US 20080280991A1

(19) **United States**

(12) **Patent Application Publication**

Gant et al.

(10) **Pub. No.: US 2008/0280991 A1**

(43) **Pub. Date: Nov. 13, 2008**

(54) **SUBSTITUTED NAPHTHALENES**

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(21) Appl. No.: **12/116,636**

(22) Filed: **May 7, 2008**

Related U.S. Application Data

(60) Provisional application No. 60/928,343, filed on May 8, 2007.

Publication Classification

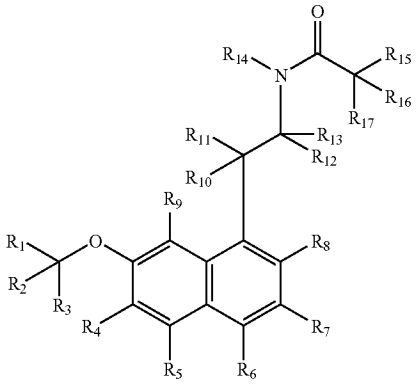
(51) **Int. Cl.**
A61K 31/165 (2006.01)
C07C 233/05 (2006.01)

(52) **U.S. Cl.** **514/630**; 564/219

(57) **ABSTRACT**

Disclosed herein are substituted naphthalene-based melatonin (MT) receptor modulators and/or 5-HT receptor modulators of Formula I, process of preparation thereof, pharmaceutical compositions thereof, and methods of use thereof.

Formula I



SUBSTITUTED NAPHTHALENES

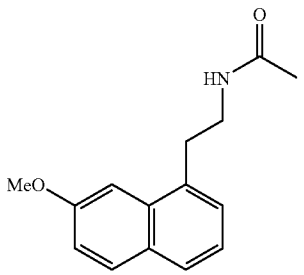
[0001] This application claims the benefit of priority of U.S. provisional application No. 60/928,343, filed May 8, 2007, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

FIELD

[0002] The present invention is directed to naphthalene-based 5-HT receptor modulators and/or melatonin receptor modulators, pharmaceutically acceptable salts and prodrugs thereof, the chemical synthesis thereof, and medical use of such compounds for the treatment and/or management of 5-HT receptor-mediated disorders and/or melatonin receptor-mediated disorders.

BACKGROUND

[0003] Agomelatine (Valdoxan®, S 20098), N-[2-(7-methoxy-naphthalen-1-yl)-ethyl]-acetamide, is an orally administered putative agonist of the melatonin MT_1 and MT_2 receptors. Agomelatine also antagonizes the 5-HT_{2C} receptor. Another drug of agomelatine's class is Ramelteon (Rozarem®). Ramelton, however, does not elicit the same effect on 5-HT_{2C} receptors as agomelatine, and therefore is not as effective as agomelatine in treating certain disorders. Agomelatine can be used to treat sleep disorders and depressive disorders. As compared with other sleep disorder and depressive disorder medications, agomelatine does not cause sexual side-effects, daytime drowsiness, and withdrawal effects upon discontinuation. Agomelatine has been shown to attenuate sexual disorders that are induced by 5-HT_{2C} receptor agonism in rats (Loo et al, *International Clinical Psychopharmacology* 2002, 17, 239-247; Chagraoui et al, *Psychopharmacology* 2003, 170, 17-22; Bertaina-Anglade et al, *Behavioural Pharmacology* 2006, 17, 703-713; Kupfer, *European Neuropsychopharmacology* 2006, 16, S639-S643; Norman, *Australian and New Zealand Journal of Psychiatry* 2006, 40, 394-401; Montgomery, *European Neuropsychopharmacology* 2006, 16, S633-S638; Zupancic et al, *CNS Drugs* 2006, 20(12), 981-992; Pjrek et al, *Psychopharmacology* 2007, 190, 575-579).



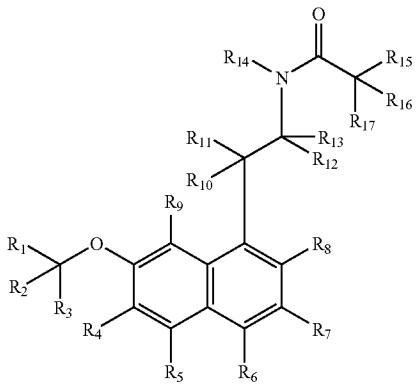
Agomelatine

[0004] The agomelatine chemical structure contains a number of moieties that we posit will produce clinically-inactive (at best) and toxic (at worst) metabolites, the formation of which can be prevented or diminished by the approach described herein. For example, agomelatine's methoxy group is ... nant metabolite is a naphthol, "S 21517," that has 100-fold less potency for the melatonin receptor than the parent compound. Long term toxicology studies of these metabolites are lacking. All of these transformations, among other potential transformations, can and do occur through polymorphically-expressed enzymes thus exacerbating interpatient variability. Further, the terminal elimination half-life is only 2.3 hours. A medicine with a longer half-life will therefore attenuate interpatient variatibility and improve efficacy.

