This disclosure relates to novel melatonin analogues or naphthyl(ethyl)acetamides, their derivatives, pharmaceutically acceptable salts, solvates, and hydrates thereof. This disclosure also provides compositions comprising a compound of acceptable salts, solvates, and hydrates thereof.


(Continued)

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(57) ABSTRACT

This disclosure relates to novel melatonin analogues or naphthyl(ethyl)acetamides, 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 dual melatoninergic agonist and serotoninergic antagonist.

18 Claims, No Drawings
OTHER PUBLICATIONS


* cited by examiner
The term “ameliorate” and “treat” are used interchangeably and include therapeutic and/or prophylactic treatment. Both terms mean decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein).

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

It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of Agomelatine 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 E et al., Seikagaku 1994, 66:15; Ganes L Z et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725. In a compound of this disclosure, when a particular position is designated as having deuterium, it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of at least 3000 (45% deuterium incorporation) at each atom designated as deuterium in said compound.

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

In other embodiments, a compound of this 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), at least 6633.3 (99% 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.

Agomelatine has been found to have a side effect profile similar to placebo. (Loo, H et al., Int J Neuropsychopharmacol, 2002, 5(Suppl. 1):Aabst P3.E.033).

Despite its apparent efficacy, it is desirable to provide a compound that has the beneficial activities of Agomelatine 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 patient compliance and, potentially, to decrease population pharmacokinetic variability and/or decrease its potential for dangerous drug-drug interactions.
compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure. 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 bisulfate, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluensulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, benzoic acid, fumaric acid, gluconic acid, glucaric 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, phosphoric acid, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloric acid, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, maleate, butyrate, 1,4-dioate, hexyline, 1,6-dioate, benzoate, chlorobenzonate, methylnbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, naphthalate, sulfonate, xylene, sulfoxonate, phenylacetate, phenylcarbonate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, t-artrate, 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.

As used herein, the term "hydrate" means a compound which further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

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 A or Formula I), 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).

The present disclosure provides a compound of Formula A:}

(A)
In an even more specific embodiment, each of R\textsuperscript{3a}, R\textsuperscript{3*}, R\textsuperscript{4a}, and R\textsuperscript{4*} is H; and R\textsuperscript{5} is CH\textsubscript{3}, the compound having the formula I:

$$\text{O}$$

In one embodiment of formula I, R\textsuperscript{1} is selected from CH\textsubscript{3}, CHD\textsubscript{2} and CD\textsubscript{3}. In a more specific embodiment, R\textsuperscript{1} is selected from CH\textsubscript{3} and CD\textsubscript{3}.

According to another embodiment of formula I, R\textsuperscript{2} is selected from H and D.

In one specific embodiment of formula I, R\textsuperscript{1} is selected from H, CH\textsubscript{3} and CD\textsubscript{3}; and R\textsuperscript{2} is selected from H and D.

In another embodiment of formula I, R\textsuperscript{2} is selected from F and OH.

In a more specific embodiment, the compound of formula A is selected from any one of the compounds (Cmpd) set forth in Table 1 (below):

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>Each R\textsuperscript{3}</th>
<th>Each R\textsuperscript{4}</th>
<th>R\textsuperscript{5}</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>CH\textsubscript{3}</td>
<td>D</td>
<td>H</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
</tr>
<tr>
<td>101</td>
<td>CD\textsubscript{3}</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
</tr>
<tr>
<td>102</td>
<td>CD\textsubscript{3}</td>
<td>D</td>
<td>H</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
</tr>
<tr>
<td>103</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
</tr>
<tr>
<td>104</td>
<td>CD\textsubscript{3}</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
</tr>
<tr>
<td>105</td>
<td>CD\textsubscript{3}</td>
<td>F</td>
<td>H</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
</tr>
<tr>
<td>106</td>
<td>CD\textsubscript{3}</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CD\textsubscript{3}</td>
</tr>
<tr>
<td>107</td>
<td>CD\textsubscript{3}</td>
<td>H</td>
<td>D</td>
<td>D</td>
<td>CD\textsubscript{3}</td>
</tr>
</tbody>
</table>

