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(54) Title: DEUTERATED MORPHINAN COMPOUNDS FOR USE IN TREATING AGITATION

(57) Abstract: This invention relates to methods of treating agitation comprising administering a morphinan compound or a pharmaceutically acceptable salt thereof. This invention also provides the use in methods of treating agitation and related disorders with such a morphinan compound in combination with quinidine, or pharmaceutically acceptable salt of either or both thereof.

DEUTERATED MORPHINAN COMPOUNDS FOR USE IN TREATING AGITATION

CLAIM OF PRIORITY

This application claims the benefit of U.S. Provisional Application number 62/198,894, filed July 30, 2015. The entire contents of the foregoing are hereby incorporated by reference.

TECHNICAL FIELD

This invention relates to methods of treating agitation comprising administering a deuterated morphinan compound or a pharmaceutically acceptable salt thereof. This invention also provides the use of such a deuterated morphinan compound in combination with quinidine, or a pharmaceutically acceptable salt of either or both thereof, in methods of treating agitation and related disorders.

BACKGROUND

Dextromethorphan, also known by its chemical name (+)-3-methoxy-17-methyl-(9α,13α,14α)-morphinan, is currently one of the most widely used antitussives.

In addition to the physiological activity noted above, dextromethorphan is also an agonist of the σ2 receptor, an N-methyl-D-aspartate (NMDA) antagonist, and an α3β4 nicotinic receptor antagonist. Dextromethorphan inhibits neurotransmitters, such as glutamate, from activating receptors in the brain. Uptake of dopamine and serotonin are also inhibited.

Dextromethorphan is approved for use in over the counter cough suppressant products. It is currently in clinical trials for treating subjects with voice spasms, and for treating Rett Syndrome (http://www. clinicaltrials.gov). Dextromethorphan is also being studied in combination with other drugs in a clinical trial characterizing pain processing mechanisms in subjects with irritable bowel syndrome (http://www.clinicaltrials.gov/).

In addition, a combination of dextromethorphan hydrobromide and quinidine sulfate is currently in clinical trials for treating diabetic neuropathic pain, central neuropathic pain in multiple sclerosis, agitation in Alzheimer's patients, autism, and major depressive disorder (http://www.clinicaltrials.gov). This drug combination, also known as NUEDEXTA®, is approved for treating Involuntary Emotional Expression Disorder (IEED), also known as pseudobulbar affect.

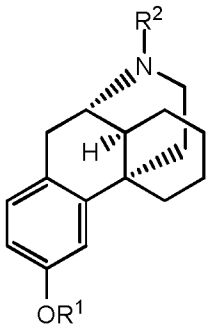
Dextromethorphan is metabolized in the liver. Degradation begins with O- and N-

demethylation to form primary metabolites dextrorphan and 3-methoxy-morphinan, both of which are further N- and O- demethylated respectively to 3-hydroxy-morphinan. These three metabolites are believed to be therapeutically active. A major metabolic catalyst is the cytochrome P450 enzyme 2D6 (CYP2D6), which is responsible for the O-demethylation reactions of dextromethorphan and 3-methoxymorphinan. N-demethylation of dextromethorphan and dextrorphan are catalyzed by enzymes in the related CYP3A family. Conjugates of dextrorphan and 3-hydroxymorphinan can be detected in human plasma and urine within hours of its ingestion.

Dextroethorphan, also known chemically as [(+)-3-ethoxy-17-methylmorphinan] is an ethyl analog of dextromethorphan and has shown anticonvulsant activity (Newman, A. et al., J Med Chem., 1992, 35(22): 4135-42 and Tortella, F. et al., J Pharmacol and Exp Therap., 1994, 268(2): 727-733) as well as neuroprotective effects in rats (Tortella, F. et al., Neurosci. Lett., 1995, 198(2): 79-82).

SUMMARY

Provided herein is a method of treating agitation comprising administering to a subject in need thereof, an effective amount of a compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein R^1 is an ethyl group optionally substituted by one to five deuterium atoms; and R^2 is a methyl group optionally substituted by one to three deuterium atoms; provided that either R^1 or R^2 comprises at least one deuterium atom, and a pharmaceutically acceptable carrier.

In some embodiments, R^1 is $-CH_2CH_3$, $-CD_2CH_3$, $-CH_2CD_3$, or $-CD_2CD_3$; and R^2 is $-CH_3$ or $-CD_3$.

In some embodiments, for the compound of Formula I, any atom not designated as deuterium is present at its natural isotopic abundance.

In some embodiments, the method comprises administering to the subject an amount of quinidine, or a pharmaceutically acceptable salt thereof, wherein the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 40 mg/day.

In some embodiments, the method comprises administering an amount of compound of Formula I, or a pharmaceutically acceptable salt thereof, in the range of 5 mg/day to 250 mg/day.

In some embodiments, the agitation is associated with a disorder selected from the group consisting of Alzheimer's disease, a degenerative neurological disorder, a mood disorder, substance abuse withdrawal, selective serotonin reuptake inhibitor (SSRI) withdrawal, withdrawal from benzodiazepines, withdrawal from drugs useful for the treatment of attention deficit disorder (ADD) and attention deficit hyperactive disorder (ADHD), traumatic brain injury, terminal illness, post-operative agitation, post-anesthetic agitation, Reye's syndrome and a pediatric disorder.

In some embodiments, the agitation is associated with a degenerative neurological disorder. In one aspect of these embodiments, the degenerative neurological disorder is Parkinson's disease. In another aspect of these embodiments, the degenerative neurological disorder is Huntington's disease.

In some embodiments, the agitation is associated with a mood disorder. In one aspect of these embodiments, the mood disorder is depression, dysthymia, schizophrenia or bipolar disorder. In one specific aspect of these embodiments, the mood disorder is depression. In one specific aspect of these embodiments, the mood disorder is dysthymia. In one specific aspect of these embodiments, the mood disorder is schizophrenia. In one specific aspect of these embodiments, the mood disorder is bipolar disorder.

In some embodiments, the agitation is associated with SSRI withdrawal. In one aspect of these embodiments, the SSRI is selected from fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine and sertraline.

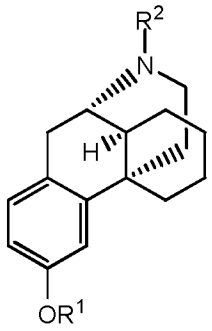
In some embodiments, the agitation is associated with withdrawal from drugs useful for the treatment of ADD and ADHD. In one aspect of these embodiments, the drug useful for the treatment of ADD and ADHD is selected from methamphetamine hydrochloride, methylphenidate hydrochloride, dextroamphetamine sulfate, mixed amphetamine salts, pemoline, dexmethylphenidate hydrochloride, and lisdexamfetamine mesilate.

In some embodiments, the agitation is associated with a pediatric disorder. In one aspect of these embodiments, the pediatric disorder is depression, attention deficit disorder, oppositional defiant disorder, or separation anxiety disorder.

In some embodiments, the agitation is associated with Alzheimer's disease.

In some embodiments, the agitation is associated with traumatic brain injury.

