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(54) Title: AMIDOETHYL AZOLE OREXIN RECEPTOR ANTAGONISTS

(57) Abstract: An amidoethyl azole compounds are provided as antagonists of orexin receptors. The compounds may be used for treatment or prevention of neurological and psychiatric disorders and diseases in which orexin receptors are involved.

AMIDOETHYL AZOLE OREXIN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

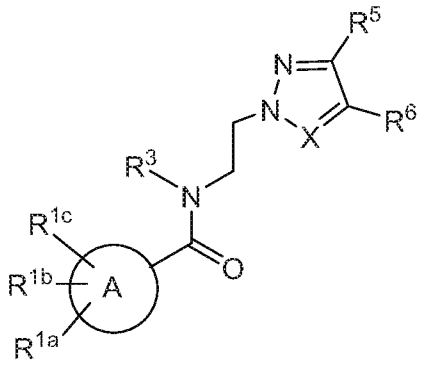
The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: orexin A (OX-A) (a 33 amino acid peptide) and the orexin B (OX-B) (a 28 amino acid peptide) (Sakurai T. et al., Cell, 1998, 92, 573-585). Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior (Sakurai T. et al., Cell, 1998, 92, 573-585). Orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches for narcoleptic or insomniac patients (Chemelli R.M. et al., Cell, 1999, 98, 437-451). Orexins have also been indicated as playing a role in arousal, reward, learning and memory (Harris, et al., Trends Neurosci., 2006, 29 (10), 571-577). Two orexin receptors have been cloned and characterized in mammals. They belong to the super family of G-protein coupled receptors (Sakurai T. et al., Cell, 1998, 92, 573-585): the orexin-1 receptor (OX or OX1R) is selective for OX-A and the orexin-2 receptor (OX2 or OX2R) is capable of binding OX-A as well as OX-B. The physiological actions in which orexins are presumed to participate are thought to be expressed via one or both of OX1 receptor and OX2 receptor as the two subtypes of orexin receptors.

SUMMARY OF THE INVENTION

The present invention is directed to amidoethyl azole compounds which are antagonists of orexin receptors. The present invention is also directed to uses of the compounds described herein in the potential treatment or prevention of neurological and psychiatric disorders and diseases in which orexin receptors are involved. The present invention is also directed to compositions comprising these compounds. The present invention is also directed to uses of these compositions in the potential prevention or treatment of such diseases in which orexin receptors are involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



I

wherein:

A is selected from the group consisting of phenyl, naphthyl and heteroaryl;

X is N or CH;

each of R^{1a}, R^{1b} and R^{1c} is independently selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) $-(C=O)_m-O_n-C_{1-6}$alkyl, where m is 0 or 1, n is 0 or 1 (wherein if m is 0 or n is 0, a bond is present) and where the alkyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(5) $-(C=O)_m-O_n-C_{3-6}$cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(6) $-(C=O)_m-C_{2-4}$alkenyl, where the alkenyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(7) $-(C=O)_m-C_{2-4}$alkynyl, where the alkynyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(8) $-(C=O)_m-O_n$-phenyl or $-(C=O)_m-O_n$-naphthyl, where the phenyl or naphthyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(9) $-(C=O)_m-O_n$-heterocycle, where the heterocycle is unsubstituted or substituted with one to three substituents independently selected from R^4,

(10) $-(C=O)_m-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from the group consisting of:

(a) hydrogen,

(b) C_{1-6}alkyl, which is unsubstituted or substituted with R^4,

(c) C_{3-6}alkenyl, which is unsubstituted or substituted with R^4,

(d) C_{3-6}alkynyl, which is unsubstituted or substituted with R^4,

(e) C_{3-6}cycloalkyl which is unsubstituted or substituted with R^4,

(f) phenyl, which is unsubstituted or substituted with R^4, and

(g) heterocycle, which is unsubstituted or substituted with R^4,

(11) $-S(O)_2-NR^{10}R^{11}$,

(12) $-S(O)_q-R^{12}$, where q is 0, 1 or 2 and where R^{12} is selected from the definitions of R^{10} and R^{11},

(13) $-CO_2H$,

(14) -CN, and

(15) $-NO_2$;

R^3 is selected from hydrogen and C_{1-6}alkyl;

R^4 is selected from the group consisting of:

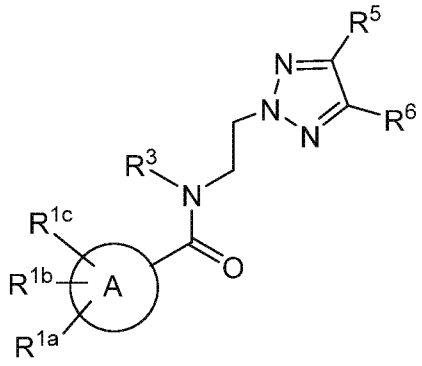
(1) hydroxyl,
(2) halogen,
(3) C_{1-6}alkyl,
(4) -C_{3-6}cycloalkyl,
(5) -O-C_{1-6}alkyl,
(6) -O(C=O)-C_{1-6}alkyl,
(7) -NH_2,
(8) -NH-C_{1-6}alkyl,
(9) -NO_2,
(10) phenyl,
(11) heterocycle,
(12) -CO_2H, and
(13) -CN;

R^5 is selected from the group consisting of:
(1) hydrogen,
(2) halogen,
(3) C_{1-6}alkyl, which is unsubstituted or substituted with halogen or hydroxyl,
(4) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen, and
(5) -(C=O)-O-C_{1-6}alkyl;

R^6 is selected from the group consisting of:
(1) hydrogen,
(2) halogen,
(3) C_{1-6}alkyl, which is unsubstituted or substituted with halogen or hydroxyl,
(4) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen, and
(5) -(C=O)-O-C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

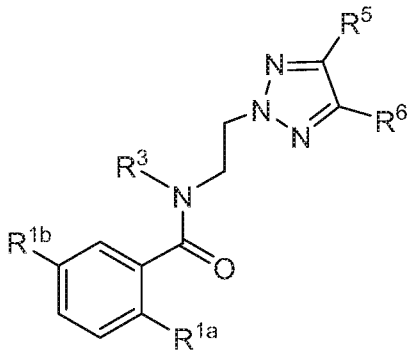
An embodiment of the present invention includes compounds of the formula Ia:



Ia

wherein A, R^{1a}, R^{1b}, R^{1c}, R^3, R^5 and R^6 are defined herein; or a pharmaceutically acceptable salt thereof.

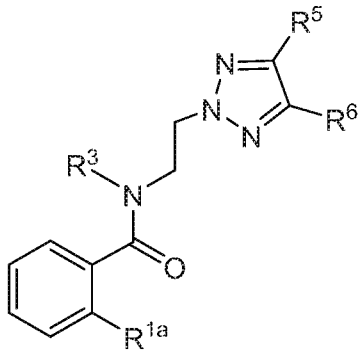
An embodiment of the present invention includes compounds of the formula Ia':



Ia'

wherein R^{1a}, R^{1b}, R^3, R^5 and R^6 are defined herein; or a pharmaceutically acceptable salt thereof.

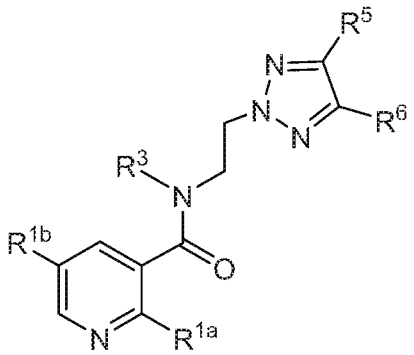
An embodiment of the present invention includes compounds of the formula Ia":



Ia"

wherein R^{1a}, R^3, R^5 and R^6 are defined herein; or a pharmaceutically acceptable salt thereof.

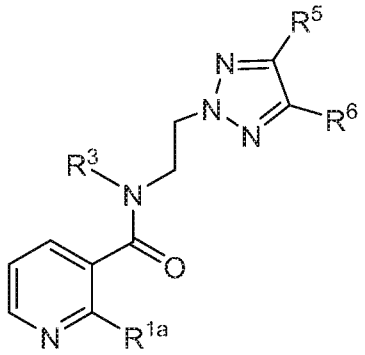
An embodiment of the present invention includes compounds of the formula Ib:



Ib

wherein R^{1a}, R^{1b}, R^3, R^5 and R^6 are defined herein; or a pharmaceutically acceptable salt thereof.