In an even more specific embodiment, a compound of formula A is selected from:

Compound 101

$$\text{O}$$

Compound 106

In another embodiment, 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 A or formula I is isolated or purified, e.g., the compound of formula A or 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 A or formula I present, respectively. Thus, in some embodiments, a composition comprising a compound of formula A or 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 A or 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 A or formula I. Thus, in some embodiments, a composition comprising a compound of formula A or 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 A or 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

Convenient methods for synthesizing compounds of this disclosure are depicted in Schemes I-III.
An appropriately-deuterated aldehyde XXX is converted to styrene derivative XXXI. Sonogashira coupling with the desired alkyne provides compound XXXII, which is cyclized to yield the desired intermediate heterocycle XXXIII. Compound XXXIII is deprotected to produce the amine XXXIV, which is then modified to produce a compound of Formula A or Formula I, wherein R\(^1\) is deuteromethyl and R\(^2\) is fluorine. General procedures for this synthetic route are found in: Xu, J et al., Org Lett, 2006, 8(12):2555-2558; Dunetz, J R et al., J Am Chem Soc, 2005, 127(16):5776-5777; and Suzuki, I et al., Tet Lett, 2004, 45(9):1955-1959.

P-anisaldehyde (X) is converted to styrene-derivative XI. Sonogashira coupling with the desired protected alkyne provides compound XII, which is then cyclized to the desired substituted intermediate naphthalene XIII. This intermediate (XIII) is then treated with boron tribromide to simultaneously remove the Boc and methyl ether groups to afford XIV. Acetylation of XIV gives a compound of Formula A or Formula I where R\(^1\) is H. General procedures for this synthetic route are found in Xu, J et al., Org Lett 2006, 8(12): 2555-2558; Dunetz, J R et al, J Am Chem Soc 2005, 127(16):5776-5777; Suzuki,
Alternatively, compound XIII can be treated with 4N HCl/ dioxane to remove the Boc, while retaining the methyl ether. Acetylation of the resulting product produces a compound of Formula A or Formula I where $R_1$ is methyl and $R_2$ is D.

Compound XV is reacted with sodium benzylationkoxide (XVI) in the presence of copper I bromide; DMF; and benzyl alcohol under refluxing conditions to produce benzyl ether XVII. Compound XVII is then reacted with methyl iodide and potassium carbonate in refluxing acetone to afford compound XVIII. The cyano compound XVIII is then reacted with sodium triethoxyaluminum hydride to produce aldehyde XIX which is then subsequently reduced to the benzylic alcohol XX via reaction with sodium borohydride in methanol. Compound XX is then converted to the benzylic bromide intermediate XXI by reaction with triphenylphosphine and carbon tetrabromide in DMF. Compound XXI is then transformed into the cyano compound XXII by reaction with potassium cyanide; a catalytic amount of sodium iodide in DMF. Reaction of compound XXII with a 1:1 complex of lithium aluminum hydride/aluminum trichloride in ether results in reduction of cyano compound XXII to amino compound XXIII. Acetylation of compound XXIII by reaction with acetyl chloride in pyridine produces compound XXIV. Treatment of compound XXIV with hydrogen gas in the presence of Pd/C catalyst in ethanol produces the Agomelatine metabolite II.

The synthetic procedure for the preparation of compound XV follows the published procedure of Mewshaw, R E et al. J.
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, R', R", etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

Additional methods of synthesizing compounds of Formula A or 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 A or 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, lechitin, 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, polycrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

If required, the solubility and bioavailability of the compounds of the present disclosure 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 disclosure optionally formulated with a poloxamer, 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 20060094744 and 20060079502.

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 formula 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 may 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 J D and Zaffaroni A C, U.S. Pat. No. 6,803,031, 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, cetzeryl alcohol, 2-octyldodecanol, 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 enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this disclosure.

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 disclosure 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 U.S. Pat. Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethylsiloxane, polycaprolactone, polyethylene glycol, polyactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polyeaacrylides, 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 disclosure 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 disclosure 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 disclosure. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, difusible polymer capsules and biodegradable polymer wafers.