Also provided herein is a method of treating a disease or disorder selected from the group consisting of diabetes, epilepsy, and depression, comprising administering to a subject in need thereof, an effective amount of a compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein R^1 is an ethyl group optionally substituted by one to five deuterium atoms; and R^2 is a methyl group optionally substituted by one to three deuterium atoms; provided that at least one deuterium atom is present at either R^1 or R^2; together with quinidine, or a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

In some embodiments, R^1 is $-CH_2CH_3$, $-CD_2CH_3$, $-CH_2CD_3$, or $-CD_2CD_3$; and R^2 is $-CH_3$ or $-CD_3$. In some embodiments, for the compound of Formula I, any atom not designated as deuterium is present at its natural isotopic abundance.

In some embodiments, the compound of Formula I is a compound selected from the table:

Compound No.	R^1	R^2
100	$-O-CD_2CD_3$	CD_3
101	$-O-CD_2CH_3$	CD_3
102	$-O-CH_2CH_3$	CD_3
103	$-O-CH_2CD_3$	CD_3
104	$-O-CD_2CD_3$	CH_3
105	$-O-CD_2CH_3$	CH_3

Compound No.	R^1	R^2
106	-O-CH_2CD_3	CH_3

or a pharmaceutically acceptable salt thereof.

In some embodiments, the amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 5 mg/day to 500 mg/day, and the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 40 mg/day. In some embodiments, the amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 5 mg/day to 250 mg/day and the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 20 mg/day. In some embodiments, the amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 10 mg/day to 150 mg/day and the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 20 mg/day.

DETAILED DESCRIPTION

Definitions

The terms "ameliorate" and "treat" are used interchangeably and include both therapeutic treatment and/or prophylactic treatment (reducing the likelihood of development). 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), lessen the severity of the disease or improve the symptoms associated with the disease.

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

As used herein, the term "subject" includes humans and non-human mammals. Non-limiting examples of non-human mammals include mice, rats, guinea pigs, rabbits, dogs, cats, monkeys, apes, pigs, cows, sheep, horses, etc.

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 dextromethorphan or dextromethorphan analogs, or dextroethorphan or dextroethorphan analogs, 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 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., the term "D" or "deuterium" indicates at least 50.1% incorporation of deuterium).

The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance of D at a specified position in a compound of this invention and the naturally occurring abundance of that isotope. The natural abundance of deuterium is 0.015%.

In other embodiments, a compound of this invention has an isotopic enrichment factor for each deuterium present at a site designated as a potential site of deuteration on the compound of at least 3500 (52.5% deuterium incorporation), 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). It is understood that the isotopic enrichment factor of each deuterium present at a site designated as a site of deuteration is independent of other deuterated sites. For example, if there are two sites of deuteration on a compound one site could be deuterated at 52.5% while the other could be deuterated at 75%. The resulting compound would be considered to be a compound wherein the isotopic enrichment factor is at least 3500 (52.5%).

The term "isotopologue" refers to a species that has the same chemical structure and formula as a specific compound of this invention, with the exception of the positions of isotopic substitution and/or level of isotopic enrichment at one or more positions, e.g., H vs. D.

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.

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 suitable 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.

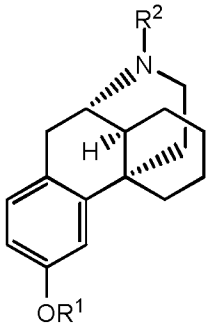
The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products,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

"Stereoisomer" refers to both enantiomers and diastereomers. "D" refers to deuterium. "Tert", "^{t}", and "t" each refer to tertiary. "US" refers to the United States of America. "FDA" refers to Food and Drug Administration. "NDA" refers to New Drug Application. "rt" and "RT" refer to room temperature. "h" refers to hours. "DMF" refers to dimethylformamide. "TsOH" refers to p-toluenesulfonic acid.

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

Therapeutic Compounds

Described herein are methods useful in the treatment of agitation such as agitation associated with Alzheimer's disease or with traumatic brain injury in a patient in need thereof. Also described herein are methods for treating a disease or disorder selected from the group consisting of diabetes, epilepsy, and depression. In certain embodiments, treatment comprises the administration of a compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein R^1 is an ethyl group optionally substituted by one to five deuterium atoms; and R^2 is a methyl group optionally substituted by one to three deuterium atoms; provided that either R^1 or R^2 comprises at least one deuterium atom.

In some embodiments, treatment comprises the administration of a compound of Formula I, as described herein, and a pharmaceutically acceptable carrier.

In some embodiments, R^1 is $-CH_2CH_3$, $-CD_2CH_3$, $-CH_2CD_3$, or $-CD_2CD_3$; and R^2 is $-CH_3$ or $-CD_3$.

In some embodiments, R^1 is $-CH_2CH_3$, or $-CD_2CD_3$; and R^2 is $-CH_3$ or $-CD_3$. In one aspect of these embodiments, R^1 is $-CH_2CH_3$ and R^2 is $-CD_3$. In another aspect of these embodiments, R^1 is $-CD_2CD_3$ and R^2 is $-CD_3$. In another aspect of these embodiments, R^1 is $-CD_2CD_3$ and R^2 is $-CH_3$.

In some embodiments, R^1 is $-CD_2CH_3$, or $-CH_2CD_3$; and R^2 is $-CH_3$ or $-CD_3$. In one aspect of these embodiments, R^1 is $-CD_2CH_3$ and R^2 is $-CD_3$. In another aspect of these embodiments, R^1 is $-CD_2CH_3$ and R^2 is $-CH_3$. In one aspect of these embodiments, R^1 is $-CH_2CD_3$ and R^2 is $-CD_3$. In another aspect of these embodiments, R^1 is $-CH_2CD_3$ and R^2 is $-CH_3$.

In some embodiments, the method comprises administering an amount of compound of Formula I, or a pharmaceutically acceptable salt thereof, in the range of 1 mg/day to 1000 mg/day. In one aspect of these embodiments, the amount of compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 5 mg/day to 500 mg/day. In one aspect of these embodiments, the amount of compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 5 mg/day to 400 mg/day. In one aspect of these embodiments, the amount of compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 5 mg/day to 250 mg/day. In one aspect of these embodiments, the amount of compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 10 mg/day to 100 mg/day.

In some embodiments, treatment comprises administration of a combination of a compound of Formula I, as described herein, and quinidine, or a pharmaceutically acceptable salt of either or both thereof.

In some embodiments, treatment comprises the administration of a combination of a compound of Formula I, as described herein, quinidine, or a pharmaceutically acceptable salt of either or both thereof, and a pharmaceutically acceptable carrier.

In some embodiments, the method comprises administering to the subject an amount of quinidine, or a pharmaceutically acceptable salt thereof, wherein the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 60 mg/day. In one aspect of these embodiments, the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 40 mg/day. In one aspect of these embodiments, the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 30 mg/day. In one aspect of these embodiments, the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 20 mg/day. In one aspect of these embodiments, the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 10 mg/day. In one aspect of these embodiments, the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 5 mg/day.

In certain embodiments, the amount of quinidine, or a pharmaceutically acceptable salt thereof, is an amount effective to increase the plasma half-life or decrease the intrinsic clearance of the compound of Formula I in the subject by at least 50%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, or 1000%, relative to the plasma half-life or the intrinsic clearance of the compound of Formula I in the subject in the absence of quinidine.

In some embodiments, the agitation is associated with a disorder selected from the group consisting of Alzheimer's disease, a degenerative neurological disorder, a mood disorder, substance abuse withdrawal, selective serotonin reuptake inhibitor (SSRI) withdrawal, withdrawal from benzodiazepines, withdrawal from drugs useful for the treatment of attention deficit disorder (ADD) and attention deficit hyperactive disorder (ADHD), traumatic brain injury, terminal illness, post-operative agitation, post-anesthetic agitation, Reye's syndrome and a pediatric disorder.