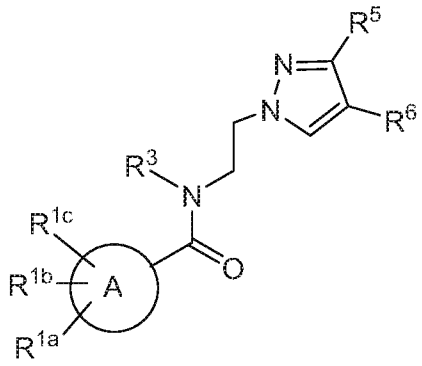
An embodiment of the present invention includes compounds of the formula Ib':



Ib'

wherein R^{1a}, R^3, R^5 and R^6 are defined herein; or a pharmaceutically acceptable salt thereof.

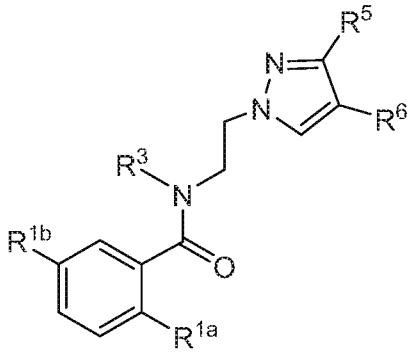
An embodiment of the present invention includes compounds of the formula Ic:



Ic

wherein R^{1a}, R^{1b}, R^2, R^3, R^5 and R^6 are defined herein; or a pharmaceutically acceptable salt thereof.

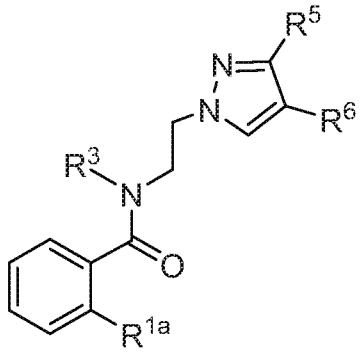
An embodiment of the present invention includes compounds of the formula Ic':



Ic'

wherein R^{1a}, R^{1b}, R^3, R^5 and R^6 are defined herein; or a pharmaceutically acceptable salt thereof.

An embodiment of the present invention includes compounds of the formula Ib":



Ic"

wherein R^{1a}, R^3, R^5 and R^6 are defined herein; or a pharmaceutically acceptable salt thereof.

An embodiment of the present invention includes compounds wherein A is selected from phenyl, pyridyl, thiophenyl, thiazolyl, isothiazolyl, and pyrazolyl. An embodiment of the present invention includes compounds wherein A is phenyl. An embodiment of the present invention includes compounds wherein A is pyridyl. An embodiment of the present invention includes compounds wherein A is thiophenyl. An embodiment of the present invention includes compounds wherein A is thiazolyl. An embodiment of the present invention includes compounds wherein A is isothiazolyl. An embodiment of the present invention includes compounds wherein A is pyrazolyl.

An embodiment of the present invention includes compounds wherein X is N. An embodiment of the present invention includes compounds wherein X is CH.

An embodiment of the present invention includes compounds wherein R^{1a}, R^{1b} and R^{1c} are independently selected from the group consisting of:

(1) hydrogen,
(2) halogen,
(3) hydroxyl,
(4) C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,
(5) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,
(6) heteroaryl, wherein heteroaryl is selected from imidazolyl, indolyl, oxazolyl, pyridyl, pyrrolyl, pyrimidinyl, tetrazolyl, and triazolyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2,
(7) phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2,
(8) -O-phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or -NO_2,
(9) -CN, and
(10) -NH-C_{1-6}alkyl, or -N(C_{1-6}alkyl)(C_{1-6}alkyl), which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, and -O-C_{1-6}alkyl.

An embodiment of the present invention includes compounds wherein R^{1a}, R^{1b} and R^{1c} are independently selected from the group consisting of:

(1) hydrogen,
(2) halogen,
(3) hydroxyl,
(4) C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,
(5) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,
(6) -CN, and
(7) heteroaryl, wherein heteroaryl is selected from imidazolyl, indolyl, oxazolyl, pyridyl, pyrrolyl, pyrimidinyl, tetrazolyl, and triazolyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2.

An embodiment of the present invention includes compounds wherein R^{1a}, R^{1b} and R^{1c} are independently selected from the group consisting of:

(1) hydrogen,
(2) halogen,
(3) C_{1-6}alkyl, which is unsubstituted or substituted with halogen,
(4) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen,
(5) -CN, and
(6) heteroaryl, wherein heteroaryl is selected from imidazolyl, indolyl, oxazolyl, pyridyl, pyrrolyl, pyrimidinyl, tetrazolyl, and triazolyl.

