This disclosure relates to novel morphinan compounds and their derivatives, pharmaceutically acceptable salts, solvates, and hydrates thereof. This disclosure also provides compositions comprising a compound of this disclosure and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering a σ₁ receptor agonist that also has NMDA antagonist activity.
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*cited by examiner
FIG. 1

- Dextromethorphan
- Compound 108
- Compound 100
- Compound 101
FIG. 2

- Dextromethorphan
- Compound 108
- Compound 100
- Compound 101

Percent Remaining vs Time (min)
Figure 3

Percent Remaining vs. Time (Min)

- ■ Dextromethorphan
- ● Compound 108
- ▲ Compound 100
- ▼ Compound 101
Figure 4

4 mg/kg of each drug P.O.
**Figure 5**

A 6 mg quinidine, 1 mg compound 101  
B 6 mg quinidine, 1 mg dextromethorphan  
C 1.5 mg quinidine, 1 mg compound 101  
D 1.5 mg quinidine, 1 mg dextromethorphan  
E 0.5 mg quinidine, 1 mg dextromethorphan  
F 0.5 mg quinidine, 1 mg compound 101
Figure 6
objects suffering from Alzheimer’s disease, stroke, Parkinson’s disease and traumatic brain injury (http://www.clinicaltrials.gov). This drug combination is also in Phase III clinical trials for treating hyperalgesia in methadone-dependent subjects (http://www.clinicaltrials.gov). Dextromethorphan is being studied with other medication(s), can lead to serious adverse events. A longer than recommended duration of a drug in the body may provide continued beneficial effects, but it may also create or prolong undesired side effects. Undesirable side effects at recommended doses of dextromethorphan therapy include nausea, loss of appetite, diarrhea, drowsiness, dizziness, and impotence.

Accordingly, it is desirable to provide a compound that has the beneficial activities of dextromethorphan and may also have other benefits, e.g., reduced adverse side effects, with a decreased metabolic liability, to further extend its pharmacological effective life, enhance subject compliance, and, potentially, to decrease population pharmacokinetic variability and/or decrease its potential for dangerous drug-drug interactions or decrease the likelihood of dextromethorphan abuse due to the formation of metabolites such as dextrorphan.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the stability over time of various compounds of the disclosure in cynomolgus monkey liver microsomes. FIG. 2 depicts the stability over time of various compounds of the disclosure in human liver microsomes. FIG. 3 depicts the stability over time of various compounds of the disclosure in 2D6 Supersomes™. FIG. 4 depicts plasma levels of Compound 101, dextromethorphan, as well as deuterated dextromethorphan isoto­pologues and dextromethorphan, in monkeys in the absence of quinidine co-dosing. FIG. 5 depicts plasma levels of Compound 101, dextromethorphan, as well as deuterated dextromethorphan isotope­logues and dextromethorphan, in monkeys co-dosed with quinidine. FIG. 6 depicts urine levels of Compound 101, dextromethorphan, as well as deuterated dextromethorphan isotope­logues and dextromethorphan, as a function of quinidine concentration in monkeys.

DETAILED DESCRIPTION

Definitions

The terms “ameliorate” and “treat” are used interchangeably and include therapeutic and/or prophylactic treatment. Both terms mean decrease, suppress, attenuate, diminish,
"Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ. It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of dextromethorphan will inherently contain small amounts of deuterated and/or 13C-containing 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 disclosure. See, for instance, Wada et al, Seikagaku 1994, 66:15; Ganes et al, Comp Biochem Physiol A Mol Integ Physiol 1998, 119:725. In a compound of this disclosure, when a particular position is "designated as H" as used deuterium, it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of at least 3000 (45% deuterium incorporation) at each atom designated as deuterium in said compound.

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

In other embodiments, a compound of this disclosure has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), 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), or at least 6633.3 (99.5% deuterium incorporation).

In the compounds of this disclosure 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.

The term "isotopologue" refers to a species that has the same chemical structure and formula as a specific compound of this disclosure, with the exception of the isotopic composition at one or more positions, e.g., H vs. D. Thus an isotopologue differs from a specific compound of this disclosure in the isotopic composition thereof.

As used herein, the term "solvate" means a compound which further includes a stoichiometric or non-stoichiometric amount of solvent such as water, acetone, ethanol, methanol, dichloromethane, 2-propanol, or the like, bound by non-covalent intermolecular forces.

The compounds of the present disclosure (e.g., compounds of Formula 1), may contain an asymmetric carbon atom, for example, as the result of deuterium substitution or otherwise. As such, compounds of this disclosure can exist as either individual enantiomers, or mixtures of the two enantiomers. Accordingly, a compound of the present disclosure will include both racemic mixtures, and also individual respective stereoisomers that are substantially free from another possible stereoisomer. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers, or less than "X"% of other stereoisomers (wherein X is a number between 0 and 100, inclusive) are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are well known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

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

"D" refers to deuterium.

"Stereoisomer" refers to both enantiomers and diastereomers.

Throughout this specification, a variable may be referred to generally (e.g., "each R") or may be referred to specifically (e.g., R1 or R2). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

Therapeutic Compounds

The present disclosure provides a compound of Formula I, including pharmaceutically acceptable salts, solvates, and hydrates thereof:

\[
\text{wherein } R^1 \text{ is selected from CH}_3, \text{ CH}_2\text{D}, \text{ CHD}_2, \text{ CD}_2, \text{ CHF}_2, \text{ and CF}_3; \text{ and }
\]

\[
R^2 \text{ is selected from CH}_3, \text{ CHD}_2, \text{ CHD}_2, \text{ and CD}_3.
\]

In certain embodiments, when R^2 is CH_3, then R^2 is not CH_3 or CD_3. In other embodiments, when R^1 is CD_3, then R^2 is not CH_3.

In one embodiment, R^1 is selected from CH_3D, CHD_2, CD_3, CHF_2, and CF_3.

In one embodiment, R^2 is selected from CH_3D, CHD_2, CD_3, and CHF_2. In another embodiment, R^2 is selected from CH_3D, CHD_2, and CD_3. In a further embodiment, R^1 is CD_3. In another embodiment, R^1 is CHF_2. In a further embodiment, R^1 is CHF_2.

In one embodiment, R^2 is CH_3, CHD_2, or CD_3. In another embodiment, R^2 is CH_3. In another embodiment, R^2 is CD_3.

