynaptic terminals. In various diseases and/or conditions where neurotransmitters are out of balance, reuptake of a particular neurotransmitter can be inhibited to improve a patient's condition and/or the disease from which the patient suffers.

[0004] Selective serotonin reuptake inhibitors (SSRIs) and dual serotonin and norepinephrine reuptake inhibitors (SNRIs) are used in treating depression. Patients, however, often complain of side effects, such as, for example, weight gain and sexual dysfunction. Additionally, not all patients have a positive therapeutic response to SSRIs and/or SNRIs. In fact, SSRIs and SNRIs are generally no more efficacious than monoamine oxidase inhibitors and tricyclic antidepressants, although they do pose less serious side effect risks. Nevertheless, tricyclic antidepressants continue to be used to treat depression.

[0005] Nomifensine, marketed in late 1970's by Hoescht, was an effective motivating and anxiolytic drug reported to be a selective NET:DAT reuptake inhibitor.

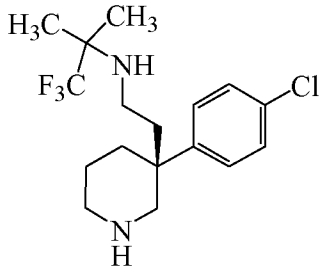
The unique NET:DAT reuptake inhibitor profile of nomifensine was thought to confer a unique therapeutic benefit to melancholic depressive patients. Nomifensine was, however, withdrawn from the market in 1980 in the wake of nomifensine-associated immune reactions appearing in the literature, several cases of autoimmune haemolytic anaemia, and some deaths. The prevailing theory suggests a reactive metabolite of nomifensine forms a complex with proteins on red blood cells (RBC) to initiate an auto-immune complex.

[0006] As the SSRIs and SNRIs are not effective in treating at least some patients suffering from depression, new treatments continue to be needed. Such treatments are particularly desirable to treat underserved subpopulations, such as, for example, patients suffering from atypical depression. As the unique NET:DAT reuptake inhibitor profile of nomifensine appeared to confer a unique therapeutic benefit to melancholic depressive patients, efforts have been undertaken to develop dual NET and DAT reuptake inhibitors that do not have the undesirable side effect profile that led to nomifensine's withdrawal.

SUMMARY OF THE INVENTION

[0007] This invention comprises, *inter alia*, piperidine compounds; methods of treatment using the piperidine compounds (*e.g.*, uses of the piperidine compounds to treat various psychiatric disorders and as pharmacological tools); use of the piperidine compounds to make medicaments; compositions comprising the piperidine compounds (*e.g.*, pharmaceutical compositions); methods for manufacturing the piperidine compounds; and intermediates used in such manufacturing methods.

[0008] Briefly, this invention is directed, in part, to the compound of Formula (I) or a salt thereof. Formula (I) corresponds to:



(I).

[0009] This invention also is directed, in part, to the compound of Formula (I) or a pharmaceutically acceptable salt thereof for use as a medicament.

[0010] This invention also is directed, in part, to the compound of Formula (I) or a pharmaceutically acceptable salt thereof for treating a disorder comprising a psychiatric disorder.

[0011] This invention also is directed, in part, to the compound of Formula (I) or a pharmaceutically acceptable salt thereof for treating a disorder comprising a disorder selected from major depressive disorders, attention-deficit and disruptive behavior disorders, and cocaine-related disorders.

[0012] This invention also is directed, in part, to the compound of Formula (I) or a pharmaceutically acceptable salt thereof for treating a disorder comprising a disorder selected from atypical depression, melancholy depression, cocaine abuse, and attention deficit hyperactivity disorder.

[0013] This invention also is directed, in part, to the compound of Formula (I) or a pharmaceutically acceptable salt thereof for treating a disorder comprising a disorder in which modulating norepinephrine transport receptors and/or dopamine transport receptors is beneficial.

[0014] This invention also is directed, in part, to a use of the compound of Formula (I) or a pharmaceutically acceptable salt thereof to manufacture a medicament.

[0015] In some embodiments, the medicament is for treating a disorder comprising a psychiatric disorder.

[0016] In some embodiments, the medicament is for treating a disorder comprising a disorder selected from major depressive disorders, attention-deficit and disruptive behavior disorders, and cocaine-related disorders.

[0017] In some embodiments, the medicament is for treating a disorder comprising a disorder selected from atypical depression, melancholy depression, cocaine abuse, and attention deficit hyperactivity disorder.

[0018] In some embodiments, the medicament is for treating a disorder comprising a disorder in which modulating norepinephrine transport receptors and/or dopamine transport receptors is beneficial.

[0019] This invention also is directed, in part, to a pharmaceutical composition. The composition comprises the compound of Formula (I) or a pharmaceutically acceptable salt thereof. The composition also comprises a pharmaceutically acceptable carrier or diluent.

[0020] This invention also is directed, in part, to a method for treating a disorder in a warm-blooded animal in need of such treatment. The method comprises administering to the animal a therapeutically effective amount the compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0021] In some embodiments, the disorder comprises a psychiatric disorder.

[0022] In some embodiments, the disorder comprises a disorder selected from major depressive disorders, attention-deficit and disruptive behavior disorders, and a cocaine-related disorders.

[0023] In some embodiments, the disorder comprises a disorder selected from melancholy depression, atypical depression, cocaine abuse, and ADHD.

[0024] In some embodiments, the disorder comprises a major depressive disorder.

[0025] In some embodiments, the disorder comprises a disorder in which modulating norepinephrine transport receptors and/or dopamine transport receptors is beneficial.

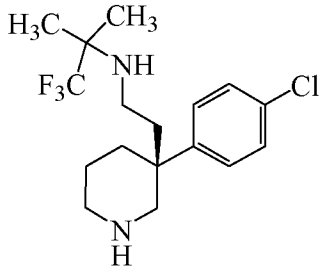
[0026] This invention also is directed, in part, to a method for modulating norepinephrine transport receptors and/or dopamine transport receptors using the compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0027] Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this specification.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0028] This description of illustrative embodiments is intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may readily adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This description and its specific examples, while indicating embodiments of this invention, are intended for purposes of illustration only. This invention, therefore, is not limited to the illustrative embodiments described in this specification, and may be variously modified. In addition, it is to be appreciated that various features of the invention that are, for clarity reasons, described in the context of separate embodiments, also may be combined to form a single embodiment. Conversely, various features of the invention that are, for brevity reasons, described in the context of a single embodiment, also may be combined to form sub-combinations thereof.

[0029] As noted above, this invention is directed, in part, to the compound of Formula (I) or a salt thereof. Formula (I) corresponds to:



(I).

[0030] Salts of the compound of Formula (I) are typically acid addition salts. In general, an acid addition salt can be prepared using various inorganic or organic acids. Such salts can typically be formed by, for example, mixing the compound with an acid (*e.g.*, a stoichiometric amount of acid) using various methods known in the art. This mixing may occur in water, an organic solvent (*e.g.*, ether, ethyl acetate, ethanol, isopropanol, or acetonitrile), or an aqueous/organic mixture.

[0031] A salt may be advantageous due to one or more of its chemical or physical properties, such as stability in differing temperatures and humidities, or a desirable solubility in water, oil, or other solvent. In some instances, a salt may be used to aid in the isolation or purification of the compound. In some embodiments (particularly where the salt is intended for administration to an animal, or is a reagent for use in making a compound or salt intended for administration to an animal), the salt is pharmaceutically acceptable.