An embodiment of the present invention includes compounds wherein R^{1c} is hydrogen, and R^{1a} and R^{1b} are independently selected from the group consisting of:

(1) hydrogen,
(2) fluoro,
(3) chloro,
(4) bromo,
(5) methyl,
(6) ethyl,
(7) methoxy,
(8) trifluoromethyl, and
(9) heteroaryl, wherein heteroaryl is selected from imidazolyl, indolyl, oxazolyl, pyridyl, pyrrolyl, pyrimidinyl, tetrazolyl, and triazolyl.

An embodiment of the present invention includes compounds wherein R^{1c} is hydrogen, and R^{1a} and R^{1b} are independently selected from the group consisting of:

(1) hydrogen,
(2) fluoro,
(3) chloro,
(4) methyl,
(5) methoxy,
(6) tetrazolyl, and
(7) triazolyl.

An embodiment of the present invention includes compounds wherein R^3 is selected from hydrogen, methyl and ethyl. An embodiment of the present invention includes compounds wherein R^3 is ethyl.

An embodiment of the present invention includes compounds wherein R^5 is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) $-C(CH_3)_2OH$,
(4) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with halogen, and
(8) $-C=O)OCH_3$.

An embodiment of the present invention includes compounds wherein R^5 is selected from the group consisting of: methyl and $-C(CH_3)_2OH$.

An embodiment of the present invention includes compounds wherein R^6 is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) $-C(CH_3)_2OH$,
(4) $-CH(OH)CF_3$,
(5) $-CH(OH)CH_3$,
(6) $-C(OH)(CH_3)CH_2CH_3$,
(7) $-C(OH)(CF_3)CH_3$, and
(8) $-C(=O)OCH_3$.

An embodiment of the present invention includes compounds wherein R^6 is selected from the group consisting of:

(1) hydrogen, and
(2) C_{1-6}alkyl, which is unsubstituted or substituted with halogen or hydroxyl.

An embodiment of the present invention includes compounds wherein R^6 is selected from the group consisting of: methyl and $-C(CH_3)_2OH$.

An embodiment of the present invention includes compounds wherein R^5 is $-C(CH_3)_2OH$ and R^6 is hydrogen or methyl. An embodiment of the present invention includes compounds wherein R^5 is $-C(CH_3)_2OH$ and R^6 is methyl. An embodiment of the present invention includes compounds wherein R^5 is $-C(CH_3)_2OH$ and R^6 is hydrogen. An embodiment of the present invention includes compounds wherein R^5 is methyl and R^6 is $-C(CH_3)_2OH$.

Certain embodiments of the present invention include a compound which is selected from the group consisting of the subject compounds of the Examples herein or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be

present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. Formula I shows the structure of the class of compounds without specific stereochemistry.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art. Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

As appreciated by those of skill in the art, halogen or halo as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C_{1-6}, as in C_{1-6}alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_{1-6}alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and hexyl. A group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents. The term " heteroaryl" as used herein includes benzoimidazolyl, benzimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzothiazolyl, benzotriazolyl, benzothiophenyl, benzoxazepin, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, dihydroindolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydroquinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and N-oxides thereof, and wherein the saturated heterocyclic moieties include azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, thiomorpholinyl, and tetrahydrothienyl, and N-oxides thereof.

The present invention also includes all pharmaceutically acceptable isotopic variations of a compound of the Formula I in which one or more atoms is replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen such as ^{2}H and ^{3}H, carbon such as ^{11}C, ^{13}C and ^{14}C, nitrogen such as ^{13}N and ^{15}N, oxygen such as ^{15}O, ^{17}O and ^{18}O, phosphorus such as ^{32}P, sulfur such as ^{35}S, fluorine such as ^{18}F, iodine such as ^{123}I and ^{125}I, and chlorine such as ^{36}Cl. Certain isotopically-labelled compounds of Formula I, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labelled compounds of Formula I can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using appropriate isotopically-labelled reagents in place of the non-labelled reagent previously employed.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particular embodiments include the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particular embodiments include the citric, hydrobromic,

hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which is selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual enantiomers or diastereomers thereof.