In yet another embodiment, the compound is selected from any one of the compounds set forth in Table 1.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R^1</th>
<th>R^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>CD_3</td>
<td>CH_3</td>
</tr>
<tr>
<td>101</td>
<td>CD_3</td>
<td>CH_3</td>
</tr>
<tr>
<td>102</td>
<td>CD_2H</td>
<td>CH_3</td>
</tr>
<tr>
<td>103</td>
<td>CD_3</td>
<td>CH_3H</td>
</tr>
<tr>
<td>104</td>
<td>CF_3</td>
<td>CH_3</td>
</tr>
<tr>
<td>105</td>
<td>CF_3</td>
<td>CD_3</td>
</tr>
<tr>
<td>106</td>
<td>CHF_2</td>
<td>CH_3</td>
</tr>
<tr>
<td>107</td>
<td>CHF_2</td>
<td>CD_3</td>
</tr>
<tr>
<td>108</td>
<td>CH_3</td>
<td>CD_3</td>
</tr>
</tbody>
</table>

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 isolated or purified, e.g., the compound of Formula I is present at a purity of at least 50% by weight (e.g., at least 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% of the isotopologues by weight are the recited compound.

In some embodiments, any position in the compound of Formula I designated as having D has a minimum deuterium incorporation of at least 45% (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 45% 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 50%, 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.


Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Exemplary Synthesis

A convenient method for synthesizing compounds of Formula I substitutes the appropriate deuterated intermediates and reagents in synthesis methods utilized for the preparation of dextromethorphan. Compounds of Formula I may be prepared from one of the known intermediates X, XI, and XII shown below, and from related intermediates that may be readily obtained from known procedures.
Scheme 1 shows a general route to the compounds of Formula I.

Various R1 groups (as defined in Formula I) may be introduced by O-alkylation of the appropriate phenol intermediate using an R1-alkylating agent, such as an alkyl halide (for example, iodo-R1), according to methods generally known in the art. Various R2 groups (as defined in Formula I) may be introduced by N-alkylation using an R2-alkylating agent (for example, iodo-R2), or by reduction of the N-formyl group with a deuterated reagent, such as deuteroborane according to methods generally known in the art.

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., R1 or R2) 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 T W 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 disclosure are only those that result in the formation of stable compounds.

Compositions

The disclosure also provides pyrogen-free compositions comprising an effective amount of a compound of Formula I (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt, solvate, or hydrate of said compound; and an acceptable carrier. Preferably, a composition of this disclosure 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 disclosure 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 compositions of the present disclosure in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipophilic excipients in the formulation. See “Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences),” David J. Hausk, 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 disclosure optionally formulated with a solubilizer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See U.S. Pat. No. 7,014,866; and United States patent publications 2006/0094744 and 2006/0079502.

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

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

In certain embodiments, the compound is administered orally. Compositions of the present disclosure 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 disclosure may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this disclosure 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 disclosure 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, U.S. Pat. No. 6,805,031, assigned to Alexza Molecular Delivery Corporation.

Topical administration of the pharmaceutical compositions of this disclosure 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 disclosure 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, cetacearyl alcohol, 2-octyldecanol, benzyl alcohol, and water. The pharmaceutical compositions of this disclosure may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable pharmaceutical composition can be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this disclosure 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, U.S. Pat. No. 6,805,031, assigned to Alexza Molecular Delivery Corporation.

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which to a subject results in a plasma exposure level that is
position”). Thus, in one embodiment, the disclosure provides
position comprising the same amount of dextromethorphan
to 350 mg, from 10 mg to 90 mg, or from 30 mg to 45 mg,
regression of the disorder being treated, or enhance or
the advancement of the disorder being treated, cause the
regimen, is sufficient to reduce or ameliorate the severity,
more of any of the above-described second therapeutic
tis), oxycodone, and gabapentin.
In another embodiment, the disclosure provides separate
dosage forms of a compound of this disclosure and one or
more of any of the above-described second therapeutic
agents, wherein the compound and second therapeutic
agent are associated with one another. The term “associated
with one another” as used herein means that the separate dosage
forms are packaged together or otherwise attached to one
another such that it is readily apparent that the separate dosage
forms are intended to be sold and administered together
(within less than 24 hours of one another, consecutively or
simultaneously).
In the pharmaceutical compositions of the disclosure, the
compound of the present disclosure 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 prophyactic 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 Chemoth. 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 a compound of
this disclosure can range from 0.4 mg to 400 mg, from 4.0 mg
to 350 mg, from 10 mg to 90 mg, or from 30 mg to 45 mg,
inclusive.
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-administration 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.
The compounds of the present disclosure and the pharma-
aceutical compositions that comprise them demonstrate a
longer clearance and produce a higher plasma exposure level
12 hours post-dosing as compared to a pharmaceutical composi-
tion comprising the same amount of dextromethorphan on a mole basis (“molar equivalent dextromethorphan composi-
tion”). Thus, in one embodiment, the disclosure provides a
pharmaceutical composition comprising an effective amount of a compound of Formula I, the administration of which to a subject results in a plasma exposure level that is greater than the plasma exposure level of a molar equivalent dextromethorphan composition that is administered using the same dosing regimen.
In another embodiment, the plasma exposure level is at
least 110%, 115%, 120%, 125%, 130%, 135%, 140%, 145%,
or more of the plasma exposure level of dextromethorphan
produced by a molar equivalent dextromethorphan composi-
tion that is administered to an equivalent subject.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, wherein the administration of the pharmaceutical
composition to a subject results in a plasma exposure level in
the range of 250-750 nanograms (ng)-hour (h)/mL (AUC).
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, wherein the administration of the pharmaceutical
composition to a subject results in a plasma exposure level in
the range of 400-1600 ng-h/mL (AUC).
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, wherein the administration of the pharmaceutical
composition to a subject results in a plasma exposure level in
the range of 1000-1500 ng-h/mL (AUC).
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising an effective amount of a
compound of Formula I, the administration of which to a subject results in a decrease in rate and amount of metabolite
production as compared to a molar equivalent dextrometho-
phan composition that is administered using the same dosing
regimen.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, the administration of which to a subject results in
a plasma exposure level of deuterated dextromethorphan isotopo-
logs less than or equal to 1000 ng-h/mL.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, the administration of which to a subject results in
a plasma exposure level of deuterated dextromethorphan isotopo-
logs less than or equal to 750 ng-h/mL.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, the administration of which to a subject results in
a plasma exposure level of deuterated dextromethorphan isotopo-
logs less than or equal to 500 ng-h/mL.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, wherein the administration of which to a subject results in a plasma exposure level of deuterated dextromethorphan isotopologues less than or equal to 1000 ng-h/mL.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, wherein the administration of which to a subject results in a plasma exposure level of deuterated dextromethorphan isotopologues less than or equal to 750 ng-h/mL.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, wherein the administration of which to a subject results in a plasma exposure level of deuterated dextromethorphan isotopologues less than or equal to 500 ng-h/mL.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising an effective amount of a
compound of Formula I, the administration of which to a subject results in a decrease in rate and amount of metabolite
production as compared to a molar equivalent dextrometho-
phan composition that is administered using the same dosing
regimen.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, wherein the administration of which to a subject results in a plasma exposure level of deuterated dextromethorphan isotopologues less than or equal to 1000 ng-h/mL.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, wherein the administration of which to a subject results in a plasma exposure level of deuterated dextromethorphan isotopologues less than or equal to 750 ng-h/mL.
In another embodiment, the disclosure provides a pharma-
caceutical composition comprising 10-60 mg of a compound of
Formula I, wherein the administration of which to a subject results in a plasma exposure level of deuterated dextromethorphan isotopologues less than or equal to 500 ng-h/mL.
For pharmaceutical compositions that comprise a second
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tic agent, an effective amount of the second therapeutic agent is between about 0.01% to 100% of the dosage
plasma exposure level of deuterated dextrorphan isotopologues as compared to the same molar amount of a compound of Formula I administered without the quinidine.