In some embodiments, the agitation is associated with a degenerative neurological disorder. In one aspect of these embodiments, the degenerative neurological disorder is Parkinson's disease. In another aspect of these embodiments, the degenerative neurological disorder is Huntington's disease.

In some embodiments, the agitation is associated with a mood disorder. In one aspect of these embodiments, the mood disorder is depression, dysthymia, schizophrenia or bipolar disorder. In one specific aspect of these embodiments, the mood disorder is depression. In one specific aspect of these embodiments, the mood disorder is dysthymia. In one specific aspect of these embodiments, the mood disorder is schizophrenia. In one specific aspect of these embodiments, the mood disorder is bipolar disorder.

In some embodiments, the agitation is associated with SSRI withdrawal. In one aspect of these embodiments, the SSRI is selected from fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine and sertraline.

In some embodiments, the agitation is associated with withdrawal from drugs useful for the treatment of ADD and ADHD. In one aspect of these embodiments, the drug useful for the treatment of ADD and ADHD is selected from methamphetamine hydrochloride, methylphenidate hydrochloride, dextroamphetamine sulfate, mixed amphetamine salts, pemoline, dexmethylphenidate hydrochloride, and lisdexamfetamine mesilate.

In some embodiments, the agitation is associated with a pediatric disorder. In one aspect of these embodiments, the pediatric disorder is depression, attention deficit disorder, oppositional defiant disorder, or separation anxiety disorder.

In some embodiments, the agitation is associated with Alzheimer's disease.

In some embodiments, the agitation is associated with traumatic brain injury.

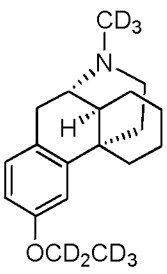
Examples of specific compounds of the Formula I where R^1 is $-CH_2CH_3$, $-CD_2CH_3$, $-CH_2CD_3$, or $-CD_2CD_3$ include those shown in Table 1:

Table 1: Exemplary Compounds of Formula I

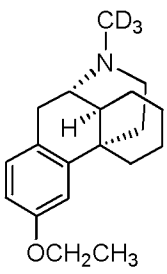
Compound No.	R^1	R^2
100	$-O-CD_2CD_3$	CD_3
101	$-O-CD_2CH_3$	CD_3
102	$-O-CH_2CH_3$	CD_3
103	$-O-CH_2CD_3$	CD_3
104	$-O-CD_2CD_3$	CH_3
105	$-O-CD_2CH_3$	CH_3
106	$-O-CH_2CD_3$	CH_3

or a pharmaceutically acceptable salt thereof, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

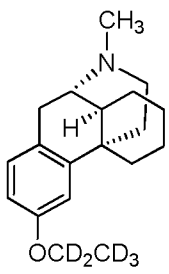
In some embodiments, the compound of Formula I is selected from any one of:



Compound 100,



Compound 102, and



Compound 104,

or a pharmaceutically acceptable salt thereof.

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.

In another set of embodiments, the compound of Formula I is purified, *e.g.*, the compound of Formula I is present at a purity of at least 50.1% by weight (e.g., at least 52.5%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 98.5%, 99%, 99.5% or 99.9%) of the total amount of isotopologues of Formula I present, respectively. Thus, in some embodiments, a composition comprising a compound of Formula I can include a distribution of isotopologues of the compound, provided at least 50.1% of the isotopologues by weight are the recited compound.

In another set of embodiments, the compounds of Formula I, or a pharmaceutically acceptable salt thereof, are provided in isolated form, e.g., the compound is not in a cell or organism and the compound is separated from some or all of the components that typically accompany it in nature.

In some embodiments, any position in the compound of Formula I designated as having D has a minimum deuterium incorporation of at least 50.1% (e.g., at least 52.5%, at least 60%, at least 67.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, at least 97%, at least 99%, or at least 99.5%) at the designated position(s) of the compound of Formula I. Thus, in some embodiments, a composition comprising a compound of Formula I can include a distribution of isotopologues of the compound, provided at least 50.1% of the isotopologues include a D at the designated position(s).

In some embodiments, a compound of Formula I is "substantially free of" other isotopologues of the compound, e.g., less than 49.9%, less than 25%, less than 10%, less than 5%, less than 2%, less than 1%, or less than 0.5% of other isotopologues are present.

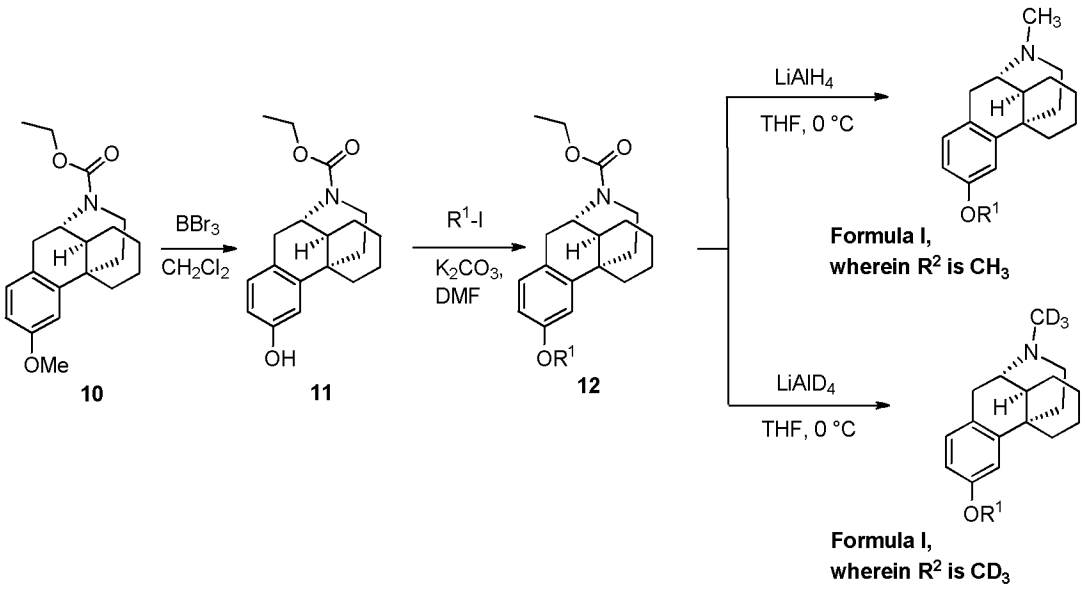
The synthesis of compounds of Formula I can be readily achieved by reference to the Exemplary Syntheses and Examples disclosed herein and in PCT application WO2010062690, and by use of procedures and intermediates analogous to those disclosed, for instance, in Schnider, O. & Grussner, A., Helv. Chim. Acta., 1951, 34: 2211; Grussner, A. & Schnider, O.; GB 713146 (1954); Toyo Pharma K. K., Japan JP 60089474 A (1983); Newman, A. H. et al., J. Med. Chem., 1992, 35: 4135. Such methods can be carried out by utilizing corresponding deuterated and, optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or by invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Exemplary Syntheses

The following deuterated reagents and building blocks which may be of use in preparing compounds of Formula I are commercially available: iodoethane-d_5, ethyl-2,2,2-d_3 iodide, and ethyl-1,1-d_2 iodide.