[0032] Examples of inorganic acids that typically may be used to form acid addition salts include hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Examples of organic acids include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids. Specific examples of organic salts include cholate, sorbate, laurate, acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid (and derivatives thereof, *e.g.*, dibenzoyltartrate), citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate (and derivatives thereof), embonate (pamoate), ethanesulfonate, benzenesulfonate, pantothenate, 2-hydroxyethanesulfonate, sulfanilate, cyclohexylaminosulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and

undecanoate. In some embodiments, the salt comprises a hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, methanesulphonate, or *p*-toluenesulphonate salt. In other embodiments, the salt comprises a citric acid salt. In other embodiments, the salt comprises an HCl salt. And, in other embodiments, the salt comprises an acetic acid salt.

[0033] It is contemplated that an amine of the compound of Formula I or a salt thereof may form an N-oxide. Such an N-oxide is intended to be encompassed by the compound of Formula I and salts thereof. An N-oxide can generally be formed by treating an amine with an oxidizing agent, such as hydrogen peroxide or a per-acid (*e.g.*, a peroxycarboxylic acid). *See, e.g.*, Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience. N-oxides also can be made by reacting the amine with m-chloroperoxybenzoic acid (m-CPBA), for example, in an inert solvent, such as dichloromethane. *See* L. W. Deady, *Syn. Comm.*, 7, pp. 509-514 (1977).

[0034] It is contemplated that the compound of Formula (I) or a salt thereof could form isolatable atropisomers in certain solvents at certain temperatures. The compound of Formula (I) and salts thereof are intended to encompass any such atropisomers. Atropisomers can generally be isolated using chiral LC.

[0035] The compound of Formula (I) and salts thereof are intended to encompass any isotopically-labeled (or "radio-labeled") derivatives of the compound of Formula (I) or a salt thereof. Such a derivative is a derivative of the compound of Formula (I) or a salt thereof wherein one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of radionuclides that may be incorporated include ^{2}H (also written as "D" for deuterium), ^{3}H (also written as "T" for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{18}F, and ^{36}Cl. The radionuclide that is used will depend on the specific application of that radio-labeled derivative. For example, for *in vitro* receptor labeling and competition assays, ^{3}H or ^{14}C are often useful. For radio-imaging applications, ^{11}C or ^{18}F are often useful. In some embodiments, the radionuclide is ^{3}H. In some embodiments, the radionuclide is ^{14}C. In some embodiments, the radionuclide is ^{11}C. And in some embodiments, the radionuclide is ^{18}F.

[0036] The compound of Formula (I) and salts thereof are intended to cover all solid state forms of the compound and salts. The compound of Formula (I) and salts thereof also are intended to encompass all solvated (*e.g.*, hydrated) and unsolvated forms of the compound and salts.

[0037] The compound of Formula (I) and salts thereof also are intended to encompass coupling partners in which the compound of Formula (I) or a salt thereof is linked to a coupling partner by, for example, being chemically coupled to the compound or salt or physically associated with it. Examples of coupling partners include a label or reporter molecule, a supporting substrate, a carrier or transport molecule, an effector, a drug, an antibody, or an inhibitor. Coupling partners can be covalently linked to a compound or salt via an appropriate functional group on the compound, such as an amino group. Other derivatives include formulating the compound or salt with liposomes.

[0038] This invention provides, in part, for methods to treat various disorders in animals, particularly mammals. Mammals include, for example, humans. Mammals also include, for example, companion animals (*e.g.*, dogs, cats, and horses), livestock animals (*e.g.*, cattle and swine); lab animals (*e.g.*, mice and rats); and wild, zoo, and circus animals (*e.g.*, bears, lions, tigers, apes, and monkeys). It is contemplated that the compound of Formula (I) or a salt thereof may generally be used to treat a range of disorders in which modulating the norepinephrine transport receptor and/or dopamine transport receptor is beneficial. Accordingly, this invention is directed, in part, to a method of using the compound of Formula (I) or a salt thereof for treating a norepinephrine transport receptor and/or dopamine transport receptor associated condition therewith.

[0039] In some embodiments, the compound of Formula (I) or a salt thereof is used to modulate at least one norepinephrine transport receptor and/or dopamine transport receptor. The terms “modulate”, “modulates”, “modulating”, or "modulation", as used in this patent, mean the activation (*i.e.*, act as an agonist) or inhibition (*i.e.*, act as antagonist) of the norepinephrine transport receptor and/or dopamine transport receptor. In some embodiments, the terms “modulate”, “modulates”, “modulating”, or "modulation" mean the inhibition of at least one norepinephrine transport receptor and/or dopamine transport receptor.

[0040] In some embodiments, the compound of Formula (I) or a salt thereof is administered to an animal in which the modulation of at least one norepinephrine transport receptor and/or dopamine transport receptor in the animal is beneficial to the animal for treating a disorder. The compound or salt is normally administered to the animal in the form of a pharmaceutical composition that also comprises at least one carrier, diluent, or excipient.

[0041] In some embodiments, the compound of Formula (I) or a salt thereof is administered to an animal to treat a psychiatric disorder in the animal. Psychiatric disorders include, for example:

(1) mood disorder(s), such as, for example:

(a) depressive disorder(s), such as major depressive disorder(s) (*e.g.*, melancholy depression and atypical depression) and dysthymic disorder(s),

(b) bipolar depression and/or bipolar mania, such as, for example, bipolar I (bipolar disorders with manic, depressive or mixed episodes) and bipolar II,

(c) cyclothymiac's disorder(s), and

(d) mood disorder(s) due to a general medical condition;

(2) attention-deficit and disruptive behavior disorder(s), such as, for example, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), and affective disorders; and

(3) substance-related disorder(s), such as, for example, substance dependence; substance abuse; substance intoxication; substance withdrawal; alcohol-related disorder(s); amphetamine (or amphetamine-like)-related disorder(s); caffeine-related disorder(s); cannabis-related disorder(s); cocaine-related disorder(s) (*e.g.*; cocaine abuse); hallucinogen-related disorder(s); inhalant-related disorder(s); nicotine-related disorder(s)s; opioid-related disorder(s)s; phencyclidine (or phencyclidine-like)-related disorder(s); and sedative-, hypnotic- or anxiolytic-related disorder(s).

Further discussion relating to psychiatric disorders may be found in, for example, the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, DC, American Psychiatric Association, 2000.

[0042] In some embodiments of this invention, the compound of Formula (I) or a salt thereof (generally a therapeutically effective amount) is used for therapy.

[0043] In some embodiments of this invention, the compound of Formula (I) or a salt thereof is used to treat a major depressive disorder. In some such embodiments, the compound or salt is administered (generally a therapeutically effective amount) to an animal to treat a major depressive disorder in the animal. In some embodiments, the disorder comprises melancholy depression. In other embodiments, the disorder comprises atypical depression.

[0044] In some embodiments of this invention, the compound of Formula (I) or a salt thereof is used to treat an attention-deficit or disruptive behavior disorder. In some

such embodiments, the compound or salt is administered (generally a therapeutically effective amount) to an animal to treat an attention-deficit or disruptive behavior disorder in the animal. In some embodiments, the disorder comprises ADHD.