In another embodiment, the disclosure provides a pharmaceutical composition comprising a compound of Formula I and quinidine, said composition providing lower urine concentrations of a compound of Formula I and higher urine concentrations of deuterated dextrorphan isotopologues in a subject as compared to urine concentrations of dextromethorphan and dextrorphan in an equivalent subject resulting from the administration of a molar equivalent dextromethorphan composition additionally comprising the same amount of quinidine and administered according to the same dosing regimen.

Methods of Treatment

In another embodiment, the disclosure provides a method of inhibiting neurotransmitters, such as glutamate, from activating receptors in the brain and/or inhibiting the uptake of dopamine and serotonin by administering a compound of Formula I.

According to another embodiment, the disclosure provides a method of treating a subject suffering from, or susceptible to, a disease that is beneficially treated by dextromethorphan comprising the step of administering to said subject an effective amount of a compound of Formula I wherein R1 is selected from CH3, CH2D, CHD2, CHF2, and CF3; and R2 is selected from CH3, CH2D, CHD2, and CD3 or a composition comprising such a compound. Such diseases are well known in the art and are disclosed in, but not limited to, those described in U.S. Pat. Nos. 4,316,888; 4,446,140; 4,694,010; 4,898,860; 5,166,207; 5,336,980; 5,350,756; 5,366,980; 5,863,927; RE38,115; 6,197,830; 6,207,164; 6,583,152; and 7,114,547; as well as in US patent publications 2001/0044446; 2002/0103010; 2004/0087479; 2005/0129783; 2005/0203125; and 2007/0191411.

Such diseases include, but are not limited to, emotional lability; pseudobulbar affect; autism; neurological disorders and neurodegenerative diseases, such as, e.g., dementia, amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig’s disease), Alzheimer’s disease, Parkinson’s, and multiple sclerosis; disturbances of consciousness disorders; brain injuries, such as, e.g., stroke, traumatic brain injury, ischemic event, hypoxic event and neuronal death; disturbances of consciousness disorders; cardiovascular diseases, such as, e.g., peripheral vascular diseases, strokes, myocardial infarctions, and atherosclerosis; glaucoma, tardive dyskinesia; diabetic neuropathy; retinopathic diseases; diseases or disorders caused by homocysteine-induced apoptosis; diseases or disorders caused by elevated levels of homocysteine; chronic pain; intractable pain; neuropathic pain, sympathetically mediated pain, such as, alldynia, hyperpathia, hyperalgesia, dysesthesia, paresthesia, deafferentation pain, and anesthesia dolorosa; pain associated with gastrointestinal dysfunction, including, e.g., irritable bowel syndrome; mouth pain; epileptic seizures; linitus; sexual dysfunction; intractable coughing; dermatitis; addiction disorders, such as, e.g., addiction to or dependence on stimulants, nicotine, morphine, heroin, other opiates, amphetamines, cocaine, and alcohol; Rett syndrome (RTT); voice disorders due to uncon-
trolled laryngeal muscle spasms, including e.g., abductor spasmodic dysphonia, adductor spasmodic dysphonia, muscular tension dysphonia, and vocal tremor; methotrexate neurotoxicity; and fatigue caused by cancer.

In one particular embodiment, the method of this disclosure is used to treat a subject suffering from or susceptible to a disease or condition selected from diabetic neuropathy, Rett syndrome (RTT); voice disorders due to uncontrolled laryngeal muscle spasms, including e.g., abductor spasmodic dysphonia, adductor spasmodic dysphonia, muscular tension dysphonia, and vocal tremor; methotrexate neurotoxicity; and fatigue caused by cancer.

In one particular embodiment, the compound of Formula I, wherein R1 is selected from CH3, CH2D, CHD2, CD3, CHF2, and CF3; and R2 is selected from CH3, CH2D, CHD2, and CD3 or a composition comprising such compound is used to treat a subject suffering from pseudobulbar affect.

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 the methods delineated herein, a pharmaceutical composition comprising an effective amount of a compound of Formula I is administered to a subject, resulting in a plasma exposure level that is greater than the plasma exposure level of a molar equivalent dextromethorphan composition that is administered using the same dosing regimen. The plasma exposure level is at least 110%, 115%, 120% 125%, 130%, 135%, 140%, 145%, or more of the plasma exposure level of dextromethorphan produced by a molar equivalent dextromethorphan composition that is administered to an equivalent subject.

In another embodiment, the disclosure provides a method for treating a disease in a subject in need of such treatment, said method comprising administering to the subject a pharmaceutical composition comprising 10-60 mg of a compound of Formula I, wherein the administration of the pharmaceutical composition to the subject results in a plasma exposure level in the range of 250-750 nanograms (ng)-hour (h)/mL (AUC).

In another embodiment, the disclosure provides a method for treating a disease in a subject in need of such treatment, said method comprising administering to the subject a pharmaceutical composition comprising 10-60 mg of a compound of Formula I, wherein the administration of the pharmaceutical composition to the subject results in a plasma exposure level in the range of 400-1600 ng-h/mL (AUC).