A convenient method for synthesizing compounds of Formula I is depicted in Scheme 1.

Scheme 1. Synthesis of a Compound of Formula I



Treatment of the known 17-ethoxycarbonyl-3-methoxy-morphinan (**10**) (for its preparation, see: Murdter, T. E. et al., Journal of Labelled Compounds and Radiopharmaceuticals 2002, 45: 1153-1158) with boron tribromide according to the procedure described by Newman, A. H. et al., Journal of Medicinal Chemistry 1992, 35: 4135-4142, affords the 17-ethoxycarbonyl-3-hydroxy-morphinan (**11**). Treatment of the 3-hydroxy-morphinan **11** with the appropriately deuterated ethyl iodide in the presence of potassium carbonate in a manner analogous to the procedure described in the aforementioned paper gives the deuterated 17-ethoxycarbonyl-3-alkoxy-morphinans (**12**). Reduction of the carbamate of the morphinan **12** with either lithium aluminum hydride or lithium aluminum deuteride in THF in a manner analogous to that described by Newman affords the appropriately deuterated 3-alkoxy-17-methyl-morphinan or the 3-alkoxy-17-trideuteromethyl-morphinan compounds of Formula I, respectively.

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 or R^2) 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.

Pharmaceutical Compositions

Provided herein are compositions for use in treating agitation comprising 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. Also provided herein are compositions for use in treating a disease or disorder selected from the group consisting of diabetes, epilepsy, and depression, comprising 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, the composition comprises an effective amount of the compound, or pharmaceutically acceptable salt thereof. In another embodiment, a composition of this invention further comprises a second therapeutic agent such as quinidine, or a pharmaceutically acceptable salt of quinidine. In one embodiment, the composition comprises an effective amount of the compound of Formula I, or pharmaceutically acceptable salt thereof, and an effective amount of quinidine or a pharmaceutically acceptable salt thereof. Preferably, 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: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000).

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 subject, 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 one embodiment, a composition of this invention further comprises a second therapeutic agent wherein the second therapeutic agent is quinidine or quinidine sulfate.

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 one embodiment of 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 subject. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

In one embodiment, an effective amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, can range from about 1 mg to 1000 mg, from about 5 mg to 500 mg, from about 5 mg to 400 mg, from about 5 mg to 250 mg, from about 10 mg to 150 mg, from about 10 mg to 100 mg, or from about 5 mg to 50 mg, which can be given once, twice, or up to three times daily depending on various factors recognized by those skilled in the art. In one embodiment the effective amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, can be given once daily. In one embodiment, the effective amount of quinidine, or a pharmaceutically acceptable salt thereof, can range from about 1 mg to 60 mg, from about 1 mg to 40 mg, from about 1 mg to 30 mg, from about 1 mg to 20 mg, from about 1 mg to 10 mg, or from about 1 mg to 5 mg, which can be given once,

twice, or up to three times daily depending on various factors recognized by those skilled in the art. In one embodiment the effective amount of quinidine, or a pharmaceutically acceptable salt thereof, can be given once daily.

In certain embodiments, the amount of quinidine, or a pharmaceutically acceptable salt thereof, is an amount effective to increase the plasma half-life or decrease the intrinsic clearance of the compound of Formula I in the subject by at least 50%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, or 1000%, relative to the plasma half-life or the intrinsic clearance of the compound of Formula I in the subject in the absence of quinidine.

In some embodiments, the method comprises administering an amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in the range of 5 mg/day to 250 mg/day and the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 20 mg/day.

In some embodiments, the method comprises administering an amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, in the range of 10 mg/day to 150 mg/day and the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 20 mg/day.

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 subject, 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 dextromethorphan.

In some embodiments, a composition of this invention further comprises an additional therapeutic agent in an effective amount for the treatment of agitation, diabetes, epilepsy, or depression. In some embodiments, the agitation is associated with a disorder selected from the group consisting of Alzheimer's disease, a degenerative neurological disorder (e.g., Parkinson's disease, Huntington's disease, etc.), a mood disorder (e.g., depression, dysthymia, schizophrenia, bipolar disorder, etc.), substance abuse withdrawal, selective serotonin reuptake inhibitor (SSRI) withdrawal, withdrawal from benzodiazepines, withdrawal from drugs useful for the treatment of attention deficit disorder (ADD) and attention deficit hyperactive disorder (ADHD), traumatic brain injury, terminal illness, post-operative agitation, post-anesthetic agitation, Reye's syndrome and a pediatric disorder (e.g., depression, attention deficit disorder, oppositional defiant disorder, separation anxiety disorder, etc.).

For pharmaceutical compositions that comprise an additional therapeutic agent, an effective amount of the additional therapeutic agent is between about 0.01 % to 100% of the dosage normally utilized in a monotherapy regime using just that agent. The normal monotherapeutic dosages of these additional 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 additional therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the additional 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 additional 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.

Methods of Treatment

Provided herein are methods for treating agitation in a subject in need thereof, comprising administering a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Methods delineated herein also include those wherein the subject is identified as in need of a particular stated treatment. 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).

In some embodiments, the agitation is associated with a disorder selected from the group consisting of Alzheimer's disease, a degenerative neurological disorder, a mood disorder, substance abuse withdrawal, selective serotonin reuptake inhibitor (SSRI) withdrawal, withdrawal from benzodiazepines, withdrawal from drugs useful for the treatment of attention deficit disorder (ADD) and attention deficit hyperactive disorder (ADHD), traumatic brain injury, terminal illness, post-operative agitation, post-anesthetic agitation, Reye's syndrome and a pediatric disorder.

In some embodiments, the agitation is associated with a degenerative neurological disorder. In one aspect of these embodiments, the degenerative neurological disorder is

Parkinson's disease. In another aspect of these embodiments, the degenerative neurological disorder is Huntington's disease.

In some embodiments, the agitation is associated with a mood disorder. In one aspect of these embodiments, the mood disorder is depression, dysthymia, schizophrenia or bipolar disorder. In one specific aspect of these embodiments, the mood disorder is depression. In one specific aspect of these embodiments, the mood disorder is dysthymia. In one specific aspect of these embodiments, the mood disorder is schizophrenia. In one specific aspect of these embodiments, the mood disorder is bipolar disorder.

In some embodiments, the agitation is associated with SSRI withdrawal. In one aspect of these embodiments, the SSRI is selected from fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine and sertraline.

In some embodiments, the agitation is associated with withdrawal from drugs useful for the treatment of ADD and ADHD. In one aspect of these embodiments, the drug useful for the treatment of ADD and ADHD is selected from methamphetamine hydrochloride, methylphenidate hydrochloride, dextroamphetamine sulfate, mixed amphetamine salts, pemoline, dexmethylphenidate hydrochloride, and lisdexamfetamine mesilate.

In some embodiments, the agitation is associated with a pediatric disorder. In one aspect of these embodiments, the pediatric disorder is depression, attention deficit disorder, oppositional defiant disorder, or separation anxiety disorder.

In some embodiments, the agitation is associated with Alzheimer's disease.

In some embodiments, the agitation is associated with traumatic brain injury.

In some embodiments, the invention provides a method of treating a subject suffering from agitation by co-administering to the subject in need thereof a compound of Formula I, or a composition comprising such compound; and quinidine, or a pharmaceutically acceptable salt of either or both thereof.