SUMMARY OF THE INVENTION

[0005] Disclosed herein is a compound having structural Formula I:

Formula I



or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

[0006] $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}$, and R_{17} are independently selected from the group consisting hydrogen and deuterium; and

[0007] at least one of $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}$, and R_{17} is deuterium.

[0008] Further disclosed herein is a method for treating, preventing, or ameliorating one or more symptoms of a melatonin (MT) receptor-mediated disorder and/or serotonin (5-HT) receptor-mediated disorder which comprises administering to a subject a therapeutically effective amount of at least one compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0009] Additionally disclosed herein is a method for treating, preventing, or ameliorating one or more symptoms of a disorder involving, but not limited to, depressive disorders, seasonal affective disorders, anxiety, sleep disorders, dysthymia, sexual side effects associated with the use of 5-HT_{2C} agonists, any disorder which can lessened, alleviated, or benefited by modulating MT receptors, and/or any disorder which can lessened, alleviated, or benefited by modulating 5-HT receptors.

[0010] Also disclosed herein are articles of manufacture and kits containing compounds as disclosed herein. By way of example only a kit or article of manufacture can include a container (such as a bottle) with a desired amount of at least one compound (or pharmaceutical composition of a compound) as disclosed herein. Further, such a kit or article of manufacture can further include instructions for using said

tainer, or can be included in a package (such as a box or a plastic or foil bag) holding the container.

[0011] In another aspect is the use of a compound as disclosed herein in the manufacture of a medicament for treating a disorder in a subject, by modulating MT receptors and/or by modulating 5-HT receptors. In a further or alternative embodiment, said disorder is depressive disorders, seasonal affective disorders, anxiety, sleep disorders, dysthymia, sexual side effects associated with the use of 5-HT_{2C} agonists, any disorder which can lessened, alleviated, or benefited by modulating MT receptors, and/or any disorder which can lessened, alleviated, or benefited by modulating 5-HT receptors.

[0012] In another aspect are processes for preparing a compound as disclosed herein as a MT receptor modulator and/or a 5-HT receptor modulator, or other pharmaceutically acceptable derivatives such as prodrug derivatives, or individual isomers and mixture of isomers or enantiomers thereof.

[0013] Also disclosed herein are processes for formulating pharmaceutical compositions with a compound disclosed herein.

[0014] In further embodiments, said pharmaceutical composition comprises a compound disclosed herein and one or more pharmaceutically acceptable carriers.

[0015] In certain embodiments said pharmaceutical composition comprises one or more release-controlling excipients.

[0016] In other embodiments said pharmaceutical composition further comprises one or more non-release controlling excipients.

[0017] In certain embodiments said pharmaceutical composition is suitable for oral, parenteral, or intravenous infusion administration.

[0018] In yet other embodiments said pharmaceutical composition comprises a tablet, or capsule.

[0019] In certain embodiments the compounds as disclosed herein are administered in a dose of 0.5 milligram to 1000 milligram.

[0020] In yet further embodiments said pharmaceutical compositions further comprise another therapeutic agent.

[0021] In other embodiments said therapeutic agent is selected from the group consisting of antipsychotic medications, antidepressants, 5-HT_{2C} receptor modulators, endothelin converting enzyme (ECE) inhibitors, thromboxane enzyme antagonists, potassium channel openers, thrombin inhibitors, growth factor inhibitors, platelet activating factor (PAF) antagonists, anti-platelet agents, Factor VIa Inhibitors, Factor Xa Inhibitors, renin inhibitors, neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, anti-atherosclerotic agents, MTP Inhibitors, calcium channel blockers, potassium channel activators, alpha-PDE5 agents, beta-PDE5 agents, antiarrhythmic agents, diuretics, anti-diabetic agents, PPAR-gamma agonists, mineralocorticoid enzyme antagonists, aP2 inhibitors, protein tyrosine kinase inhibitors, antiinflammatories, antiproliferatives, chemotherapeutic agents, immunosuppressants, anticancer agents, cytotoxic agents, antimetabolites, farnesyl-protein transferase inhibitors, hormonal agents, microtubule-disruptor agents, microtubule-stabilizing agents, topoisomerase inhibitors, prenyl-protein transferase inhibitors, cyclosporins, TNF-alpha inhibitors,

[0022] In other embodiments said therapeutic agent is an antipsychotic medication.

[0023] In further embodiments said antipsychotic medication is selected from the group consisting of chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, haloperidol, haloperidol decanoate, droperidol, pimozide, amisulpride, aripiprazole, bifeprunox, clozapine, melperone, norclozapine, olanzapine, risperidone, paliperidone, quetapine, symbyax, tetrabenazine, and ziprazidone.