In another embodiment, the disclosure provides a method for treating a disease in a subject in need of such treatment, said method comprising administering to the subject a pharmaceutical composition comprising 10-60 mg of a compound of Formula I, wherein the administration of the pharmaceutical composition to the subject results in a plasma exposure level in the range of 500-1500 ng-h/mL (AUC).

In another embodiment, the disclosure provides a method for treating a disease in a subject in need of such treatment, said method comprising administering to the subject a pharmaceutical composition comprising 10-60 mg of a compound of Formula I, wherein the administration of the pharmaceutical composition to the subject results in a plasma exposure level in the range of 1000-1500 ng-h/mL (AUC).

In another embodiment, the disclosure provides a method for treating a disease in a subject in need of such treatment, said method comprising administering to the subject a pharmaceutical composition comprising an amount of a compound of Formula I, effective to decrease in rate and amount of metabolite production as compared to a molar equivalent dextromethorphan composition that is administered using the same dosing regimen.

In another embodiment, the disclosure provides a method for treating a disease in a subject in need of such treatment, said method comprising administering to the subject a pharmaceutical composition comprising 10-60 mg of a compound of Formula I, the administration of which to a subject results in a plasma exposure level of deuterated dextrorphan isotopologues less than or equal to 1000 ng-h/mL.

In another embodiment, the disclosure provides a method for treating a disease in a subject in need of such treatment, said method comprising administering to the subject a pharmaceutical composition comprising 10-60 mg of a compound of Formula I, the administration of which to a subject results in a plasma exposure level of deuterated dextrorphan isotopologues less than or equal to 500 ng-h/mL.

In another embodiment, the disclosure provides a method for treating a disease in a subject in need of such treatment, said method comprising administering to the subject a pharmaceutical composition comprising 10-60 mg of a compound of Formula I, the administration of which to a subject results in an increase in the plasma exposure level of a compound of Formula I and a decrease in the plasma exposure level of deuterated dextrorphan metabolite isotopologues, particularly deuterated dextrorphan isotopologues, as compared to the plasma exposure levels of dextromethorphan and dextrorphan produced from a molar equivalent dextromethorphan composition that is administered in the same dosing regimen.

In another embodiment, the disclosure provides a method for treating a disease in a subject in need of such treatment, said method comprising administering to the subject a pharmaceutical composition comprising 10-60 mg of a compound of Formula I, said composition providing a plasma exposure level of a compound of Formula I of from about 1750 to about 2500 ng-h/mL after repeated administration to a subject every 12 hours through steady-state conditions.

In another embodiment, any of the above methods of treatment comprises the further step of co-administering to the subject one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for co-administration with dextromethorphan. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of second therapeutic agents that may be employed in the methods of this disclosure are those set forth above for use in combination compositions comprising a compound of this disclosure and a second therapeutic agent.

In particular, the combination therapies of this disclosure include co-administering to a subject in need thereof a compound of Formula I, wherein R1 is selected from CH3, CH2D, CHD2, CD3, CHF2, and CF3; and R2 is selected from CH3, CH2D, CHD2, and CD3 or a composition comprising such compound; and quinidine sulfate wherein the subject is suffering from or susceptible to diabetic neuropathy.

In another embodiment the disclosure provides a method for treating a disease in a subject suffering from non-small cell lung cancer or malignant pleural mesothelioma by co-administering to the subject in need thereof a compound of Formula I, wherein R1 is selected from CH3, CH2D, CHD2, CD3, CHF2, and CF3; and R2 is selected from CH3, CH2D, CHD2, and CD3 or a composition comprising such compound; and LBF189.
The term “co-administered” as used herein means that the second therapeutic agent may be administered together with a compound of this disclosure as part of a single dosage form (such as a composition of this disclosure comprising a compound of the disclosure and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this disclosure. In such combination therapy treatment, both the compounds of this disclosure and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this disclosure, comprising both a compound of the disclosure and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this disclosure to said subject at another time during a course of treatment.

Effective amounts of these second 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 second therapeutic agent’s optimal effective-amount range.

In one embodiment of the disclosure, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this disclosure is less than its effective amount where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount where the compound of this disclosure is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimen and/or reduced drug cost) will be apparent to those of skill in the art.

In yet another aspect, the disclosure provides the use of a compound of Formula I alone or together with one or more of the above-described second therapeutic agents 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 disclosure is a compound of Formula I for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

Thus, in another embodiment, the disclosure provides a method of treating a disease in a subject in need of such treatment, the method comprising co-administering 10-60 mg of a compound of Formula I and 2.5-30 mg quinidine, so that the composition provides a maximum plasma exposure level after repeated administration every 12 to 24 hours through steady-state conditions of a compound of Formula I in a subject of from about 1750 to about 250 ng-h/mL, wherein the administration of said composition to a subject results in a reduction in the plasma exposure level of deuterated dextrorphan isotopologues as compared to the same molar amount of a compound of Formula I administered without the quinidine.

Thus, in another embodiment, the disclosure provides a method of treating a disease in a subject in need of such treatment, the method comprising co-administering 10-60 mg of a compound of Formula I and 2.5-30 mg quinidine, so that the composition provides a maximum plasma exposure level after repeated administration every 12 to 24 hours through steady-state conditions of a compound of Formula I in a subject of from about 1750 to about 250 ng-h/mL, wherein the administration of said composition to a subject results in a reduction in the plasma exposure level of deuterated dextrorphan isotopologues as compared to the same molar amount of a compound of Formula I administered without the quinidine.

Among other uses, diagnostic methods and kits are provided for detecting the presence of deuterated dextrorphan isotopologues in a subject or other entities, such as in samples such as plasma. The methods and kits may also be used to determine the presence of deuterated dextrorphan isotopologues in biological samples such as plasma, examining the metabolism of dextromethorphan and dextrorphan in an equivalent subject resulting from the administration of the same amount of quinidine and comparing the difference in the maximum plasma exposure level of deuterated dextrorphan isotopologues in a subject as compared to the same molar amount of quinidine administered alone.

Diagnostic Methods and Kits

The compounds and compositions of this disclosure are also useful as reagents in methods for determining the concentration of dextromethorphan in solution or biological sample such as plasma, examining the metabolism of dextromethorphan and other analytical studies.