The term "co-administered" as used herein means that quinidine may be administered together with a compound of Formula I as part of a single dosage form (such as a composition of this invention comprising a compound of Formula and quinidine as described above) or as separate, multiple dosage forms. Alternatively, quinidine, or a pharmaceutically acceptable salt thereof, may be administered prior to, consecutively with, or following the administration of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In such combination therapy treatment, both the compound of Formula I and quinidine, or a pharmaceutically acceptable salt of either or both thereof, are administered by conventional methods. The administration of a composition of this invention, comprising both a

compound of Formula I and quinidine, to a subject does not preclude the separate administration of a compound of Formula I, quinidine, or any other additional therapeutic agent to said subject at another time during a course of treatment.

In some embodiments, a method of this invention further comprises administering an additional therapeutic agent in an effective amount for the treatment of agitation, diabetes, epilepsy, or depression. In some embodiments, the agitation is associated with a disorder selected from the group consisting of Alzheimer's disease, a degenerative neurological disorder (e.g., Parkinson's disease, Huntington's disease, etc.), a mood disorder (e.g., depression, dysthymia, schizophrenia, bipolar disorder, etc.), substance abuse withdrawal, selective serotonin reuptake inhibitor (SSRI) withdrawal, withdrawal from benzodiazepines, withdrawal from drugs useful for the treatment of attention deficit disorder (ADD) and attention deficit hyperactive disorder (ADHD), traumatic brain injury, terminal illness, post-operative agitation, post-anesthetic agitation, Reye's syndrome and a pediatric disorder (e.g., depression, attention deficit disorder, oppositional defiant disorder, separation anxiety disorder, etc.).

Effective amounts of these additional therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in 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), and other medical texts. However, it is well within the skilled artisan's purview to determine the additional therapeutic agent's optimal effective-amount range.Methods delineated herein also include those wherein the subject is identified as in need of a particular stated treatment. 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).

In yet another aspect, the invention provides the use of a compound of Formula I alone or together with quinidine, or a pharmaceutically acceptable salt of either or both thereof, in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

Another aspect of the present invention is directed to methods for treating a disease or disorder selected from the group consisting of diabetes, epilepsy, and depression, comprising administering to a subject in need thereof an effective amount of a compound of Formula I, as described herein, or a pharmaceutically acceptable salt thereof, and quinidine or a pharmaceutically acceptable salt thereof. (See *Nature Medicine* **21**, 363–372 (2015) doi:10.1038/nm.3822; and WO 2013/029762) In some embodiments, treatment comprises the administration of a compound of Formula I, quinidine, or a pharmaceutically acceptable salt of either or both thereof, and a pharmaceutically acceptable carrier.

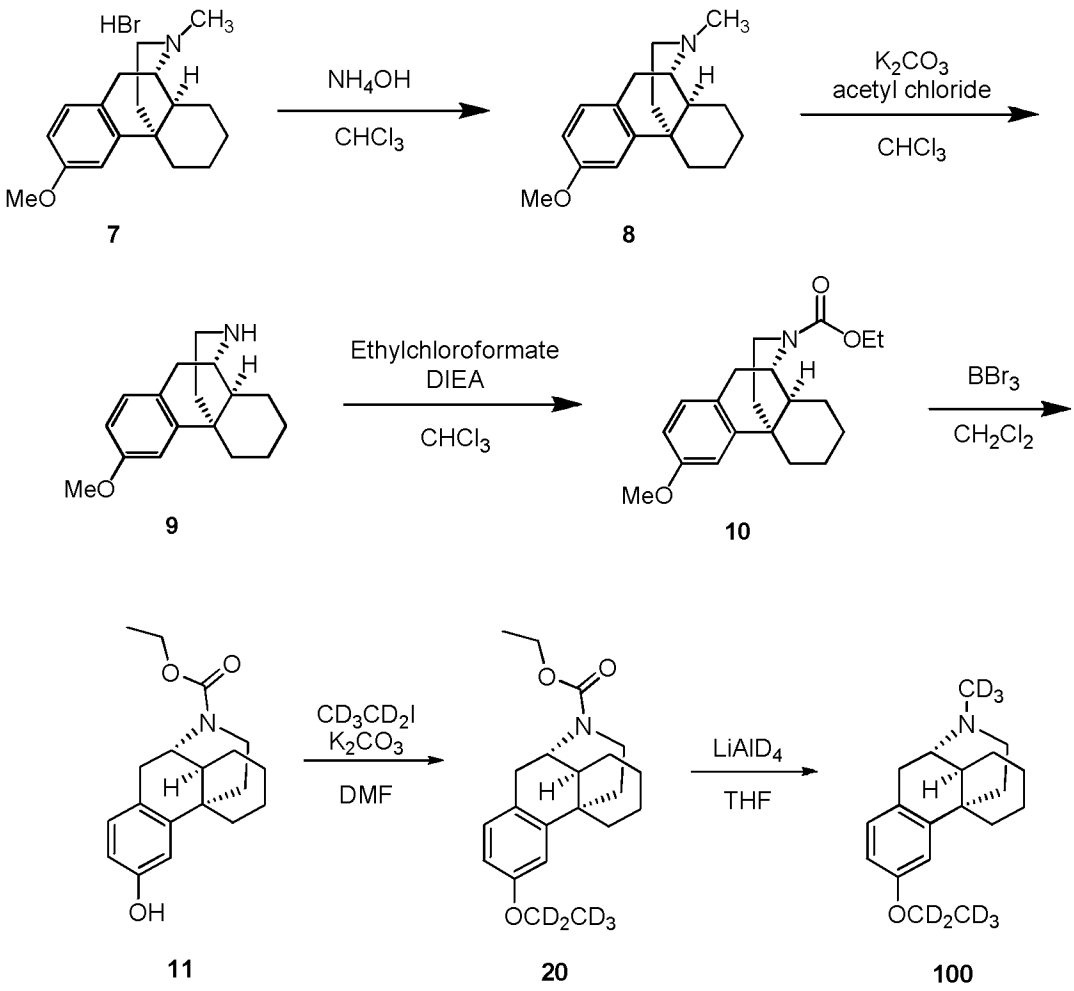
In some embodiments, the method comprises administering to the subject an amount of compound of Formula I, or a pharmaceutically acceptable salt thereof, in the range of 1 mg/day to 1000 mg/day, 5 mg/day to 500 mg/day, 5 mg/day to 400 mg/day, 5 mg/day to 250 mg/day, 10 mg/day to 150 mg/day, 10 mg/day to 100 mg/day, or 5 mg/day to 50 mg/day.

In some embodiments, the method comprises administering to the subject an amount of quinidine, or a pharmaceutically acceptable salt thereof, in the range of 1 mg/day to 60 mg/day, 1 mg/day to 40 mg/day, 1 mg/day to 30 mg/day, 1 mg/day to 20 mg/day, 1 mg/day to 10 mg/day, or 1 mg/day to 5 mg/day.

In certain embodiments, the method comprises administering to the subject an amount of quinidine, or a pharmaceutically acceptable salt thereof, effective to increase the plasma half-life or decrease the intrinsic clearance of the compound of Formula I in the subject by at least 50%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, or 1000%, relative to the plasma half-life or the intrinsic clearance of the compound of Formula I in the subject in the absence of quinidine.

Examples

Example 1. Synthesis of (+)-3-(Ethoxy-d_5)-17-(methyl-d_3)-(9α,13α,14α)-morphinan hydrochloride (**100**). Compound 100 was prepared as outlined below. Details of the synthesis follow.