[0024] In other embodiments said therapeutic agent is an antidepressant.

[0025] In further embodiments said antidepressant is selected from the group consisting of amitriptyline, bupropion, citalopram, clomipramine, dapoxetine, desipramine, dothiepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, iofepramine, nortriptyline, paroxetine, protriptyline, sertraline, trazodone, trimipramine, and venlafaxine.

[0026] In other embodiments said therapeutic agent is a 5-HT_{2C} receptor modulator.

[0027] In yet other embodiments said 5-HT_{2C} receptor modulator is selected from the group consisting of alpha-methyl-5-HT, DOI, lysergic acid diethylamide (LSD), and mesulergine.

[0028] In further embodiments, a method for the treatment, prevention, or amelioration of one or more symptoms of a MT receptor-mediated disorder, a 5-HT receptor mediated disorder, or a MT receptor-mediated disorder and 5-HT receptor mediated disorder in a subject comprises administering a therapeutically effective amount of a compound as disclosed herein.

[0029] In other embodiments said MT receptor-mediated disorder, said 5-HT receptor mediated disorder, or said MT receptor-mediated disorder and 5-HT receptor mediated disorder is selected from the group consisting of depressive disorders, seasonal affective disorders, anxiety, sleep disorders, dysthymia, and sexual side effects associated with the use of 5-HT_2C agonists.

[0030] In further embodiments, said 5-HT receptor mediated disorder, or said MT receptor-mediated disorder and 5-HT receptor mediated disorder can be lessened, alleviated, or prevented by administering a 5HT receptor modulator.

[0031] In further embodiments, said MT receptor-mediated disorder, or said MT receptor-mediated disorder and 5-HT receptor mediated disorder can be lessened, alleviated, or prevented by administering a MT receptor modulator.

[0032] In other embodiments said compound has at least one of the following properties:

[0033] a) decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound;

[0034] b) increased average plasma levels of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;

[0035] c) decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;

[0036] d) increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and

[0037] e) an improved clinical effect during the treat-

[0038] In yet further embodiments said compound has at least two of the following properties:

[0039] a) decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the non-isotopically enriched compound;

[0040] b) increased average plasma levels of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;

[0041] c) decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound;

[0042] d) increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and

[0043] e) an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0044] In certain embodiments said compound has a decreased metabolism by at least one polymorphically-expressed cytochrome P_{450} isoform in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0045] In other embodiments said cytochrome P_{450} isoform is selected from the group consisting of CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

[0046] In yet further embodiments said compound is characterized by decreased inhibition of at least one cytochrome P_{450} or monoamine oxidase isoform in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0047] In certain embodiments said cytochrome P_{450} or monoamine oxidase isoform is selected from the group consisting of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, CYP51, MAOA, and MAOB.

[0048] In other embodiments said method affects the treatment of the disorder while reducing or eliminating a deleterious change in a diagnostic hepatobiliary function endpoint, as compared to the corresponding non-isotopically enriched compound.

[0049] In yet further embodiments said diagnostic hepatobiliary function endpoint is selected from the group consisting of alanine aminotransferase ("ALT"), serum glutamic-pyruvic transaminase ("SGPT"), aspartate aminotransferase ("AST," "SGOT"), ALT/AST ratios, serum aldolase, alkaline phosphatase ("ALP"), ammonia levels, bilirubin, gamma-glutamyl transpeptidase ("GGTP," "γ-GTP," "GGT"), leucine aminopeptidase ("LAP"), liver biopsy, liver ultrasonography, liver nuclear scan, 5'-nucleotidase, and blood protein.

INCORPORATION BY REFERENCE

[0050] All publications and references cited herein, including those in the background section, are expressly incorporated herein by reference in their entirety. However, with put forth or defined in this document, then those terms definitions or meanings expressly put forth in this document shall control in all respects.

DETAILED DESCRIPTION

[0051] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood in the art to which this disclosure belongs. In the event that there is a plurality of definitions for a term used herein, those in this section prevail unless stated otherwise.

[0052] As used herein, the singular forms "a," "an," and "the" may refer to plural articles unless specifically stated otherwise.

[0053] The term "subject" refers to an animal, including, but not limited to, a primate (e.g., human monkey, chimpanzee, gorilla, and the like), rodents (e.g., rats, mice, gerbils, hamsters, ferrets, and the like), lagomorphs, swine (e.g., pig, miniature pig), equine, canine, feline, and the like. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human patient.

[0054] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder; or alleviating or abrogating one or more of the symptoms associated with the disorder; and/or alleviating or eradicating the cause (s) of the disorder itself.

[0055] The terms "prevent," "preventing," and "prevention" refer to a method of delaying or precluding the onset of a disorder; delaying or precluding its attendant symptoms; barring a subject from acquiring a disorder; and/or reducing a subject's risk of acquiring a disorder.