[0045] In some embodiments of this invention, the compound of Formula (I) or a salt thereof is used to treat a cocaine-related disorder. In some such embodiments, the compound or salt is administered (generally a therapeutically effective amount) to an animal to treat a cocaine-related disorder in the animal. In some such embodiments, the disorder comprises cocaine abuse.

[0046] In some embodiments, the compound of Formula (I) or a salt thereof is used to make a medicament (*i.e.*, a pharmaceutical composition). In general, the pharmaceutical composition comprises a therapeutically effective amount of the compound or salt. Pharmaceutical compositions comprising the compound of Formula (I) or a salt thereof can vary widely. Although it is contemplated that the compound of Formula (I) or a salt thereof could be administered by itself (*i.e.*, without any other active or inactive ingredient), the pharmaceutical composition normally will instead comprise one or more additional active ingredients and/or inert ingredients. The inert ingredients present in the pharmaceutical compositions of this invention are sometimes collectively referred to as "carriers, diluents, and excipients." Methods for making pharmaceutical compositions and the use of carriers, diluents, and excipients are well known in the art. *See, e.g.*, for example, *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, PA, 15th Edition, 1975.

[0047] In some embodiments of this invention, the compound of Formula (I) or a salt thereof (generally a therapeutically effective amount) is used to make a medicament for treating a major depressive disorder. In some such embodiments, the disorder comprises melancholy depression. In other embodiments, the disorder comprises atypical depression.

[0048] In some embodiments of this invention, the compound of Formula (I) or a salt thereof (generally a therapeutically effective amount) is used to make a medicament for treating a cocaine-related disorder. In some such embodiments, the disorder comprises cocaine abuse.

[0049] In some embodiments of this invention, the compound of Formula (I) or a salt thereof (generally a therapeutically effective amount) is used to make a medicament for treating an attention-deficit or disruptive behavior disorder. In some such embodiments, the disorder comprises ADHD.

[0050] It is contemplated that compositions comprising the compound of Formula (I) or a salt thereof may be formulated for a variety of suitable routes and means of administration, including oral, rectal, nasal, topical, buccal, sublingual, vaginal, inhalation, insufflation, or parenteral administration. In some embodiments, the compound or salt is administered orally. In some embodiments, the compound or salt is administered intravenously. In some embodiments, the compound or salt is administered intramuscularly. In some embodiments, the compound or salt is administered subcutaneously. And, in some embodiments, the compound or salt is administered intraperitoneally, intrathoracially, epidurally, intrathecally, intracerebroventricularly, and injection into the joints.

[0051] It is contemplated that pharmaceutical compositions of this invention may, for example, be in the form of solids, aqueous or oily solutions, suspensions, emulsions, creams, ointments, mists, gels, nasal sprays, suppositories, finely divided powders, and aerosols or nebulisers for inhalation. In some embodiments, the composition comprises a solid or liquid dosage form that may be administered orally.

[0052] Solid form compositions may include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier may comprise one or more substances. Such substances are generally inert. A carrier also may act as, for example, a diluent, flavoring agent, solubilizer, lubricant, preservative, stabilizer, suspending agent, binder, or disintegrating agent. It also may act as, for example, an encapsulating material. Examples of often suitable carriers include pharmaceutical grade mannitol, lactose, magnesium carbonate, magnesium stearate, talc, lactose, sugar (*e.g.*, glucose and sucrose), pectin, dextrin, starch, tragacanth, cellulose, cellulose derivatives (*e.g.*, methyl cellulose and sodium carboxymethyl cellulose), sodium saccharin, low-melting wax, and cocoa butter.

[0053] In powders, the carrier is typically a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is typically mixed with the carrier having the desirable binding properties in suitable proportions and compacted into the desired shape and size.

[0054] For preparing suppository compositions, a low-melting wax (*e.g.*, a mixture of fatty acid glycerides and cocoa butter) is typically first melted, followed by dispersing the active ingredient therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify. Examples of non-irritating excipients that may be present in suppository compositions include, for

example, cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol.

[0055] Liquid compositions can be prepared by, for example, dissolving or dispersing the compound of Formula (I) or a salt thereof in a carrier, such as, for example, water, water/propylene glycol solutions, saline aqueous dextrose, glycerol, or ethanol. In some embodiments, aqueous solutions for oral administration can be prepared by dissolving the compound of Formula (I) or a salt thereof in water with a solubilizer (*e.g.*, a polyethylene glycol). Colorants, flavoring agents, stabilizers, and thickening agents, for example, also may be added. In some embodiments, aqueous suspensions for oral use can be made by dispersing the compound of Formula (I) or a salt thereof in a finely divided form in water, together with a viscous material, such as, for example, one or more natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, or other suspending agents. If desired, the liquid composition also may contain other non-toxic auxiliary inert ingredients, such as, for example, wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Such compositions also may contain other ingredients, such as, for example, one or more pharmaceutical adjuvants.

[0056] In some embodiments, the pharmaceutical composition comprises from about 0.05% to about 99% (by weight) of the compound of Formula (I) or a salt thereof. In some such embodiments, for example, the pharmaceutical composition comprises from about 0.10% to about 50% (by weight) of the compound of Formula (I) or a salt thereof.

[0057] When the compound of Formula (I) or a salt thereof is administered as a sole therapy for treating a disorder, a "therapeutically effective amount" is an amount sufficient to reduce or completely alleviate symptoms or other detrimental effects of the disorder; cure the disorder; reverse, completely stop, or slow the progress of the disorder; reduce the risk of the disorder getting worse; or delay or reduce the risk of onset of the disorder.

[0058] The optimum dosage and frequency of administration will depend on the particular condition being treated and its severity; the species of the patient; the age, sex, size and weight, diet, and general physical condition of the particular patient; brain/body weight ratio; other medication the patient may be taking; the route of administration; the

formulation; and various other factors known to physicians (in the context of human patients), veterinarians (in the context of non-human patients), and others skilled in the art.

[0059] It is contemplated that, in some embodiments, the optimum amount of the compound of Formula (I) or a salt thereof is from about 0.05 to about 300 mg/kg body weight per day. In other embodiments, the optimum amount is less than about 200 mg/kg body weight per day. In other embodiments, the optimum amount is from about 1 to about 1000 mg/kg body weight per day, or from about 1 to about 100 mg/kg body weight per day (*e.g.*, about 15 mg/kg body weight per day).

[0060] It is contemplated that the pharmaceutical compositions can be in one or more unit dosage forms. Accordingly, the composition may be divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be, for example, a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these in packaged forms. The unit dosage form alternatively can be a packaged preparation in which the package contains discrete quantities of the composition, such as, for example, packeted tablets, capsules, or powders in vials or ampoules. Unit dosage forms may be prepared by, for example, various methods well known in the art of pharmacy.

[0061] It is contemplated that a dosage can be given once daily or in divided doses, such as, for example, from 2 to 4 times per day. In some embodiments, the dose is conventionally formulated in an oral dosage form by compounding from about 5 to about 250 mg per unit of dosage with, for example, one or more inert or active ingredients using accepted pharmaceutical practices.