Synthesis of (+)-3-methoxy-17-methyl-(9α,13α,14α)-morphinan (free base, 8). To a reaction vessel was added (+)-3-methoxy-17-methyl-(9α,13α,14α)-morphinan, HBr salt (**7**; 3.00g, 8.5 mmol, commercially available), NH_3 in CH_3OH (2.0 M, 8.5 mL, 17.0 mmol), and a stir bar. The reaction mixture was stirred at RT for 1 h. The resulting material was concentrated on a rotary evaporator, then diluted with $CHCl_3$ (50 mL) and H_2O (50 mL). The layers were separated and the water layer was extracted with $CHCl_3$ (50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated on a rotary evaporator to yield 2.88 g of **8** as a fluffy white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12 (ddd, J_1=24.7, J_2=12.6, J_3=3.8, 1H), 1.23-1.43 (m, 5H), 1.49-1.52 (m, 1H), 1.62-1.65 (m, 1H), 1.72 (td, J_1=12.6, J_2=4.9, 1H), 1.81 (dt, J_1=12.6, J_2=3.3, 1H), 2.07 (td, J_1=12.6, J_2=3.3, 1H), 2.33-2.47 (m, 5H), 2.57 (dd, J_1=18.1, J_2=5.5, 1H), 2.79 (dd, J_1=5.5, J_2=3.3, 1H), 2.98 (d, J=18.1, 1H), 6.68 (dd, J_1=8.2, J_2=2.7, 1H), 6.80 (d, J =2.7, 1H), 7.02 (d, J =8.8, 1H).

Synthesis of (+)-3-methoxy-(9α,13α,14α)-morphinan (9). The solid (+)-3-methoxy-17-methyl-(9α,13α,14α)-morphinan (**8**; 6.79 g, 25.1 mmol) was placed in a reaction vessel with $CHCl_3$ and a stir bar. K_2CO_3 (13.85 g, 100.2 mmol) was added and the mixture was stirred at RT under an atmosphere of N_2 for 10 min before the addition of acetyl chloride (7.866 g, 100.2 mmol). The resulting reaction mixture, still under an atmosphere of N_2, was stirred under reflux conditions for 7 h, then filtered through a pad of celite. The organic filtrate was concentrated on a rotary evaporator and the resulting crude material was dissolved in CH_3OH then stirred under reflux conditions for 1 h. The solution was concentrated on a rotary evaporator then dried under vacuum to yield 6.78 g of **9** as an off-white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.04-1.13 (m, 1H), 1.19-1.29 (m, 1H), 1.37-1.66 (m, 6H), 2.37 (d, J=13.5, 2H), 2.54 (bs, 1H), 2.80 (s, 2H), 2.95-2.99 (m, 1H), 3.12-3.18 (m, 2H), 3.48 (s, 1H), 3.71 (s, 3H), 6.76 (dd, J_1=8.3, J_2=2.6, 1H), 6.80 (d, J =2.3, 1H), 7.07 (d, J =8.3, 1H).

Synthesis of (+)-17-ethylcarbamate-3-methoxy-(9α,13α,14α)-morphinan (10). To a reaction vessel fit with a stirbar was added **9** (6.025g, 2.48 mmol) dissolved in $CHCl_3$ (100 mL). Diisopropylethylamine (DIEA; 16.32 g, 126.3 mmol) was added and the mixture was stirred for 10 min at room temperature under nitrogen before the addition of ethylchloroformate (13.094 g, 76.8 mmol). The reaction mixture was stirred under reflux conditions under nitrogen for 3 h, at which point TLC (20% ethylacetate/hexane) showed complete consumption of the starting material. The organic layer was removed and washed first with 1M HCl, and then with saturated $NaHCO_3$. The aqueous layers from each wash were combined and back extracted with 50 ml of $CHCl_3$. The organic layer from the back extraction was combined with the organic layer from the washes and the combined organic layers were dried over Na_2SO_4. The organic solution was then filtered, concentrated on a rotary evaporator then was purified via automated flash column chromatography (0-30% ethylacetate/hexane) to yield 5.37 g of **10** as a clear light yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.06 (ddd, J_1=25.3, J_2=12.6, J_3=3.8, 1H), 1.21-1.39 (m, 7H), 1.45-1.60 (m, 3H), 1.65-1.70 (m, 2H), 2.34-2.37 (m, 1H), 2.54-2.69 (m, 2H), 3.04-3.12 (m, 1H), 3.78 (s, 3H), 3.86 (ddd, J_1=42.3, J_2=13.7, J_3=3.8, 1H), 4.12 (q, J=7.14, 2H), 4.31 (dt, J_1=56.6, J_2=4.3, 1H), 6.71 (dd, J_1=8.8, J_2=2.2, 1H), 6.82 (d, J =2.7, 1H), 7.00 (apparent t, J =8.2, 1H).

Synthesis of (+)-17-ethylcarbamate-3-hydroxy-(9α,13α,14α)-morphinan (11). In a reaction vessel fit with a stirbar the carbamate **10** (2.43 g, 7.4 mmol) was dissolved in CH_2Cl_2 (20 mL) and the resulting solution was cooled to 0 °C. BBr_3 (9.24 g, 36.9 mmol) was added and the reaction mixture was stirred under an atmosphere of N_2 at 0 °C for 20 min (at which time tlc in 20% ethylacetate/hexane showed the reaction to be complete). A solution of 27% NH_4OH in ice was placed in a beaker with a stir bar and the reaction mixture was slowly added with stirring. The resulting mixture was stirred for 20 min then was extracted with 4:1 $CHCl_3/CH_3OH$ (200 mL). The organic layer was dried over Na_2SO_4, filtered, then concentrated on a rotary evaporator. The crude material was purified via automated flash column chromatography (CH_3OH with 1% NH_4OH / $CHCl_3$, 0-10%). The pure fractions were concentrated on a rotary evaporator to yield 1.48 g of **11** as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.04-1.12 (m, 1H), 1.22-1.36 (m, 7H), 1.45-1.59 (m, 3H), 1.63-1.67 (m, 2H), 2.30-2.33 (m, 1H), 2.52-2.66 (m, 2H), 3.06 (dt, J_1=18.4, J_2=5.9, 1H), 3.84 (ddd, J_1=35.8, J_2=13.8, J_3=6.1, 1H), 4.10-4.18 (m, 2H), 4.31 (dt, J_1=53.9, J_2=3.1, 1H), 6.64 (m, 1H), 6.78 (s, 1H), 6.93 (apparent t, J =7.8, 1H).

Synthesis of (+)-3-(ethoxy-d_5)-17-ethoxycarbonyl-(9α,13α,14α)-morphinan (20). To a solution of alcohol **11** (1.50 g, 4.8 mmol) in DMF (25 mL), was added K_2CO_3 (2.00 g, 14.5 mmol, 3.05 eq) and iodoethane-d_5 (1.15 g, 7.1 mmol, 1.50 eq) with stirring. The reaction mixture was stirred overnight at room temperature (rt) under an atmosphere of N_2, was quenched by the addition of H_2O, and extracted with Et_2O (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to a yellow oil.

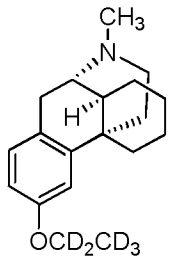
Purification via automated flash column chromatography (0-40% EtOAc/hexanes) afforded intermediate **20** (1.53 g, 91% yield).