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

According to another embodiment, the disclosure provides a method of coating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this disclosure. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, difusible polymer capsules and biodegradable polymer wafers.

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

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

In another embodiment, a composition of this disclosure further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as Agomelatine. Such agents include those indicated as being useful in combination with Agomelatine, including but not limited to, those described in WO 2007028904 and WO 2005002562.

Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from depression, anxiety, bipolar disorder, and sleep disorder.

In one embodiment, the second therapeutic agent is selected from Reboxetine mesilate, Citalopram hydrobro-
therapy. This has the advantage of minimizing toxic side  

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 prophylactic or therapeutic effect(s) of another therapy.


In one embodiment, an effective amount of a compound of this disclosure can range from 0.25 to 500 mg per day. In more specific embodiments the range is from 2.5 to 250 mg/day, or from 5 to 100 mg/day or from 25 to 50 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 patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for Agomelatine.

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

It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this disclosure. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this disclosure to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent or a compound of this disclosure, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

In another embodiment, the disclosure provides a method of stimulating MT1 and MT2 receptors and blocking 5-HT2B and 5-HT2C receptors in a cell, comprising contacting a cell with one or more compounds of Formula A or Formula I herein.

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 Agomelatine comprising the step of administering to said subject an effective amount of a compound or a composition of this disclosure. Such diseases are well known in the art and are disclosed in, but not limited to the following patents and published applications: WO 2007028904, WO 2005002562, WO 2005077887, WO 2006111653, WO 2006096435, and US 2006199805. Such diseases include, but are not limited to, depression, anxiety, bipolar disorder, and sleep disorders.

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 depression and bipolar disorder.

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 another embodiment, any of the above methods of treatment comprises the further step of co-administering to said patient 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 Agomelatine. 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 a compound of Formula A or Formula I and a second therapeutic agent for treatment of the following conditions: depression (Reboxetine mesilate); anxiety and depression (Citalopram hydrobromide, Fluvoxamine maleate, Paroxetine, Fluoxetine hydrochloride, Escitalopram oxalate, and Sertraline hydrochloride).

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, Stam-
two compounds that differ from one another only in isotopic
position or as separate dosage forms, for treatment or preven-
tion in a subject of a disease, disorder or symptom set forth
above. Another aspect of the disclosure is a compound of
Formula A or Formula I for use in the treatment or prevention
in a subject of a disease, disorder or symptom thereof delineated
herein.

Diagnostic Methods and Kits

The compounds and compositions of this disclosure are
also useful as reagents in methods for determining the concen-
tration of Agomelatine in solution or biological sample
such as plasma, examining the metabolism of Agomelatine
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 Agomelatine, comprising the steps of:
a) adding a known concentration of a compound of For-

da) detecting at least one signal for a compound of Formula

A or Formula I to the solution of biological sample;
b) detecting at least one signal for a compound of Formula

A or Formula I and at least one signal for Agomelatine in a
measuring device that is capable of distinguishing the two
compounds;
c) correlating the at least one signal detected for a com-

pound of Formula A or Formula I with the known amount of
the compound of Formula A or Formula I added to the solution
or the biological sample; and
d) determining the amount of Agomelatine in the solution
or biological sample using the correlation between the at least
one signal detected of the compound of Formula A or Formu-
la I and the amount added to the solution or biological sample
of a compound of Formula A or Formula I.

In another embodiment, the disclosure provides a method
of evaluating the metabolic stability of a compound of For-

mula A or Formula I comprising the steps of contacting the
compound of Formula A or Formula I with a metabolizing
enzyme source for a period of time and comparing the amount
of the compound of Formula A or Formula I with the meta-

bolic products of the compound of Formula A or 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 For-

mula A or Formula I in a subject following administration
of the compound of Formula A or Formula I. This method com-

prises the steps of obtaining a serum, blood, tissue, urine or
feeces sample from the subject at a period of time following
the administration of the compound of Formula A or Formula I
to the subject; and comparing the amount of the compound of
Formula A or Formula I with the metabolic products of the
compound of Formula A or Formula I in the serum, blood,
tissue, urine or feces sample.