According to one embodiment, the disclosure provides a method of determining the concentration, in a solution or a biological sample, of dextromethorphan, comprising the steps of:

a) adding a known concentration of a compound of Formula I to the solution of biological sample;

b) subjecting the solution or biological sample to a measuring device that distinguishes dextromethorphan from a compound of Formula I;
c) calibrating the measuring device to correlate the detected quantity of the compound of Formula I with the known concentration of the compound of Formula I added to the biological sample or solution; and

Cladding the measuring device to correlate the determined concentration of dextromethorphan in the solution of sample using the correlation between detected quantity and concentration obtained for a compound of Formula I.

Measuring devices that can distinguish dextromethorphan from the corresponding compound of Formula I include any measuring device that can distinguish between two compounds that differ from one another only in isotopic abundance. Exemplary measuring devices include a mass spectrometer, NMR spectrometer, or IR spectrometer.

In another embodiment, a method for determining the amount of dextromethorphan in a solution or a biological sample is provided, comprising:

a) adding a known amount of a compound of Formula I to the solution or biological sample; b) detecting at least one signal for a compound of Formula I and at least one signal for dextromethorphan in a measuring device that is capable of distinguishing the two compounds; c) correlating the at least one signal detected for a compound of Formula I with the known amount of the compound of Formula I added to the solution or the biological sample; and

Cladding the amount of dextromethorphan in the solution or biological sample using the correlation between the at least one signal detected of the compound of Formula I and the amount added to the solution or biological sample of a compound of Formula I.

In another embodiment, the disclosure provides a method of evaluating the metabolic stability of a compound of Formula I comprising the steps of contacting the compound of Formula I with a metabolizing enzyme source for a period of time and comparing the amount of the compound of Formula I with the metabolic products of the compound of Formula I after the period of time.

In a related embodiment, the disclosure provides a method of evaluating the metabolic stability of a compound of Formula I where in a subject following the administration of the compound of Formula I. This method comprises the steps of obtaining a serum, blood, tissue, urine or feces sample from the subject at a period of time following the administration of the compound of Formula I to the subject; and comparing the amount of the compound of Formula I with the metabolite products of the compound of Formula I after the period of time.

The present disclosure also provides kits for use to treat diabetic neuropathy: Rett syndrome (RTT); voice disorders due to uncontrolled laryngeal muscle spasms, including e.g., abductor spasmodic dysphonia, adductor spasmodic dysphonia, muscular tension dysphonia, and vocal tremor; methotrexate neurotoxicity; and fatigue caused by cancer. These kits comprise (a) a pharmaceutical composition comprising a compound of Formula I or a salt, hydrate, or solvate thereof, wherein said pharmaceutical composition is in a container; and (b) instructions describing a method of using the pharmaceutical composition to treat pseudobulbar affect; diabetic neuropathy: Rett syndrome (RTT); voice disorders due to uncontrolled laryngeal muscle spasms, including e.g., abductor spasmodic dysphonia, adductor spasmodic dysphonia, muscular tension dysphonia, and vocal tremor; methotrexate neurotoxicity; and fatigue caused by cancer.

The container may be any vessel or other sealed or sealable apparatus that can hold said pharmaceutical composition. Examples include bottles, ampules, divided or multi-chambered holders, bottles wherein each division or chamber comprises a single dose of said composition, a divided foil packet wherein each division comprises a single dose of said composition, or a dispenser that dispenses single doses of said composition. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule.

The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box. In an embodiment, the container is a blister pack.

The kits of this disclosure may also comprise a device to administer or to measure out a unit dose of the pharmaceutical composition. Such device may include an inhaler if said composition is an inhalable composition; a syringe and needle if said composition is an injectable composition; a syringe, spoon, pump, or a vessel with or without volume markings if said composition is an oral liquid composition; or any other measuring or delivery device appropriate to the dosage formulation of the composition present in the kit.

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

EXAMPLES

Example 1

Syntheses of Compounds 100, 101, and 108

Each of the steps and numbered intermediates described below refer to the corresponding steps and intermediates in Scheme 1, supra.

(+)-3-methoxy-17-methyl-(9a,13a,14a)-morphinan (10b). To a reaction vessel was added (+)-3-methoxy-17-methyl-(9a,13a,14a)-morphinan, HBr salt (3.00 g, 8.5 mmol), NH3 in CH3OH (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 CHCl3 (50 mL) and H2O (50 mL). The layers were separated and the water layer was extracted with CHCl3 (50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated on a rotary evaporator to yield 2.88 g of 10b as a fluffy white solid.

1H-NMR (300 MHz, CDCl3): δ 1.12 (ddd, J1=24.7, J2=12.6, J3=3.8, 1H), 1.23-1.43 (m, 5H), 1.49-1.52 (m, 1H), 1.62-1.65 (m, 1H), 1.72 (td, J1=12.6, J2=4.9, 1H), 1.81 (dt, J1=12.6, J2=3.3, 1H), 2.07 (td, J1=12.6, J2=3.3, 1H), 2.33-2.47 (m, 5H), 2.57 (dd, J1=18.1, J2=5.5, 1H), 2.79 (dd, J1=5.5, J2=3.3, 1H), 2.98 (d, J=18.1, 1H), 6.68 (dk, J=8.2, J2=2.7, 1H), 6.80 (d, J=2.7, 1H), 7.02 (d, J=8.8, 1H).

(+)-3-methoxy-(9a,13a,14a)-morphinan (11). The solid 10b (6.79 g, 25.1 mmol) was placed in a reaction vessel with CHCl3 and a stir bar. K2CO3 (13.85 g, 100.2 mmol) was added and the mixture was stirred at RT under an atmosphere of N2 for 10 min before the addition of acetyl chloride (7.866 g, 100.2 mmol). The resulting reaction mixture, still under an atmosphere of N2, 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 CH3OH then stirred under reflux...
reaction. The mixture was diluted with H2O then was extracted with CHCl3/CH3OH (200 mL). The resulting solution was cooled to 0°C followed by the addition of 20% ethylacetate/hexane showed the reaction to be complete. The mixture was then quenched by the addition of magnesium sulfate hexahydrate until cessation of gas evolution. Ethyl ether (25 mL) was added to the flask, the slurry was filtered, and the organic filtrate was concentrated on a rotary evaporator to an oil. The crude product was purified via automated flash column chromatography (CH3OH with 1%NH4OH/CHCl3, 0-10%), concentrated on a rotary evaporator, then dissolved in a saturated solution of HBr in dioxane. The mixture was stirred for 10 min, was concentrated on a rotary evaporator, then dried under vacuum for 3 d to yield 204 mg of Compound 101.