Synthesis of (+)-3-(ethoxy-d_5)-17-(methyl-d_3)-(9α,13α,14α)-morphinan hydrochloride (100). To a slurry of $LiAlD_4$ (0.184 g, 4.4 mmol, 2.0 eq) in THF (10 mL) stirring at -78 °C was added a solution of the carbamate **20** (0.763 g, 2.2 mmol) in THF (5 mL). After 1 h of stirring at rt, no reaction was detected by tlc and an additional 2.0 eq of $LiAlD_4$ (0.184 g, 4.4 mmol, 2.0 eq) was added. The reaction mixture was stirred overnight at rt, then was quenched by the addition of magnesium sulfate heptahydrate until cessation of gas evolution. The mixture was filtered, concentrated *in vacuo* and the resultant crude material was purified via automated flash column chromatography ($CHCl_3/CH_3OH/NH_3OH$ –

90/10/1) to yield the free amine **100**. This material was dissolved in 1.25 M HCl in CH_3OH then was concentrated under reduced pressure and dried under high vacuum to yield 14.3 mg of product **100** as the HCl salt.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.94-1.63 (m, 8H), 1.72-1.80 (m, 1H), 1.94 (d, J=11.9, 1H), 2.43-2.47 (m, 1H), 2.96 (dd, J_1=19.2, J_2=6.1, 2H), 3.09-3.17 (m, 2H), 3.57-3.61 (m, 1H), 6.79-6.82 (m, 2H), 7.11 (d, J=8.8, 1H), 9.58 (br s, 1H). **HPLC** (method: 150 mm C18-RP column – gradient method 5–95% ACN; Wavelength: 280 nm): retention time: 3.08 min, purity: 95%. **MS** (M+H): 294.2.

Example 2. Synthesis of (+)-3-(Ethoxy-d_5)-17-methyl-(9α,13α,14α)-morphinan hydrochloride (**104**). Compound 104 was prepared as outlined in Example 1 above with the exception that $LiAlH_4$ was used in place of $LiAlD_4$ for the reduction of the carbamate **20** to **104**.



104

Synthesis of (+)-3-(ethoxy-d_5)-17-methyl-(9α,13α,14α)-morphinan hydrochloride (104). To a slurry of $LiAlH_4$ (0.166 g, 4.4 mmol, 2.0 eq) in THF (10 mL) stirring at -78 °C was added a solution of the carbamate **20** (0.763 g, 2.2 mmol) in THF (5 mL). After 1 h an additional 2.0 eq of $LiAlH_4$ (0.184 g, 4.4 mmol, 2.0 eq) was added. The reaction mixture was stirred overnight at rt, then was quenched by the addition of magnesium sulfate heptahydrate until cessation of gas evolution. The mixture was filtered, concentrated *in vacuo* and the resultant crude material was purified via automated flash column chromatography ($CHCl_3/CH_3OH/NH_3OH$ – 90/10/1) to yield the free-amine **104**. This material was dissolved in 1.25 M HCl in CH_3OH then was concentrated under reduced pressure and dried under high vacuum to yield 31 mg of product **104** as the HCl salt.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.94-1.64 (m, 8H), 1.74-1.82 (m, 1H), 1.97 (d, J=12.4, 1H), 2.44-2.47 (m, 1H), 2.81 (s, 3H), 2.96 (dd, J_1=20.0, J_2=5.8, 2H), 3.09-3.18 (m, 2H), 3.55-3.62 (m, 1H), 6.79-6.82 (m, 2H), 7.12 (d, J=9.1, 1H), 9.68 (br s, 1H). **HPLC** (method: 150 mm C18-RP column – gradient method 5–95% ACN; Wavelength: 280 nm):

retention time: 3.00 min, purity: 95%. **MS** (M+H): 291.2.

Example 3. Evaluation of Metabolic Stability in CYP2D6 SUPERSOMES™.

Human CYP2D6 SUPERSOMES™ were purchased from GenTest (Woburn, MA, USA). 7.5 mM stock solutions of test compounds (Compounds **100**, **102**, and the ethyl ether analog of dextromethorphan ("dextroethorphan") were prepared in DMSO. The 7.5 mM stock solutions were diluted to 50 μM in acetonitrile (ACN). The 1000 pmol/mL CYP2D6 supersomes were diluted to 62.5 pmol/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted SUPERSOMES™ were added to wells of a 96-well deep-well polypropylene plate in triplicate. 10 μL of the 50 μM test compound was added to the supersomes and the mixture was pre-warmed for 10 minutes. Reactions were initiated by addition of pre-warmed NADPH solution. The final reaction volume was 0.5 mL and contained 50 pmol/mL CYP2D6 SUPERSOMES™, 1 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 were incubated at 37°C and 50 μL aliquots were removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contained 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates were stored at 4 °C for 20 minutes after which 100 μL of water was added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants were 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 *in vitro* half-life ($t_{1/2}$) for each of the test compounds was calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship: in vitro $t_{1/2} = 0.693/k$, where k = -[slope of linear regression of % parent remaining(ln) vs incubation time]. Data analysis was performed using Microsoft Excel Software.

Table 2, below, shows the results of the SUPERSOMES™ experiment.

Table 2. Calculated Half-life in SUPERSOMES™.

Compound	$t_{1/2}$ ± SD (min)
Dextromethorphan	1.7 ± 0.3
Dextroethorphan	10.3 ± 2.1
Compound **104**	49.1 ± 4.1
Compound **100**	51.3 ± 3.7

Each of the deuterated compounds tested demonstrated a longer half-life when incubated with CYP2D6 SUPERSOMES™ than any of the corresponding undeuterated test compounds or a deuterated version of dextromethorphan (Test Compound). Thus, in this assay, the compounds of this invention were more resistant to metabolism than dextromethorphan or deuterated dextromethorphan (Test Compound).

Example 4. Determination of Metabolic Stability of Test Compounds using Human Liver Microsomes. Human liver microsomes (20 mg/mL) were obtained from Xenotech, LLC (Lenexa, KS). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich.

7.5 mM stock solutions of test compounds were prepared in DMSO. The 7.5 mM stock solutions were diluted to 50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes were diluted to 1.25 mg/mL (1 mg/mL final) in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes (375 μL) were added to wells of a 96-well polypropylene plate in triplicate. 10 μL of the 50 μM test compound was added to the microsomes and the mixture was pre-warmed for 10 minutes. Reactions were initiated by addition of 125 μL of pre-warmed NADPH solution. The final reaction volume was 0.5 mL and contained 1.0 mg/mL human liver microsomes, 1 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 were incubated at 37 °C, and 50 μL aliquots were removed at 0, 5, 10, 20, and 30 minutes and added to shallow 96-well plates which contained 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates were stored at 4 °C for 20 minutes after which 100 μL of water was added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants were 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. 7-ethoxy coumarin was used as a positive control.

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

in vitro $t_{1/2} = 0.693/k$, where k = -[slope of linear regression of % parent remaining(ln) vs incubation time]

Data analysis was performed using Microsoft Excel Software.

Tables 3 and 4, below, show the results of these experiments.