The present disclosure also provides kits for use to treat
depression and bipolar disorder. These kits comprise (a) a
pharmaceutical composition comprising a compound of For-

mula A or 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 phar-

maceutical composition to treat depression and bipolar dis-

order.

The container may be any vessel or other sealed or scalable
apparatus that can hold said pharmaceutical composition.
Examples include bottles, ampules, divided or multi-cham-
bered 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 pharmaceuti-
cally 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
generally be used to hold a liquid suspension. It is feasible
that more than one container can be used together in a single
package to market a single dosage form. For example, tablets
may be contained in a bottle, which is in turn contained within
a box. In one embodiment, the container is a blister pack.

The kits of this 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 com-
position 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.

**EXEMPLARY EXAMPLES**

**Example 1**

Synthesis of N-(2-(7-(methoxy-d3)-naphthalen-1-yl)ethyl)acetamide-d3 (106). Compound 106 was prepared as outlined in Scheme IV below. Details of the synthesis are set forth below.

Scheme IV: Preparation of N-(2-(7-(methoxy-d3)-naphthalen-1-yl)ethyl)acetamide-d3 (106).

![Scheme IV](image)

**Synthesis of 2-(7-hydroxynaphthalen-1-yl)acetonitrile (11).** To a solution of nitrile 10 (0.500 g, 2.5 mmol) in DCM (20 mL) at -78°C, was added BBr3 (0.337 mL, 6.3 mmol, 2.5 eq) with stirring. The reaction mixture was stirred at -78°C for 1 h then poured into cold (0° C.) CH3OH (100 mL). The resulting solution was concentrated under reduced pressure then dried under high vacuum to yield a brown solid. Purification via automated flash column chromatography afforded intermediate 11 (218 mg, 48% yield).

Synthesis of 2-(7-(methoxy-d3)naphthalen-1-yl)acetonitrile (12). To a solution of alcohol 11 (0.218 g, 1.0 mmol) in DCM (20 mL) was added with stirring, K2CO3 (0.197 g, 1.4 mmol, 1.2 eq) and CD3I (0.164 g, 1.1 mmol, 0.95 eq). The mixture was stirred at RT under N2 overnight followed by the addition of H2O (20 mL) and extraction with EtOAc (2x30 mL). The combined organic layers were washed with brine solution (30 mL), dried over Na2SO4, filtered and concentrated in vacuo to yield the product 12 (206 mg, 86% yield, 95% purity).

Synthesis of 2-(7-(methoxy-d3)naphthalen-1-yl)ethanal, (13). A solution of 12 (0.206 g, 1.0 mmol) in THF (20 mL) was cooled to 0° C. to this solution was added 1.0 M BH3 in THF (2.21 mL, 2.2 mmol, 2.2 eq). The resulting mixture was stirred under an atmosphere of N2 at RT for 1 h, then under reflux conditions for 15 h. The mixture was then cooled to 0° C., and CH3OH was added to quench the reaction. The resulting mixture was stirred under reflux conditions for 1 h. Concentration of the mixture under reduced pressure afforded 13 (236 mg, quantitative yield). Synthesis of N-(2-(7-(methoxy-d3)-naphthalen-1-yl)ethyl)acetamide-d3 (106). To a solution of the amine, 13 (0.236 g, 1.2 mmol) in THF (20 mL) was added pyridine (0.097 mL, 1.2 mmol, 1.0 eq), DMAP (0.141 g, 1.2 mmol, 1.0 eq), and acetic anhydride-d3 (0.120 mL, 1.2 mmol, 1.0 eq) with stirring. The reaction mixture was stirred for 1 h at RT then was concentrated in vacuo and purified by reverse phase HPLC to yield Compound 106 as the formic acid salt (32 mg, 95% purity).