1H-NMR (300 MHz, CDC13): δ 1.08 (dd, J=5.1, J=6.6, 1H), 1.12-1.32 (m, 1H), 1.35-1.48 (m, 4H), 1.59 (dd, J=41.0, J=12.6, 1H), 1.94 (t, J=12.6, 1H), 2.06 (d, J=13.2, 1H), 2.75 (m, 1H). The reaction mixture was stirred under an atmosphere of N2 for 2 h at which time tlc (20% ethylacetate/hexane) showed the reaction to be complete. The mixture was then concentrated on a rotary evaporator, then dried under vacuum for 3 d to yield 204 mg of Compound 101.

1H-NMR (300 MHz, CDC13): δ 1.08 (dd, J=5.1, J=6.6, 1H), 1.12-1.32 (m, 1H), 1.35-1.48 (m, 4H), 1.59 (dd, J=41.0, J=12.6, 1H), 1.94 (t, J=12.6, 1H), 2.06 (d, J=13.2, 1H), 2.75 (m, 1H). The reaction mixture was stirred under an atmosphere of N2 for 2 h at which time tlc (20% ethylacetate/hexane) showed the reaction to be complete. The mixture was then concentrated on a rotary evaporator, then dried under vacuum for 3 d to yield 204 mg of Compound 101.
Microsomal Assays

Certain in vitro liver metabolism studies have been described previously in the following references, each of which is incorporated herein in their entirety: Obach, R S Drug Metab Disp 1999, 27:1350; Houston, J B Biochem Pharmacol 1994, 47:1469; Iwatsubo, T et al, Pharmacol Ther 1997, 73:147; and Lave, Τ et al, Pharm Res 1997, 14:152.

The objectives of this study were to determine the metabolic stability of the test compounds in pooled human and chimpanzee liver microsomal incubations. Samples of the test compounds, exposed to pooled human or chimpanzee liver microsomes, were analyzed using HPLC-MS (or MS/MS) detection. For determining metabolic stability, multiple reaction monitoring (MRM) was used to measure the disappearance of the test compounds.

Experimental Procedures: Human liver and Cynomolgus monkey liver microsomes were obtained from Xenotech, LLC (Lexena, Kans.). The incubation mixtures were prepared as follows:

<table>
<thead>
<tr>
<th>Liver Microsomes</th>
<th>0.5, 1.0 or 2.0 mg/mL</th>
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<tbody>
<tr>
<td>NADPH</td>
<td>1 mM</td>
</tr>
<tr>
<td>Potassium Phosphate, pH 7.4</td>
<td>100 mM</td>
</tr>
<tr>
<td>Magnesium Chloride</td>
<td>10 mM</td>
</tr>
<tr>
<td>Test Compound (Dextromethorphan, Compound 100, Compound 101, Compound 108)</td>
<td>0.10, 0.25, 1 μM</td>
</tr>
</tbody>
</table>

Incubation of Test Compounds with Liver Microsomes: The reaction mixture, minus cofactors, was prepared. An aliquot of the reaction mixture (without cofactors) was incubated in a shaking water bath at 37°C for 3 minutes. The reaction mixture was prepared as a blank control, by the addition of plain organic solvent (no test compound is added). The reaction was initiated by the addition of cofactors (not added to the negative controls) and then incubated in a shaking water bath at 37°C. Aliquots (200 μL) were withdrawn in triplicate at multiple time points and combined with 800 μL of ice-cold 50/50 acetonitrile/D2O to terminate the reaction. The positive controls, testosterone and propranolol, as well as dextromethorphan, were each run simultaneously with the test compounds in separate reactions.

A portion of the supernatant (100 μL) was then removed, washed with ethyl ether, filtered, and the organic filtrate was concentrated on a rotary evaporator to an oil. The crude product was purified via automated flash column chromatography (CH3OH with 1% NH4OH/CHCl3, 90%), concentrated on a rotary evaporator to an oil. The mixture was stirred for 10 min, and then concentrated on a rotary evaporator to yield 74 mg of product.

1H-NMR (300 MHz, CDC13): δ 0.96 (ddd, J1=25.4, J2=12.7, J3=3.9, 1H), 1.08-1.18 (m, 1H), 1.24-1.36 (m, 2H), 1.43-1.52 (m, 3H), 1.62 (d, J=12.7, 1H), 1.78 (dd, J=13.7, J=4.4, 1H), 1.96 (d, J=12.2, 1H), 2.41-2.47 (m, 2H), 2.97 (dd, J=19.5, J=5.9, 1H), 3.10-3.18 (m, 2H), 3.60-3.63 (m, 1H), 3.73 (s, 3H), 6.81-6.84 (m, 2H), 7.13 (d, J=9.3, 1H), 9.60 (bs, 1H).

HPLC (method: 150 mm C18-RP column—gradient method 5-95% ACN; Wavelength: 280 nm): retention time: 6.91 min. MS (M+H+): 275.7.

Example 2

Evaluation of Metabolic Stability in CYP2D6 SUPERSOMES™

Human CYP2D6+P450 Reductase SUPERSOMES™ were purchased from GenTest (Woburn, Mass., USA). A 1.0 mL reaction mixture containing 25 pmole of SUPERSOMES™, 2.0 mM NADPH, 3.0 mM MgCl, and 0.1 μM of various compounds of Formula I (Compounds 100, 101, and 108) in 100 mM potassium phosphate buffer (pH 7.4) was incubated at 37°C in triplicate. Positive controls contained 0.1 μM dextromethorphan instead of a compound of Formula I. Negative controls used Control Insect Cell Cytosol (insect cell microsomes that lacked any human metabolic enzyme) purchased from GenTest (Woburn, Mass., USA). Aliquots (50 μL) were removed from each sample and placed in wells of a multi-well plate at 0, 2, 5, 7, 12, 20, and 30 minutes and to each was added 50 μL of ice cold acetonitrile with 3 μM haloperidol as an internal standard to stop the reaction.

Plates containing the removed aliquots were then placed in –20°C freezer for 15 minutes to cool. After cooling, 100 μL of deionized water was added to all wells in the plate. Plates were then spun in the centrifuge for 10 minutes at 3000 rpm. A portion of the supernatant (100 μL) was then removed, placed in a new plate and analyzed using Mass Spectrometry.