Table 3. Calculated Half-life in Human Liver Microsomes

Compound	$t_{1/2}$ ± SD (min)	Change over non-deuterated compound
Dextroethorphan	28.3 ± 0.6	n/a
Compound **104**	59.1 ± 2.2	109%
Compound **100**	59.2 ± 1.7	109%

Table 4. Calculated Half-life in Human Liver Microsomes

Compound	$t_{1/2}$ ± SD (min)	Change over non-deuterated compound
Dextroethorphan	37.1±5.6	n/a
Compound **105**	89.6 ± 26.3	142%
Compound **101**	82.8 ± 21.0	123%

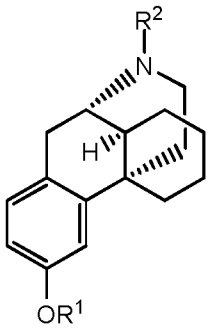
Deuteration of the alkyl ether (R^1) resulted in a significant increase in half life ($t_{1/2}$) in human liver microsomes as compared to the nondeuterated counterpart.

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.

CLAIMS

We claim:

1. A method of treating agitation comprising administering to a subject in need thereof, an effective amount of a compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein R^1 is an ethyl group optionally substituted by one to five deuterium atoms; and R^2 is a methyl group optionally substituted by one to three deuterium atoms; provided that at least one deuterium atom is present at either R^1 or R^2, and a pharmaceutically acceptable carrier.

2. The method of claim 1, wherein R^1 is $-CH_2CH_3$, $-CD_2CH_3$, $-CH_2CD_3$, or $-CD_2CD_3$; and R^2 is $-CH_3$ or $-CD_3$.

3. The method of claim 1 or 2, wherein for the compound of Formula I, any atom not designated as deuterium is present at its natural isotopic abundance.

4. The method of claim 3, wherein the compound of Formula I is a compound selected from the table:

Compound No.	R^1	R^2
100	$-O-CD_2CD_3$	CD_3
101	$-O-CD_2CH_3$	CD_3
102	$-O-CH_2CH_3$	CD_3
103	$-O-CH_2CD_3$	CD_3
104	$-O-CD_2CD_3$	CH_3
105	$-O-CD_2CH_3$	CH_3
106	$-O-CH_2CD_3$	CH_3

or a pharmaceutically acceptable salt thereof.

5. The method of claim 3, further comprising administering to the subject an amount of quinidine, or a pharmaceutically acceptable salt thereof, wherein the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 40 mg/day.

6. The method of claim 5, wherein the amount of the compound of Formula I is in the range of 5 mg/day to 250 mg/day.

7. The method of any one of claims 1 to 6, wherein the agitation is associated with a disorder selected from the group consisting of Alzheimer's disease, a degenerative neurological disorder, a mood disorder, substance abuse withdrawal, selective serotonin reuptake inhibitor (SSRI) withdrawal, withdrawal from benzodiazepines, withdrawal from drugs useful for the treatment of attention deficit disorder (ADD) and attention deficit hyperactive disorder (ADHD), traumatic brain injury, terminal illness, post-operative agitation, post-anesthetic agitation, Reye's syndrome and a pediatric disorder.

8. The method of claim 7 wherein the degenerative neurological disorder is Parkinson's disease or Huntington's disease.

9. The method of claim 7 wherein the mood disorder is depression, dysthymia, schizophrenia or bipolar disorder.

10. The method of claim 7 wherein the SSRI is selected from fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine and sertraline

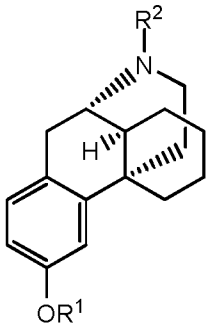
11. The method of claim 7 wherein the drug useful for the treatment of ADD or ADHD is selected from methamphetamine hydrochloride, methylphenidate hydrochloride, dextroamphetamine sulfate, mixed amphetamine salts, pemoline, dexmethylphenidate hydrochloride, and lisdexamfetamine mesilate.

12. The method of claim 7 wherein the pediatric disorder is depression, attention deficit disorder, oppositional defiant disorder, or separation anxiety disorder.

13. The method of claim 7, wherein the agitation is associated with Alzheimer's disease.

14. The method of claim 7, wherein the agitation is associated with traumatic brain injury.

15. A method of treating a disease or disorder selected from the group consisting of diabetes, epilepsy, and depression, comprising administering to a subject in need thereof, an effective amount of a compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein R^1 is an ethyl group optionally substituted by one to five deuterium atoms; and R^2 is a methyl group optionally substituted by one to three deuterium atoms; provided that at least one deuterium atom is present at either R^1 or R^2;

quinidine or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

16. The method of claim 15, wherein R^1 is $-CH_2CH_3$, $-CD_2CH_3$, $-CH_2CD_3$, or $-CD_2CD_3$; and R^2 is $-CH_3$ or $-CD_3$.

17. The method of claim 15 or 16, wherein for the compound of Formula I, any atom not designated as deuterium is present at its natural isotopic abundance.

18. The method of claim 17, wherein the compound of Formula I is a compound selected from the table:

Compound No.	R^1	R^2
100	$-O-CD_2CD_3$	CD_3
101	$-O-CD_2CH_3$	CD_3
102	$-O-CH_2CH_3$	CD_3
103	$-O-CH_2CD_3$	CD_3

Compound No.	R^1	R^2
104	-O-CD_2CD_3	CH_3
105	-O-CD_2CH_3	CH_3
106	-O-CH_2CD_3	CH_3

or a pharmaceutically acceptable salt thereof.

19. The method of any one of claims 15-18, wherein the amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 5 mg/day to 500 mg/day, and the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 40 mg/day

20. The method of any one of claims 15-18, wherein the amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 5 mg/day to 250 mg/day and the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 20 mg/day.

21. The method of any one of claims 15-18, wherein the amount of the compound of Formula I, or a pharmaceutically acceptable salt thereof, is in the range of 10 mg/day to 150 mg/day and the amount of quinidine, or a pharmaceutically acceptable salt thereof, is in the range of 1 mg/day to 20 mg/day.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/044841

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/485 A61P25/00
ADD.

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)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, FSTA, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/062692 A1 (CONCERT PHARMACEUTICALS INC [US]; THOMAS AMANDA [US]) 3 June 2010 (2010-06-03) claim 1	1-14
X	WO 2010/033801 A1 (CONCERT PHARMACEUTICALS INC [US]; GRAHAM PHILIP B [US]; SILVERMAN I RO) 25 March 2010 (2010-03-25) claim 1	1-14
T	WO 2016/040930 A1 (AVANIR PHARMACEUTICALS INC [US]) 17 March 2016 (2016-03-17) claim 1	

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* 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
11 October 2016	23/12/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Baurand, Petra

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"AAIC 2015 Press Briefing, 7/22/15: Drug Treatments / Developing Topics 2 (Part 2 of 5)", youtube, 22 July 2015 (2015-07-22), page 1 pp., XP054976800, Retrieved from the Internet: URL:https://www.youtube.com/watch?v=V3RSNZ7IP50 [retrieved on 2016-09-26] the whole document	1-14
Y	EP 2 357 183 A1 (CONCERT PHARMACEUTICALS INC [US]) 17 August 2011 (2011-08-17) claim 1	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/044841

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/044841

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

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

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

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

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

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

1-14

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14

   Compounds of formula (I) for use in the treatment of agitation

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2. claims: 15-21(partially)

   Compounds of formula (I) for use in the treatment of diabetes

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3. claims: 15-21(partially)

   Compounds of formula (I) for use in the treatment of epilepsy

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4. claims: 15-21(partially)

   Compounds of formula (I) for use in the treatment of depression

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/044841

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