[0062] In some embodiments, the compound of Formula (I) or a salt thereof is administered concurrently, simultaneously, sequentially, or separately with one or more other pharmaceutically active compounds. In some such embodiments, the other pharmaceutically active compound(s) is/are selected from the following:

(i) Antidepressants, which are contemplated to include, for example, one or more of agomelatine, amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin duloxetine, elzasonan, escitalopram, fluvoxamine, fluoxetine, gepirone, imipramine, ipsapirone, maprotiline, mirtazeprine, nortriptyline, nefazodone, paroxetine, phenelzine, protriptyline, ramelteon, reboxetine, robalzotan, selegiline, sertraline, sibutramine, thionisoxetine, tranylcypromaine, trazodone, trimipramine,

venlafaxine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(ii) Antipsychotics, which are contemplated to include, for example, one or more of quetiapine and pharmaceutically active isomer(s) and metabolite(s) thereof; and amisulpride, aripiprazole, asenapine, benzisoxidil, bifeprunox, carbamazepine, clozapine, chlorpromazine, debenzapine, dibenzapine, divalproex, droperidol, duloxetine, eszopiclone, fluphenazine, haloperidol, iloperidone, lamotrigine, lithium, loxapine, mesoridazine, molindone, olanzapine, paliperidone, perlapine, perphenazine, phenothiazine, phenylbutylpiperidine, pimozide, prochlorperazine, risperidone, sertindole, sulpiride, suproclone, suriclone, thioridazine, thiothixene, trifluoperazine, trimetozine, valproate, valproic acid, zopiclone, zotepine, ziprasidone, and equivalents thereof.

(iii) Anxiolytics, which are contemplated to include, for example, one or more of alnespirone, azapirones, benzodiazepines, barbiturates such as adinazolam, alprazolam, balezepam, bentazepam, bromazepam, brotizolam, buspirone, clonazepam, clorazepate, chlordiazepoxide, cyprazepam, diazepam, diphenhydramine, estazolam, fenobam, flunitrazepam, flurazepam, fosazepam, lorazepam, lormetazepam, meprobamate, midazolam, nitrazepam, oxazepam, prazepam, quazepam, reclazepam, suriclone, tracazolate, trepipam, temazepam, triazolam, uldazepam, zolazepam and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(iv) Anticonvulsants, which are contemplated to include, for example, one or more of carbamazepine, oxcarbazepine, valproate, lamotrogine, gabapentin, topiramate, phenytoin, ethoxuximide, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(v) Alzheimer's therapies, which are contemplated to include, for example, donepezil, galantamine, memantine, rivastigmine, tacrine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(vi) Parkinson's therapies and agents for treating extrapyramidal symtpoms, which are contemplated to include, for example, one or more of levodopa, carbidopa, amantadine, pramipexole, ropinirole, pergolide, cabergoline, apomorphine, bromocriptine, MAOB inhibitors (*e.g.*, selegine and

rasagiline), COMT inhibitors (*e.g.*, entacapone and tolcapone), alpha-2 inhibitors, anticholinergics (*e.g.*, benztropine, biperiden, orphenadrine, procyclidine, and trihexyphenidyl), dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists, and inhibitors of neuronal nitric oxide synthase, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(vii) Migraine therapies, which are contemplated to include, for example, one or more of almotriptan, amantadine, bromocriptine, butalbital, cabergoline, dichloralphenazone, eletriptan, frovatriptan, lisuride, naratriptan, pergolide, pramipexole, rizatriptan, ropinirole, sumatriptan, zolmitriptan, zomitriptan, and equivalents, and pharmaceutically active isomer(s) and metabolite(s) thereof.

(viii) Stroke therapies, which are contemplated to include, for example, one or more of abciximab, activase, disufenton sodium, citicoline, crobenetine, desmoteplase,repinotan, traxoprodil, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(ix) Urinary incontinence therapies, which are contemplated to include, for example, one or more of darafenacin, dicyclomine, falvoxate, imipramine, desipramine, oxybutynin, propiverine, propanthedine, robalzotan, solifenacin, alfazosin, doxazosin, terazosin, tolterodine, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(x) Neuropathic pain therapies, which are contemplated to include, for example, one or more of gabapentin, lidoderm, pregablin, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xi) Nociceptive pain therapies, which are contemplated to include, for example, one or more of celecoxib, cideine, etoricoxib, fentanyl, hydrocodone, hydromorphone, levo-alpha-acetylmethadol, lumiracoxib, meperidine, methadone, morphine, oxycodone, rofecoxib, valdecoxib, diclofenac, loxoprofen, naproxen, paracetamol, propoxyphene, sufentanyl, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xii) Insomnia therapies, which are contemplated to include, for example, one or more of allobarbital, alonimid, amobarbital, benzoctamine, butabarbital, capuride, chloral, cloperidone, clorethate, dexclamol, estazolam,

eszopicline, ethchlorvynol, etomidate, flurazepam, glutethimide, halazepam, hydroxyzine, mecloqualone, melatonin, mephobarbital, methaqualone, midaflur, midazolam, nisobamate, pagoclone, pentobarbital, perlapine, phenobarbital, propofol, quazepam, ramelteon, roletamide, suproclone, temazepam, triazolam, triclofos,secobarbital, zaleplon, zolpidem, zopiclone, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xiii) Mood stabilizers, which are contemplated to include, for example, one or more of carbamazepine, divalproex, gabapentin, lamotrigine, lithium, olanzapine, quetiapine, valproate, valproic acid, verapamil, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xiv) Medications for treating obesity, such as, for example, orlistat, sibutramine, rimonabant, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xv) Agents for treating ADHD, which are contemplated to include, for example, one or more of amphetamine, methamphetamine, dextroamphetamine, atomoxetine, methylphenidate, dexmethylphenidate, modafinil, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(xvi) Agents used to treat substance abuse disorders, dependence, and withdrawal, which are contemplated to include, for example, one or more of nicotine replacement therapies (*e.g.*, gum, patches, and nasal spray); nicotinergic receptor agonists, partial agonists, and antagonists, (*e.g.*, varenicline); acomprosate; bupropion; clonidine; disulfiram; methadone; naloxone; naltrexone; and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

[0063] In some embodiments, the other pharmaceutically active ingredient(s) comprises a cognitive enhancing agent.

[0064] In some embodiments, the other pharmaceutically active ingredient(s) comprises a memory enhancing agent.

[0065] In some embodiments, the other pharmaceutically active ingredient(s) comprises a choline esterase inhibitor.

[0066] In some embodiments, the other pharmaceutically active ingredient(s) comprises anti-inflammatory agent.

[0067] In some embodiments, the antipsychotic comprises an atypical antipsychotic agent. Atypical antipsychotic agents include, for example, olanzapine (marketed as Zyprexa), aripiprazole (marketed as Abilify), risperidone (marketed as Risperdal), quetiapine (marketed as Seroquel), clozapine (marketed as Clozaril), ziprasidone (marketed as Geodon), and olanzapine/fluoxetine (marketed as Symbyax).

[0068] In some embodiments, the other pharmaceutically active ingredient(s) comprises a selective serotonin reuptake inhibitor (or "serotonin-specific reuptake inhibitor" or SSRI"). Such agents include, for example, fluoxetine (marketed as, for example, Prozac), paroxetine (marketed as, for example, Paxil), citalopram (marketed as, for example, Celexa), dapoxetine, mesembrine, excitalopram (marketed as, for example, Lexapro), fluvoxamine (marketed as, for examle, Luvox), zimelidine (marketed as, for example, Zelmid), and sertraline (marketed as, for example, Zoloft).

[0069] In some embodiments, the compound of Formula (I) or a salt thereof is administered as part of a combination therapy with chemotherapy.