**Evaluation of Metabolic Stability**

Certain in vitro liver metabolism studies have been described previously in the following references, each of which incorporated herein in their entirety: Obach, R. S. Drug Metab Disip 1999, 27, p. 1350; Houston, J. B. et al., Drug Metab Rev 1997, 29, p. 891; Houston, J. B. Biochem Pharmacol 1994, 47, p. 1469; Iwatsubo, T et al., Pharmacol Ther 1997, 73, p. 147; and Lave, T. et al., Pharm Res 1997, 14, p. 152.

**Microsomal Assay:** The metabolic stability of compounds of Formula A or Formula I is tested using pooled liver microsomal incubations. Full scan LC-MS analysis is then performed to detect major metabolites. Samples of the test compounds, exposed to pooled human liver microsomes, are analyzed using UPLC-MS (or MS/MS) detection. For determining metabolic stability, multiple reaction monitoring (MRM) is used to measure the disappearance of the test compounds. For metabolite detection, Q1 full scans are used as survey scans to detect the major metabolites.

**Experimental Procedures:** Human liver microsomes are obtained from a commercial source (e.g., Absorption Systems L. P. (Exton, Pa.), or XenoTech, LLC (Lenexa, Kans.)). The incubation mixtures are prepared as follows:
Incubation of Test Compounds with Liver Microsomes: The reaction mixture, minus cofactors, is prepared. An aliquot of the reaction mixture (without cofactors) is incubated in a shaking water bath at 37° C. for 3 minutes. Another aliquot of the reaction mixture is prepared as the negative control. The test compound is added into both the reaction mixture and the negative control at a final concentration of 1 µM. An aliquot of the reaction mixture is prepared as a blank control, by the addition of plain organic solvent (no test compound is added). The reaction is 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) are withdrawn at multiple time points (e.g., 0, 15, 30, 60, and 120 minutes) and combined with 800 µL of ice-cold 50/50 acetonitrile/dH₂O to terminate the reaction. The positive controls, testosterone and propranolol, as well as agomelatine, are each run simultaneously with the test compounds in separate reactions.

All samples are analyzed using LC-MS (or MS/MS). An LC-MRM-MS/MS method is used for metabolic stability. Also, Q1 full scan LC-MS methods are performed on the blank matrix and the test compound incubation samples. The Q1 scans serve as survey scans to identify any sample unique peaks that might represent the possible metabolites. The masses of these potential metabolites can be determined from 35 peaks that might represent the possible metabolites. The Q1 full scan LC-MS/MS method is used for metabolic stability. The positive controls, testosterone and propranolol, as well as agomelatine, are each run simultaneously with the test compounds in separate reactions.

All samples are analyzed using LC-MS (or MS/MS). An LC-MRM-MS/MS method is used for metabolic stability. Also, Q1 full scan LC-MS methods are performed on the blank matrix and the test compound incubation samples. The Q1 scans serve as survey scans to identify any sample unique peaks that might represent the possible metabolites. The masses of these potential metabolites can be determined from 35 peaks that might represent the possible metabolites.
13. The composition of claim 12, wherein said second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from depression, anxiety, bipolar disorder, and sleep disorder.

14. The composition of claim 13, wherein the second therapeutic agent is selected from reboxetine mesilate, citalopram hydrobromide, fluvoxamine maleate, paroxetine, fluoxetine hydrochloride, escitalopram oxalate, and sertraline hydrochloride.

15. A method of treating a subject suffering from, or susceptible to, a disease selected from depression, anxiety, bipolar disorder, and sleep disorders comprising the step of administering to the subject in need thereof a composition of claim 10.

16. The method of claim 15, wherein the disease or condition selected from depression, and bipolar disorder.

17. The method of claim 15, comprising the additional step of co-administering to the subject in need thereof a second therapeutic agent.

18. The method of claim 17, wherein the second therapeutic agent is selected from:

   a. reboxetine mesilate when the subject is suffering from, or susceptible to depression; and
   b. citalopram hydrobromide, fluvoxamine maleate, paroxetine, fluoxetine hydrochloride, escitalopram oxalate, and/or sertraline hydrochloride when the subject is suffering from, or susceptible to anxiety and depression.

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