The present invention is also directed to the use of the compounds disclosed herein as antagonists of orexin receptor activity. The subject compounds and pharmaceutically acceptable salts thereof are useful in a method of antagonizing orexin receptor activity in a subject such as a mammal comprising the administration of an amount of the compound. In addition to primates, especially humans, a variety of other mammals may be administered with a compound of the present invention. The present invention is directed to a compound of the present invention or a pharmaceutically acceptable salt thereof that could be useful in thereapy. The present invention may further be directed to a use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for antagonizing orexin receptor activity or treating the disorders and diseases noted herein in humans and animals.

A subject administered with a compound of the present invention, or a pharmaceutically acceptable salt thereof, is generally a mammal, such as a human being, male or female. The amount of compound administered to the subject is an amount sufficient to antagonize the orexin receptor in the subject. In an embodiment, the amount of compound can be an "effective amount", wherein the subject compound is administered in an amount that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. An effective amount does not necessarily include considerations of toxicity and safety related to the administration of the compound. It is recognized that one skilled in the art may affect neurological and psychiatric disorders associated with orexin receptor activation by treating a subject presently afflicted with the disorders, or by prophylactically treating a subject likely to be afflicted with the disorders, with an effective amount of a compound of the present invention. As used herein, the terms "treatment" and "treating" refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the neurological and psychiatric disorders described herein, but does not necessarily indicate a total elimination of all disorder symptoms, as well as the prophylactic therapy of the mentioned conditions, particularly in a subject that is predisposed to such disease or disorder. The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to to the subject.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which

results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The utility of the compounds in accordance with the present invention as orexin receptor OX1R and/or OX2R antagonists may be readily determined without undue experimentation by methodology well known in the art, including the "FLIPR Ca^{2+} Flux Assay" (Okumura et al., Biochem. Biophys. Res. Comm. 280:976-981, 2001). In a typical experiment the OX1 and OX2 receptor antagonistic activity of the compounds of the present invention was determined in accordance with the following experimental method. For intracellular calcium measurements, Chinese hamster ovary (CHO) cells expressing the rat orexin-1 receptor or the human orexin-2 receptor, are grown in Iscove's modified DMEM containing 2 mM L-glutamine, 0.5 g/ml G418, 1% hypoxanthine-thymidine supplement, 100 U/ml penicillin, 100 µg/ml streptomycin and 10 % heat-inactivated fetal calf serum (FCS). The cells are seeded at 20,000 cells / well into Becton-Dickinson black 384-well clear bottom sterile plates coated with poly-D-lysine. All reagents were from GIBCO-Invitrogen Corp. The seeded plates are incubated overnight at 37°C and 5% CO2. Ala-6,12 human orexin-A as the agonist is prepared as a 1 mM stock solution in 1% bovine serum albumin (BSA) and diluted in assay buffer (HBSS containing 20 mM HEPES, 0.1% BSA and 2.5mM probenecid, pH7.4) for use in the assay at a final concentration of 70pM. Test compounds are prepared as 10 mM stock solution in DMSO, then diluted in 384-well plates, first in DMSO, then assay buffer. On the day of the assay, cells are washed 3 times with 100 µl assay buffer and then incubated for 60 min (37° C, 5% CO2) in 60 µl assay buffer containing 1 µM Fluo-4AM ester, 0.02 % pluronic acid, and 1 % BSA. The dye loading solution is then aspirated and cells are washed 3 times with 100 µl assay buffer. 30 µl of that same buffer is left in each well. Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), test compounds are added to the plate in a volume of 25 µl, incubated for 5 min and finally 25 µl of agonist is added. Fluorescence is measured for each well at 1 second intervals for 5 minutes and the height of each fluorescence peak is compared to the height of the fluorescence peak induced by 70 pM Ala-6,12 orexin-A with buffer in place of antagonist. For each antagonist, IC50 value (the concentration of compound needed to inhibit 50 % of the agonist response) is determined. Alternatively, compound potency can be assessed by a radioligand binding assay (described in Bergman et. al. Bioorg. Med. Chem. Lett. 2008, 18, 1425 - 1430) in which the inhibition constant (K_i) is determined in membranes prepared from CHO cells expressing either the OX1 or OX2 receptor. The intrinsic orexin receptor antagonist

activity of a compound which may be used in the present invention may be determined by these assays.