[0070] In some embodiments in which a combination therapy is used, the amount of the compound of Formula (I) or a salt thereof and the amount of the other pharmaceutically active agent(s) are, when combined, therapeutically effective to treat a targeted disorder in the animal patient. In this context, the combined amounts are "therapeutically effective amount" if they are, when combined, sufficient to reduce or completely alleviate symptoms or other detrimental effects of the disorder; cure the disorder; reverse, completely stop, or slow the progress of the disorder; reduce the risk of the disorder getting worse; or delay or reduce the risk of onset of the disorder. Typically, such amounts may be determined by one skilled in the art by, for example, starting with the dosage range described in this patent for the compound of Formula (I) or a salt thereof and an approved or otherwise published dosage range(s) of the other pharmaceutically active compound(s).

[0071] When used in a combination therapy, it is contemplated that the compound of Formula (I) or a salt thereof and the other active ingredients may be administered in a single composition, completely separate compositions, or a combination thereof. It also is contemplated that the active ingredients may be administered concurrently, simultaneously, sequentially, or separately. The particular composition(s) and dosing frequency(ies) of the combination therapy will depend on a variety of factors, including, for example, the route of administration, the condition being treated, the species of the patient, any potential interactions between the active ingredients when combined into a

single composition, any interactions between the active ingredients when they are administered to the animal patient, and various other factors known to physicians (in the context of human patients), veterinarians (in the context of non-human patients), and others skilled in the art.

EXAMPLES

[0072] The invention is further defined in the following Examples. It should be understood that the Examples are given by way of illustration only. From the above discussion and the Examples, one skilled in the art can ascertain the essential characteristics of the invention, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the invention to various uses and conditions. As a result, the invention is not limited by the illustrative examples below, but rather defined by the claims appended hereto.

Examples 1-3. Compound Preparation

[0073] Unless otherwise stated, operations were carried out at room or ambient temperature (18-25°C). Unless otherwise stated reaction progress was monitored by HPLC, LC-MS, or TLC. Oven-dried standard laboratory glassware was used and routine manipulations were conducted at ambient temperature under a blanket of N_2 unless otherwise indicated. Commercially available reagents and anhydrous solvents were typically used as received. Evaporations were typically performed under reduced pressure using a rotary evaporator. Preparative chromatography was performed using ICN silica gel 60, 32-63μ or a suitable equivalent. Drying was conducted under reduced pressure at 40°C or a suitable temperature.

[0074] Mass Spectrometer Conditions.

[0075] One or more of the following methods were used to analyze the intermediates and final compound below. Unless otherwise indicated, all m/z ratios are reported as the M+1 ion.

[0076] Mass Spectrometer Method 1 (referred to as "MS1")

Instrumentation: Agilent TOF 6210 fronted by an Agilent 1200 LC

Ionization mode: Electrospray

Column: Zorbax SB-C8 2.1x30mm x 1.8um

Mobile phase A: Water:Acetonitrile:Formic acid (98:2:0.1 v/v)

Mobile Phase B: Water:Acetonitrile:Formic acid (2:98:0.05 v/v)

Gradient: Time in min (%B): 0(5); 1.5(95); 1.9(95); 2(5).

[0077] This instrument can be run in both a 'standard' and 'high resolution mode.' The only difference between the 'standard' and 'high resolution' method is the infusion of reference lock mass ions for the 'high resolution' calibration adjustment. All data reported to 5 decimal places was recorded in 'high resolution' mode.

[0078] Mass Spectrometer Method 1A (referred to as "MS1A")

Instrumentation: Agilent TOF 6210 fronted by an Agilent 1200 LC

Ionization mode: Electrospray

Column: Zorbax SB-C8 2.1x30mm x 1.8um

Mobile phase A: Water:Methanol:Formic acid (98:2:0.1 v/v)

Mobile Phase B: Water:Methanol:Formic acid (2:98:0.05 v/v)

Gradient: Time in min (%B): 0(5); 1.5(95); 1.9(95); 2(5).

[0079] This instrument can be run in both a 'standard' and 'high resolution mode.' The only difference between the 'standard' and 'high resolution' method is the infusion of reference lock mass ions for the 'high resolution' calibration adjustment. All data reported to 5 decimal places was recorded in 'high resolution' mode.

[0080] Mass Spectrometer Method 2 (referred to as "MS2")

Instrumentation: Waters Acquity SQD

Ionization mode: Electrospray

Column: Acquity UPLC BEH C18 2.1x50mm x 1.7um

Mobile phase A: Water:Acetonitrile:Formic acid (98:2:0.1 v/v)

Mobile Phase B: Water:Acetonitrile:Formic acid (2:98:0.05 v/v)

Gradient: Time in min (%B): 0(5); 0.9(95); 1.2(95); 1.3(5); 1.4(5).

[0081] Mass Spectrometer Method 3 (referred to as "MS3")

Instrumentation:	Waters ZMD fronted with an Agilent 1100 LC
Ionization mode:	APCI
Column:	Zorbax SB-C8 2.1x50mm x 5um
Mobile phase A:	Water:Acetonitrile:Formic acid (98:2:0.1 v/v)
Mobile Phase B:	Water:Acetonitrile:Formic acid (2:98:0.05 v/v)
Gradient:	Time in min (%B): 0(5); 3(90); 4(90); 4.5(5); 5(5).

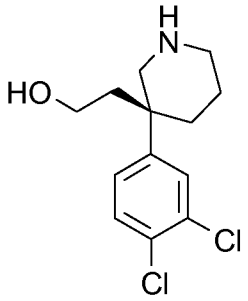
[0082] NMR Conditions.

[0083] At least one of the following two methods was used to determine nuclear magnetic resonance spectrometry: a Varian Unity Inova 400 spectrometer operating at 400 MHz for ^{1}H equipped with a 5 mm inverse detection triple resonance probe for detection of ^{1}H, ^{13}C, ^{31}P with the magnetic field provided by a 9.4 Tesla Oxford instruments super-conducting magnet and Sun Microsystems SunBlade 1000 workstation as host, or, alternatively, a Bruker Avance DRX 400 or DPX 300 spectrometer operating at 300 mHz, 400 or 500 mHz equipped with a 5 mm inverse detection triple resonance TXI probe for detection of ^{1}H, ^{13}C, ^{15}N with the magnetic field provided by a 9.4 Tesla Oxford instruments super-conducting magnet and an HP workstation wx5000 operating under Windows XP with the WIN-NMR software as host computer.

[0084] Chemical shifts are reported in parts-per-million (δ) from a tetramethylsilane internal standard. Chemical shifts are reported using the automatic processing features within ACDLABS V10.0.

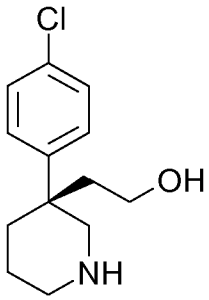
[0085] The multiplicities of the NMR spectra absorptions may be abbreviated by: s, singlet; br, broad peak; bs, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet.

[0086] Example 1. (S)-(-)-2-(3-(3,4-dichloro-phenyl)-piperidine-3-yl)ethanol.