FIG. 3 shows the results of the Supersomes experiment. Once again Compounds 100 and 101 were much more stable to metabolism than dextromethorphan or Compound 108. Approximately 47% of Compound 101 and 40% of Compound 100 remained intact after a 30 minute incubation with the 2D6 Supersomes™. In contrast, no intact dextromethorphan could be detected at the 20 minute time point.

The above results all suggest that the presence of deuterium at the R' position in the compounds of this disclosure imparts greater metabolic stability to the compound as compared to dextromethorphan.
Example 4

Evaluation of Pharmacokinetics of Test Articles C20148, and C10003 in Cynomolgus Monkeys Following Oral Administration in Combination with Quinidine

OBJECTIVE—The objective of this study was to collect plasma samples from Cynomolgus Monkeys at various time points following oral administration of test articles in combination. The samples were used for the determination of plasma drug levels by LC/MS/MS for estimating pharmacokinetic parameters. This study was conducted in accordance with Shanghai Medicilon Inc. Standard Operating Procedures (SOPs). The Sponsor provided the test compounds and internal standard compound.

Animal Husbandry—The animals used were cynomolgus monkeys, who at the age of initiation of treatment, were 3-4 years of age, and weighed between 4-6 kg.

Environment and Acclimation—Environmental controls for the animal room were set to maintain a temperature of 23±2° C., humidity of 50-70%, and a 12-hour light/12-hour dark cycle. As needed, the 12-hour dark cycle was temporarily interrupted to accommodate study procedures. Animals were previously acclimated to study procedures prior to initial dose administration.

Food and Water—SL-M1 (Shanghai Shilin Biotech Incorporation) were provided ad libitum throughout the in-life portion of the study. Water was available ad libitum. There were no known contaminants in the food or water that interfered with this study.

Animal Selection and Fasting—Animals to be used on test were selected based on overall health and acclimation to caging. Oral arm was be fasted overnight.

Justification—Studies using common mammalian laboratory animals such as mice, rats, dogs, and monkeys are essential and routinely used for the evaluation of the pharmacokinetic characteristics of new chemical entities. The number of animals in each group is the minimum number needed for the assessment of variability between test animals.

EXPERIMENTAL DESIGN—Four Cynomolgus Monkeys were used in this study.

<table>
<thead>
<tr>
<th>No. of Animals</th>
<th>Treatment</th>
<th>Dose Level* (mg/kg)</th>
<th>Dose Cone* (mg/mL)</th>
<th>Dose Volume (mL/kg)</th>
<th>Vehicle**</th>
<th>Dosing</th>
<th>Collect</th>
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<td>1.5</td>
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</tr>
</tbody>
</table>

*Dex" means dextromethorphan
*Each test article will be dissolved at a concentration of 2 mg/mL, and dosed at 1 mg/kg.
**The formulation will consist of 10% dimethylsulfoxide, 15% ethanol, 35% propylene glycol (v/v/v) in D5W. 

Example 4

Dosing Preparation and Administration—Compound 101 and dextromethorphan were each dissolved in water up to 2 mg/mL. The combination dose was prepared by mixing both by 1:1 to yield a concentration of 1 mg/mL for each compound. The concentration of each compound in the dosing solution was re-confirmed by HPLC. Quinidine was prepared in DMLETOH:PG:water (10:15:35:40, v/v/v/v) at 3 mg/mL and dosed separately. The doses were given BID orally with an interval of 12 hours. Dosing volume of the dextromethorphan/Compound 100 mixture was 1 mL/kg. Dosing volume of Quinidine was determined based on the dose each animal was getting. Dose volumes for each test animal was determined based on individual body weight. Body weights were taken on each day of dose administration and were be recorded.

Blood Sample Collection—Blood sampling took place on Day 6 after oral administration of the last dose (Dose 11). Blood (approximately 1 mL) was collected via femoral vein into tubes containing sodium heparin anticoagulant at 0.25, 0.5, 1, 1.5, 3, 3.5, 6 and 8 hours. The plasma was separated via centrifugation and stored in -20° C. before analysis.

Urine Sample Collection—Urine samples in between two doses on Day 5 (for 12 hours between doses 9 and 10) were collected in a plate and quantified by volume. After collection, the urine samples were be stored in -20° C. and then shipped back to client.

Acceptable Time Ranges—Blood samples for each time point were collected within 10% for the time points before the first hour and within ±5 minutes for the time points after 1 hour.

Sample Handling and Storage—Blood was stored on ice, or at approximately 5° C. prior to centrifugation to obtain plasma samples. Centrifugation took place within 30 minutes of blood collection to harvest plasma (maximum volume). Plasma samples were stored on dry ice or at approximately -20° C. until analysis.

Antemortem Observations—During dosing and at the times of blood collections, animals were observed for any clinically relevant abnormalities including food consumption, weight, injection position, activity, or feces and urine, for example.
Sample Analysis—Analyses of plasma samples was conducted by the Bioanalytical Group of Medicilon/MPI Inc. The concentrations of both parent compounds (dextromethorphan and Compound 100) and 2 metabolites (Dextrorphan and Dextrorphan-D3) in plasma & urine were determined using a high performance liquid chromatography/mass spectrometry (HPLC/MS/MS API 3000) method. Dilution using cynomolgus monkey plasma blank were applied if the sample concentration was over the ULOQ of calibration standard curve. The data acquisition and control system was created using Analyst 1.4 software from ABI Inc.

The results are summarized in FIGS. 4, 5, and 6. FIG. 4 depicts the plasma levels of Compound 101 and deuterated dextromethorphan compared to dextromethorphan and dextorphan without quinidine co-administration. FIG. 4 demonstrates that higher plasma concentration levels of Compound 101 are observed compared to dextromethorphan when Compound 101 and dextromethorphan are administrated to monkeys at the same dose (4 mg). FIG. 4 also shows that metabolism of Compound 101 to deuterated dextromethorphan isopologues is reduced relative to metabolism of dextromethorphan to dextorphan. As indicated in the Background section of this application, the abuse potential of dextromethorphan are more reliably attributable to dextorphan, and abuse potential in humans of dextromethorphan metabolism to dextromethorphan. FIG. 4 thus suggests that the compounds of the disclosure may be useful in reducing metabolism of dextromethorphan isopologues to dextromethorphan isopologues, and thus in reducing the abuse potential of such compounds.

FIG. 5 summarizes dosing data. The results indicate that Compound 101 plasma levels are greater than dextromethorphan plasma levels when each compound is co-administered with the same amount of quinidine. The relative effect of increasing quinidine dose has a greater effect on the plasma level of Compound 101 than it has on dextromethorphan.