[0056] The term "therapeutically effective amount" refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder being treated. The term "therapeutically effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0057] The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. Each component must be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation. It must also be suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenecity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. See, *Remington: The Science and Practice of Pharmacy,* 21 st Edition; Lippincott Williams & Wilkins: Philadelphia, Pa., 2005*; Handbook of Pharmaceutical Excipients,* 5th Edition; Rowe et al., Eds., The Pharmaceuti-

tion; Ash and Ash Eds., Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, Gibson Ed., CRC Press LLC: Boca Raton, Fla., 2004).

[0058] The term "deuterium enrichment" refers to the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The deuterium enrichment can be determined using conventional analytical methods, such as mass spectrometry and nuclear magnetic resonance spectroscopy.

[0059] The term "is/are deuterium," when used to describe a given position in a molecule such as R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16} and R_{17} or the symbol "D," when used to represent a given position in a drawing of a molecular structure, means that the specified position is enriched with deuterium above the naturally occurring distribution of deuterium. In an embodiment deuterium enrichment is of no less than about 1%, in another no less than about 5%, in another no less than about 10%, in another no less than about 20%, in another no less than about 50%, in another no less than about 70%, in another no less than about 80%, in another no less than about 90%, or in another no less than about 98% of deuterium at the specified position.

[0060] The term "isotopic enrichment" refers to the percentage of incorporation of a less prevalent isotope of an element at a given position in a molecule in the place of the more prevalent isotope of the element.

[0061] The term "non-isotopically enriched" refers to a molecule in which the percentages of the various isotopes are substantially the same as the naturally occurring percentages.

[0062] The terms "substantially pure" and "substantially homogeneous" mean sufficiently homogeneous to appear free of readily detectable impurities as determined by standard analytical methods, including, but not limited to, thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), and mass spectrometry (MS); or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, or biological and pharmacological properties, such as enzymatic and biological activities, of the substance. In certain embodiments, "substantially pure" or "substantially homogeneous" refers to a collection of molecules, wherein at least about 50%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% of the molecules are a single compound, including a racemic mixture or single stereoisomer thereof, as determined by standard analytical methods.

[0063] The term "about" or "approximately" means an acceptable error for a particular value, which depends in part on how the value is measured or determined. In certain embodiments, "about" can mean 1 or more standard deviations.

[0064] The terms "active ingredient" and "active substance" refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable

[0065] The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder.

[0066] The term "disorder" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disease," "sydrome" and "condition" (as in medical condition), in that all reflect an abnormal condition of the body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms.

[0067] The term "release controlling excipient" refers to an excipient whose primary function is to modify the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

[0068] The term "nonrelease controlling excipient" refers to an excipient whose primary function do not include modifying the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

[0069] The term "Melatonin receptor" or "MT receptor" refers to receptors which bind the hormone melatonin. For example, "Melatonin receptor" or "MT receptor" would include the G-protein coupled melatonin M_1 receptor (also known as MTNR1A) and the G-protein coupled melatonin M_2 receptor (also known as MTNR1B).

[0070] The term "5-HT receptor" refers to the receptors for the neurotransmitter and peripheral signal mediator serotonin, also known as 5-hydroxytryptamine or 5-HT. 5-HT receptors are located on the cell membrane of nerve cells and other cell types including smooth muscle in animals, and mediate the effects of serotonin (the endogenous ligand) as well as a broad range of pharmaceutical and hallucinogenic drugs. 5-HT receptors affect the release and activity of other neurotransmitters such as glutamate, dopamine and GABA. The term "5-HT receptor" refers to all the various subtypes of the 5-HT receptor. For example, "5-HT receptor" would include the $5\text{-}HT_{2C}$ receptor. $5\text{-}HT_{2C}$ receptors may control intracellular levels of inositol triphosphate (IP_3) and/or diacylglycerol (DAG). The $5\text{-}HT_{2C}$ receptor was formerly called the "$5\text{-}HT_{1C}$ receptor" in some previous publications.

[0071] The term "MT receptor modulator" or "modulation of MT receptors" refers to the ability of a compound disclosed herein to alter the function of an MT receptor. A modulator may activate the activity of an MT receptor, may activate or inhibit the activity of an MT receptor depending on the concentration of the compound exposed to the MT receptor, or may inhibit the activity of an MT receptor. Such activation or inhibition may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway, and/or may be manifest only in particular cell types. The term "MT receptor modulator" or "modulation of MT receptors" also refers to altering the function of an MT receptor by increasing or decreasing the probability that a complex forms between an MT receptor and a natural binding partner. A MT receptor modulator may increase the probability that such a complex forms between the MT receptor and the natural binding partner, may increase or decrease the probability that a complex forms between the MT receptor and the natural binding partner depending on the concentration of the com-

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