This compound was prepared according to the method described in Patent No. EP591040B1. m/z (ES+) (M+1)+ =274.07529; HPLC r_t = 0.69 min (MS1). $[a]_D$= -8.7° (C=1, MeOH). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.53 (d, *J*=2.44 Hz, 1H) 7.48 (d, *J*=8.55 Hz, 1H) 7.33 (d, *J*=8.55 Hz, 1H) 3.14 (t, *J*=7.32 Hz, 2H) 3.08 (d, *J*=12.82 Hz, 1H) 2.92 (s, 2H) 2.80 (d, *J*= 12.21 Hz, 1H) 2.66 (dq, *J*=11.60, 11.39 Hz, 2H) 1.91 (dd, *J*=11.90, 3.97 Hz, 1H) 1.81 (t, *J*= 7.02 Hz, 1H) 1.68-1.77 (m, 2H) 1.43-1.54 (m, *J*=13.43, 9.77, 3.66, 3.66 Hz, 1H) 1.29 (dddd, *J*=12.82, 8.85, 4.58, 4.27 Hz, 1H).

[0087] Example 2. (S)-2-(3-(4-chlorophenyl)piperidin-3-yl)ethanol.

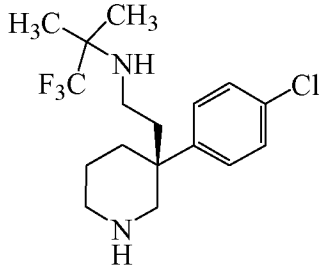


[0088] To a dry flask under N_2, with stir bar was added LAH in ether (10.94 mL, 10.94 mmol). THF (25 mL) and then MeOH (0.443 mL, 10.94 mmol) were added and gas evolved. After stirring 10 min, a solution of (S)-(-)-2-(3-(3,4-dichloro-phenyl)-piperidine-3-yl)ethanol (0.5 g, 1.82 mmol) in THF (15 mL) was added via syringe over 2 min. Some gas evolved, no exotherm. After 0.5 hr, another 27 ml 1M LAH in ether was added. The reaction was stirred at room temperature for 2 days and then quenched by slowly adding solid $Na_2SO_4.10H_2O$. After 2 hr, 80 ml of ether was added to form a thin slurry that was filtered through a 0.45 μm PTFE filter and washed with ether. After being evaporated, there was a small amount of water in the residue. The residue was redissolved in DCM, dried with $MgSO_4$, and filtered to obtain ~100 mg product. Extracted aluminum salts with 2 to 1 CH_2Cl_2 and MeOH and combined all product fractions, which were dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved/suspended in CH_2Cl_2 and filtered through 0.45 μm PTFE filter. The filtrate was evaporated to yield 200 mg semi-solid. This material was purified using preparative reverse phase HPLC (gradient elution on a Phenomenex Gemini NX C18 column (150 x 30mm, 5 μm) as stationary phase and ACN gradient in buffer (pH=9, NH_4CO_3 in water) as the mobile phase) to yield **title compound** (r_t = 9.20 min, 18 mg, 4% yield). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.35 (4H, d), 4.02-4.29 (1H, m), 2.95-3.12 (3H, m), 2.75-2.83 (1H, m), 2.54-2.73 (2H, m),

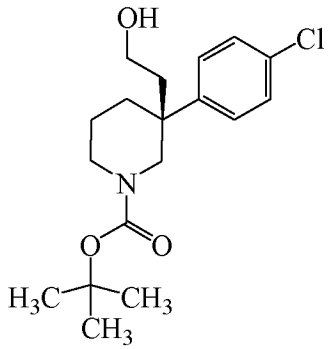
1.78-1.95 (2H, m), 1.65-1.78 (2H, m), 1.41-1.54 (1H, m), 1.27 (1H, m). m/z (ES+) (M+H)+= 240.1388; HPLC r_t = 0.55 min (MS1).

[0089] It is contemplated that (S)-2-(3-(4-chlorophenyl)piperidin-3-yl)ethanol also can be prepared in a manner analogous to that reported for the dichloro derivative, (S)-(-)-2-(3-(3,4-dichloro-phenyl)-piperidine-3-yl)ethanol, in Example 1 above using the method generally described in Patent No. EP591040B1. It is further contemplated that the enantiomers in that method can be separated by fractional crystallization of diastereomeric salts or preparative chiral stationary phase supercritical fluid chromatography (CSP SFC).

[0090] Example 3: (S)-N-(2-(3-(4-chlorophenyl)piperidin-3-yl)ethyl)- 1,1,1-trifluoro-2-methylpropan-2-amine.



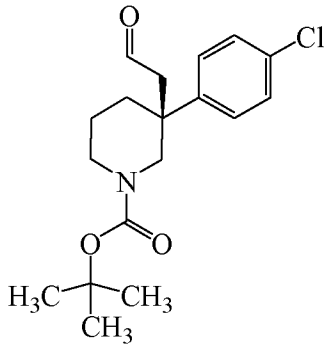
[0091] Product 3A: (S)-tert-butyl 3-(4-chlorophenyl)-3-(2-hydroxyethyl)piperidine-1-carboxylate



(S)-2-(3-(4-chlorophenyl)piperidin-3-yl)ethanol (330 mg, 1.38 mmol) was dissolved in tetrahydrofuran (20 mL). To this was added di-tert-butyl dicarbonate (1.45 mL, 1.45 mmol) at 25°C. The resulting mixture was stirred under N_2 for 18 hr. The mixture was then concentrated, extracted with DCM and $NaHCO_3$ solution, dried over Na_2SO_4, filtered, concentrated, and purified using flash silica gel chromatography with 25% EtOAc/DCM as eluent (TLC development with UV (weak) and Iodine stain). This resulted in (S)-tert-butyl 3-(4-chlorophenyl)-3-(2-hydroxyethyl)piperidine-1-carboxylate (465 mg, 105 %) as a clear gum. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.28 - 7.40 (m, 4H) 4.64 (br. s., 1H) 3.90 (d, *J*=13.43 Hz, 1H) 3.36 - 3.45 (m, 1H) 3.29 (d, *J*=14.04 Hz, 1H) 3.18 (ddd,

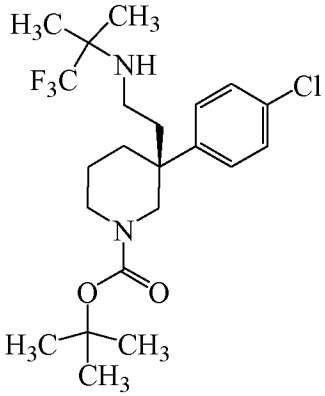
J=12.82, 8.85, 3.97 Hz, 1H) 3.13 (t, *J*=7.32 Hz, 2H) 1.99 - 2.09 (m, 1H) 1.69 - 1.80 (m, 3H) 1.53 (dd, *J*=7.32, 3.66 Hz, 1H) 1.39 (s, 9H) 1.32 (ddd, *J*=13.58, 9.31, 4.58 Hz, 1H). m/z (ES+) (M-tBu)+ = 284.10391; HPLC r_t = 1.57 min (MS1A).