FIG. 6 depicts urine levels of Compound 101, and dextromethorphan, as well as deuterated dextromethorphan isopologues and dextrophan as a function of quinidine concentration in monkeys. Compound 101 and dextromethorphan levels are affected by increasing quinidine concentration. At the same quinidine concentration, there is less Compound 101 in the urine than dextromethorphan. Quinidine concentration also affects metabolite levels in the urine. The data indicate that there is less deuterated dextromethorphan isopologues than dextromethorphan in the urine for a given quinidine concentration.

Example 5

Radioligand Assay Data Measuring Binding of Compounds to NMDA, Glycine, Sigma and Phencyclidine Receptors


Assay Methods:

<table>
<thead>
<tr>
<th>Source</th>
<th>Glutamate, NMDA, Glycine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand</td>
<td>Winter rat cerebral cortex</td>
</tr>
<tr>
<td>Vehicle</td>
<td>1% DMSO</td>
</tr>
<tr>
<td>Incubation Time/Temp</td>
<td>30 minutes @ 4°C</td>
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<tr>
<td>Incubation Buffer</td>
<td>50 mM HEPES, pH 7.7</td>
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<tr>
<td>Non-specific Ligand</td>
<td>10 mM MDL-105519</td>
</tr>
<tr>
<td>KD</td>
<td>6 nM *</td>
</tr>
<tr>
<td>BMAX</td>
<td>3.7 pmole/mg Protein *</td>
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<tr>
<td>Specific Binding</td>
<td>85% *</td>
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<tr>
<td>Quantitation Method</td>
<td>Radioligand Binding</td>
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<tr>
<td>Significance Criteria</td>
<td>≥50% of max stimulation or inhibition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Glutamate, NMDA, Phenecyclidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand</td>
<td>Human Jurkat cells</td>
</tr>
<tr>
<td>Vehicle</td>
<td>1% DMSO</td>
</tr>
<tr>
<td>Incubation Time/Temp</td>
<td>4 hours @ 25°C</td>
</tr>
<tr>
<td>Incubation Buffer</td>
<td>5 mM Potassium Phosphate, pH 7.5</td>
</tr>
<tr>
<td>Non-specific Ligand</td>
<td>10 mM Haloperidol</td>
</tr>
<tr>
<td>KD</td>
<td>5.8 nM *</td>
</tr>
<tr>
<td>BMAX</td>
<td>0.71 pmole/mg Protein *</td>
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<tr>
<td>Specific Binding</td>
<td>94% *</td>
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<tr>
<td>Quantitation Method</td>
<td>Radioligand Binding</td>
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<tr>
<td>Significance Criteria</td>
<td>≥50% of max stimulation or inhibition</td>
</tr>
</tbody>
</table>

* Historical Value

Results:

The binding results are summarized in the following table for Compound 101 compared to dextromethorphan.

<table>
<thead>
<tr>
<th>Source</th>
<th>Dextromethorphan</th>
<th>Compound 101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand</td>
<td>NMDA (PCP)</td>
<td></td>
</tr>
<tr>
<td>Specific Binding</td>
<td>2.79 ± 0.39 nM</td>
<td>3.46 ± 0.34 nM</td>
</tr>
<tr>
<td>Sigma σ1</td>
<td>3.55 ± 0.19 nM</td>
<td>2.02 ± 0.24 nM</td>
</tr>
</tbody>
</table>

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 disclosure 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 disclosure. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.
The invention claimed is:

1. A method for treating a subject suffering from or susceptible to Parkinson’s Disease, the method comprising administering to the subject a compound of formula (I):

\[
\text{or a pharmaceutically acceptable salt thereof,}
\]

wherein \( R^1 \) is selected from \( \text{CH}_3, \text{CH}_2\text{D}, \text{CHD}_2, \text{and CD}_3; \)
and
\( R^2 \) is selected from \( \text{CH}_3, \text{CH}_2\text{D}, \text{CHD}_2, \text{and CD}_3; \)
wherein any atom not designated as deuterium in the compound is present at its natural isotopic abundance, and wherein when \( R^1 \) is \( \text{CH}_3 \), then \( R^2 \) is not \( \text{CH}_3 \).

2. The method of claim 1, wherein \( R^1 \) is \( \text{CD}_3 \), and \( R^2 \) is selected from \( \text{CH}_3, \text{CH}_2\text{D}, \text{CHD}_2, \text{and CD}_3.

3. The method of claim 2, wherein \( R^1 \) is \( \text{CD}_3 \), and \( R^2 \) is \( \text{CD}_3 \).

4. The method of claim 2, wherein \( R^1 \) is \( \text{CD}_3 \), and \( R^2 \) is \( \text{CH}_3 \).

5. The method of claim 1, wherein the compound of formula (I):

\[
\text{or a pharmaceutically acceptable salt thereof,}
\]

wherein \( R^1 \) is selected from \( \text{CH}_3, \text{CH}_2\text{D}, \text{CHD}_2, \text{and CD}_3; \)
and
\( R^2 \) is selected from \( \text{CH}_3, \text{CH}_2\text{D}, \text{CHD}_2, \text{and CD}_3; \)
wherein any atom not designated as deuterium in the compound is present at its natural isotopic abundance, and wherein when \( R^1 \) is \( \text{CH}_3 \), then \( R^2 \) is not \( \text{CH}_3 \), is administered in a pharmaceutical composition which comprises a pharmaceutically acceptable carrier.

6. The method of claim 1, wherein the pharmaceutically acceptable salt thereof is the HBr salt.

7. The method of claim 1, further comprising administering to the subject in need thereof a second therapeutic agent selected from quinidine or a salt thereof, oxycodone, and gabapentin.

8. The method of claim 7, wherein \( R^1 \) is \( \text{CD}_3 \), and \( R^2 \) is selected from \( \text{CH}_3, \text{CH}_2\text{D}, \text{CHD}_2, \text{and CD}_3.

9. The method of claim 8, wherein \( R^1 \) is \( \text{CD}_3 \), and \( R^2 \) is \( \text{CD}_3 \).

10. The method of claim 8, wherein \( R^1 \) is \( \text{CD}_3 \), and \( R^2 \) is \( \text{CH}_3 \).

11. The method of claim 7, wherein the second therapeutic agent is quinidine or quinidine sulfate.

* * * * *