[0092] Product 3B: (S)-tert-butyl 3-(4-chlorophenyl)-3-(2-oxoethyl)piperidine-1-carboxylate



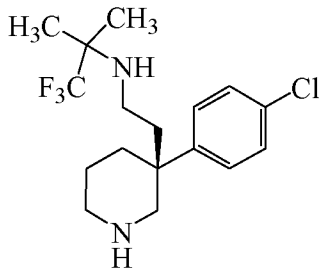
3A (465 mg, 1.38 mmol) was dissolved in DMSO (5 mL). The reaction flask was placed into a cooling bath to maintain the temperature at 25°C. Triethylamine (1.20 mL, 8.65 mmol) was then added while the mixture was stirred. Afterward, pyridine sulfur trioxide complex (688 mg, 4.33 mmol) was dissolved in DMSO (5 mL) (endothermic) and then added dropwise over 10 min. The resulting mixture was then allowed to stir for an additional 10 min while in the cooling bath. At the end of this time, the completion of the reaction was confirmed by LCMS. The mixture was then poured into 0.5 N HCl solution and extracted with EtOAc (caution: mild exotherm). The organic layer was washed with 0.5 N HCl and then with 1% $NaHCO_3$ solution. Afterward, the organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography on silica gel using a gradient of 20-35% EtOAC in hexanes as eluent (TLC development with UV (weak) and Iodine stain). The desired fractions were dried under high vacuum to form (S)-tert-butyl 3-(4-chlorophenyl)-3-(2-oxoethyl)piperidine-1-carboxylate (398 mg, 99 %) as a clear oil. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 9.42 (s, 1H) 7.43 (d, *J*=8.54 Hz, 2H) 7.32 - 7.37 (m, 2H) 3.84 (d, *J*=13.43 Hz, 1H) 3.57 (d, *J*=13.43 Hz, 1H) 3.27 - 3.39 (m, 2H) 2.66 (dd, *J*=7.02, 2.75 Hz, 2H) 2.08 (td, *J*=8.85, 4.27 Hz, 1H) 1.91 (td, *J*=8.85, 4.27 Hz, 1H) 1.53 - 1.63 (m, 1H) 1.40 - 1.45 (m, 1H) 1.39 (s, 9H). m/z (ES+) (M-tBu)+ = 282.08868 ; HPLC r_t = 1.58 min (MS1A).

[0093] Product 3C: (S)-tert-butyl 3-(4-chlorophenyl)-3-(2-(1,1,1-trifluoro-2-methylpropan-2-amine) piperidine-1-carboxylate



3B (200 mg, 0.59 mmol) was dissolved in $ClCH_2CH_2Cl$ (20 mL). Afterward, 1,1,1-trifluoro-2-methylpropan-2-amine (94 mg, 0.74 mmol) was added. The resulting mixture was allowed to stir for 30 min. Afterward, sodium triacetoxyborohydride (314 mg, 1.48 mmol) was added as a solid, and the mixture was stirred at 25°C for 18 hr. At the end of this time, completion of the reaction was confirmed by LCMS. The reaction was then quenched with Na_2CO_3 solution. The resulting product was dissolved in DCM and washed with 1N NaOH solution. The organic layers were dried over Na_2SO_4, filtered, and concentrated to give a crude product. This material was purified by silica gel chromatography using 15% EtOAc in DCM as eluent (TLC development with UV (weak) and iodine stain) to form (S)-tert-butyl 3-(4-chlorophenyl)-3-(2-(1,1,1-trifluoro-2-methylpropan-2-amine) ethyl) piperidine-1-carboxylate (240 mg, 90 %) as a clear oil. ^1H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.28 - 7.40 (m, 4H) 3.85 (d, *J*=13.43 Hz, 1H) 3.35 - 3.42 (m, 1H) 3.32 (d, *J*=13.43 Hz, 1H) 3.22 (ddd, *J*=12.82, 8.54, 4.27 Hz, 1H) 2.21 - 2.35 (m, 2H) 1.97 - 2.07 (m, 1H) 1.74 (ddd, *J*=13.73, 9.46, 3.66 Hz, 1H) 1.62 - 1.69 (m, 2H) 1.49 - 1.58 (m, 1H) 1.42 - 1.49 (m, 1H) 1.40 (s, 9H) 1.33 (dddd, *J*=13.05, 9.00, 8.77, 3.97 Hz, 1H) 1.04 (s, 6H). 19F NMR (471 MHz, *DMSO-d*$_6$) δ ppm -77.88 (s, 3 F). m/z (ES+) (M+H)+ = 449.21811; HPLC r_t = 1.62 min (MS1A).

[0094] Title Compound : (S)-N-(2-(3-(4-chlorophenyl)piperidin-3-yl)ethyl)- 1,1,1-trifluoro-2-methylpropan-2-amine



3C (240 mg, 0.53 mmol) was dissolved in DCM (2 mL). Afterward, TFA (2 mL) was added. The resulting mixture was stirred for 2 hr at 25°C. Completion of the reaction was confirmed by LCMS. The mixture was then concentrated to remove excess TFA. The residue was redissolved in DCM, and then washed with 1N NaOH solution. The organic layer was dried over Na_2SO_4, filtered, concentrated, and dried to form a crude product, which was further purified by silica gel chromatography using 2% of a 7N ammonia in methanol solution in DCM as eluent (TLC development with UV (weak) and Iodine stain). Concentration of the fractions produced (S)-N-(2-(3-(4-chlorophenyl)piperidin-3-yl)ethyl)- 1,1,1-trifluoro-2-methylpropan-2-amine (174 mg, 93 %) as a colorless solid. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.34 (s, 4H) 3.19 (d, *J*=13.43 Hz, 1H) 2.90 (d, *J*=13.43 Hz, 1H) 2.69 - 2.83 (m, 2H) 2.36 (dt, *J*=10.38, 5.19 Hz, 1H) 2.29 (td, *J*=10.22, 5.80 Hz, 1H) 2.13 (ddd, *J*=13.12, 3.97, 3.66 Hz, 1H) 1.69 - 1.87 (m, *J*=10.38, 10.07, 9.92, 9.92 Hz, 3H) 1.62 (ddd, *J*=13.73, 6.41, 3.66 Hz, 1H) 1.51 (td, *J*=8.54, 4.27 Hz, 1H) 1.09 (s, 6H). 19F NMR (471 MHz, *DMSO-d*$_6$) δ ppm -80.11 (s, 3 F). m/z (ES+) (M+H)+ = 349.16443; HPLC r_t = 1.01 min (MS1A).

Example 4. Biological Evaluation

[0095] The compound of Formula (I) was tested with the *in vitro* assay described below to determine its activity toward norepinephrine transport receptors and dopamine transport receptors. More specifically, the compound was tested in the assay to determine whether it is an effective norepinephrine transport receptor and/or dopamine transport receptor ligand. In the *in vitro* assay, a compound can be tested for its activity toward norepinephrine transport receptors and dopamine transport receptors, and Ki values can be obtained to determine the activity for a particular compound toward both receptors. While the *in vitro* activity of a compound may be related to *in vivo* activity, it may not be linearly correlated with binding affinity.

[0096] In the assay, the compound of Formula (I) was evaluated in an eleven point IC50 curve for ability to inhibit uptake of a fluorescent substrate (dye) that mimics biogenic amine neurotransmitters. A stable population of HEK293F cells transfected with the human transporter (NET: norepinephrine, DAT: dopamine) were cryopreserved, then plated and used on the day of the assay. Cells were at 60K/well. Final dye concentration was 7% (NET) or 50% (DAT) of the vendor-recommended reconstitution concentration (100%). The compound of Formula (I) was diluted 1:20 in buffer and incubated with the cells for 30 min before adding dye. In this fluorescence intensity assay, plates were read

after a 20 min (NET or DAT) dye incubation to determine percent effect with respect to total signal (0.5% DMSO, final) and background signal (NET: 10μM desipramine, DAT: 10μM GBR12909). The IC_{50}, half of the control response, was converted to Ki using the standard Cheng-Prusoff equation. Set forth in **Table 1** below are Ki values for the compound of Formula I (**Example 3**) that were generated in accordance with the above assay.

Table 1

Example	NET Ki (nM)	DAT Ki (nM)
3	2.3	3.8

* * * * * * * * *

[0097] Unless otherwise indicated, the following apply in this patent:

[0098] The chemical nomenclature used in this patent generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979. Compound names in the above examples were generated using AutoNom 2000 within ISIS/Draw or ChemDraw Ultra 8.0. AutoNom (Automatic Nomenclature) is a chemical-name-generating program that assigns systematic IUPAC (International Union of Pure and Applied Chemistry) chemical names to drawn structures at the press of a button.

[0099] The term “pharmaceutically acceptable” is used to characterize a moiety (*e.g.*, a salt, dosage form, carrier, diluent, or excipient) as being appropriate for use in accordance with sound medical judgment. In general, a pharmaceutically acceptable moiety has one or more benefits that outweigh any deleterious effect that the moiety may have. Deleterious effects may include, for example, excessive toxicity, irritation, allergic response, and other problems and complications.

[00100] References made in the singular may also include the plural. For example, “a” and “an” may refer to either one or more than one.

[00101] The words "comprise," "comprises," and “comprising" in this patent (including the claims) are to be interpreted inclusively rather than exclusively. This interpretation is intended to be the same as the interpretation that these words are given under United States patent law.

[00102] The term “ACN” means acetonitrile.

[00103] The term “CH_2Cl_2” means dichloromethane.

[00104] The term "CO_2" means carbon dioxide.

[00105] The term "DAT" means dopamine transport receptor.

[00106] The term "DCM" means dichloromethane.

[00107] The term "DMSO" means dimethyl sulfoxide.

[00108] The term "DMSO-d6" means deuterated dimethyl sulfoxide.

[00109] The term "EtOAc" means ethyl acetate.

[00110] The term "^{1}H NMR" means proton nuclear magnetic resonance.

[00111] The term "H_2O" means water.

[00112] The term "HCl" means hydrochloric acid.

[00113] The term "HPLC" means high performance liquid chromatography.

[00114] The term "hr" means hour or hours.

[00115] The term "LAH" means Lithium aluminum hydride.

[00116] The term "LCMS" means liquid chromatography mass spectral detection.

[00117] The term "m/z" means mass to charge ratio.

[00118] The term "MeOH" means methanol.

[00119] The term "$MgSO_4$" means magnesium sulfate.

[00120] The term "min" means minute or minutes.

[00121] The term "MS" means mass spectrum.

[00122] The term "N_2" means nitrogen gas.

[00123] The term "$NaHCO_3$" means sodium bicarbonate.

[00124] The term "NaOH" means sodium hydroxide.

[00125] The term "Na_2SO_4" means sodium sulfate.

[00126] The term "NET" means norepinephrine transport receptor.

[00127] The term "NMR" means nuclear magnetic resonance.

[00128] The term "psig" means pound per square inch.

[00129] The term "r_t" means retention time.

[00130] The term "SFC" means supercritical fluid chromatography.

[00131] The term "TFA" means trifluoroacetic acid.

[00132] The term "THF" means tetrahydrofuran.

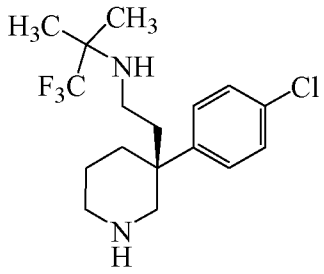
[00133] The term "UV" means ultraviolet.

[00134] The above detailed description of preferred embodiments is intended only to acquaint others skilled in the art with the invention, its principles, and its practical

application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This invention, therefore, is not limited to the above embodiments, and may be variously modified.

We claim:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein Formula (I) corresponds to:



(I).

2. The compound or a pharmaceutically acceptable salt thereof according to claim 1 for use as a medicament.

3. The use of the compound or a pharmaceutically acceptable salt thereof according to claim 1 in the manufacture of a medicament for the therapy of a disorder comprising a disorder selected from major depressive disorders, attention-deficit and disruptive behavior disorders, and cocaine-related disorders.

4. The compound or a pharmaceutically acceptable salt thereof according to claim 1 for the treatment of a disorder comprising a disorder selected from atypical depression, melancholy depression, cocaine abuse, and attention deficit hyperactivity disorder.

5. A pharmaceutical composition, wherein the composition comprises:

the compound or a pharmaceutically acceptable salt thereof according to claim 1, and

a pharmaceutically acceptable carrier or diluent.

6. A method for treating a disorder in a warm-blooded animal in need of such treatment, wherein:

the disorder comprises a disorder selected from a major depressive disorders, attention-deficit and disruptive behavior disorders, and cocaine-related disorders; and

the method comprises administering to the animal a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof of claim 1.

7. A method for treating a disorder in a warm-blooded animal in need of such treatment, wherein:

the disorder comprises a disorder selected from melancholy depression, atypical depression, cocaine abuse, and ADHD; and

the method comprises administering to the animal a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof of claim 1.

8. A method for treating a major depressive disorder in a warm-blooded animal in need of such treatment, wherein the method comprises administering to the animal a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof of claim 1.

9. A method for treating a disorder a warm-blooded animal in need of such treatment, wherein:

the disorder comprises a disorder in which modulating norepinephrine transport receptors and/or dopamine transport receptors is beneficial, and

the method comprises administering to the animal a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof of claim 1.

10. A method according to any one of claims 6-9, wherein the warm-blooded animal is a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/60255

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/40; A61K 31/445 (2011.01)
USPC - 514/315
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/315

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/317; 514/642 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: dopamine neurotransmission, modulators, piperidines, administering, human, treatment, mood disorders, depression, substance abuse, attention-deficit hyperactivity disorder, dopamine transporter, DAT, piperidine analogs, crystal structure, molecular modeling, docking, binding site, drug binding pockets

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/121092 A1 (SONESSON et al.) 22 December 2005 (22.12.2005) pg 1, ln 7-8; pg 7, ln 9-31; pg 9, ln 1-8; pg 20, ln 5-18; pg 20, ln 30 - pg 21, ln 2; pg 23, ln 10-14; Claim 22	1-10
Y	WO 2009/094428 A2 (DUTTA) 30 July 2009 (30.07.2009) pg 1, ln 12-14; pg 7, ln 18 - pg 9, ln 16; pg 29, ln 25 - pg 30, ln 2; pg 30, ln 4	1-10
Y	RAVNA et al. Structure and localisation of drug binding sites on neurotransmitter transporters, J Mol Model, 2009 (published online: 24 February 2009), Vol 15, pp 1155-1164; Abstract; pg 1156 - pg 1163	1-10
P/X	WO 2010/071575 A1 (BERNSTEIN et al.) 24 June 2010 (24.06.2010) pg 2, ln 20 - pg 5, ln 24; pg 6, ln 7 - pg 17, ln 7; pg 19, ln 12-29; pg 20, ln 10 - pg 22, ln 15	1-10

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2011 (23.01.2011)	09 FEB 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)