All of the final compounds of the following examples had activity in antagonizing the human orexin-2 receptor in the aforementioned assays with an IC_{50} of about 0.1 nM to 1500 nM. All of the final compounds of the following examples had activity in the FLIPR assay with an IC50 of about 5 nM to 500 nM against the orexin-2 receptor. Additional data is provided in the following Examples. Such a result is indicative of the intrinsic activity of the compounds in use as antagonists of orexin-1 receptor and/or the orexin-2 receptor. In general, one of ordinary skill in the art would appreciate that a substance is considered to effectively antagonize the orexin receptor if it has an IC50 of less than about 50 μM, or more specifically less than about 1000 nM.

The orexin receptors have been implicated in a wide range of biological functions. This has suggested a potential role for these receptors in a variety of disease processes in humans or other species. The compounds of the present invention could therefore potentially have utility in treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with orexin receptors, including one or more of the following conditions or diseases: sleep disorders, sleep disturbances, including enhancing sleep quality, improving sleep quality, increasing sleep efficiency, augmenting sleep maintenance; increasing the value which is calculated from the time that a subject sleeps divided by the time that a subject is attempting to sleep; improving sleep initiation; decreasing sleep latency or onset (the time it takes to fall asleep); decreasing difficulties in falling asleep; increasing sleep continuity; decreasing the number of awakenings during sleep; decreasing intermittent wakings during sleep; decreasing nocturnal arousals; decreasing the time spent awake following the initial onset of sleep; increasing the total amount of sleep; reducing the fragmentation of sleep; altering the timing, frequency or duration of REM sleep bouts; altering the timing, frequency or duration of slow wave (i.e. stages 3 or 4) sleep bouts; increasing the amount and percentage of stage 2 sleep; promoting slow wave sleep; enhancing EEG-delta activity during sleep; decreasing nocturnal arousals, especially early morning awakenings; increasing daytime alertness; reducing daytime drowsiness; treating or reducing excessive daytime sleepiness; increasing satisfaction with the intensity of sleep; increasing sleep maintenance; idiopathic insomnia; sleep problems; insomnia, hypersomnia, idiopathic hypersomnia, repeatability hypersomnia, intrinsic hypersomnia, narcolepsy, interrupted sleep, sleep apnea, wakefulness, nocturnal myoclonus, REM sleep interruptions, jet-lag, shift workers' sleep disturbances, dyssomnias, night terror, insomnias associated with depression, emotional/mood disorders, Alzheimer's disease or cognitive impairment, as well as sleep walking and enuresis, and sleep disorders which accompany aging; Alzheimer's sundowning; conditions associated with circadian rhythmicity as well as mental and physical disorders associated with travel across time zones and with rotating shift-work schedules, conditions due to drugs which cause reductions in REM sleep as a side effect; fibromyalgia; syndromes which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with

respiratory disturbances during sleep; conditions which result from a diminished quality of sleep; increasing learning; augmenting memory; increasing retention of memory; eating disorders associated with excessive food intake and complications associated therewith, compulsive eating disorders, obesity (due to any cause, whether genetic or environmental), obesity-related disorders overeating, anorexia, bulimia, cachexia, dysregulated appetite control, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, lung disease, abnormal heart rhythms and arrythmias, myocardial infarction, congestive heart failure, coronary heart disease, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardinal infarction; ischemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; sudden death, polycystic ovary disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia, metabolic syndrome, also known as syndrome X, insulin resistance syndrome, reproductive hormone abnormalities, sexual and reproductive dysfunction, such as impaired fertility, infertility, hypogonadism in males and hirsutism in females, fetal defects associated with maternal obesity, gastrointestinal motility disorders, intestinal motility dyskinesias, obesity-related gastro-esophageal reflux, hypothalmic diseases, hypophysis diseases, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), breathlessness, cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, kidney cancer, increased anesthetic risk, reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy; diseases or disorders where abnormal oscillatory activity occurs in the brain, including depression, migraine, neuropathic pain, Parkinson's disease, psychosis and schizophrenia, as well as diseases or disorders where there is abnormal coupling of activity, particularly through the thalamus; enhancing cognitive function, including cognitive dysfunctions that comprise deficits in all types of attention, learning and memory functions occurring transiently or chronically in the normal, healthy, young, adult or aging population, and also occurring transiently or chronically in psychiatric, neurologic, cardiovascular and immune disorders; enhancing memory; increasing memory retention; increasing immune response; increasing immune function; hot flashes; night sweats; extending life span; schizophrenia; muscle-related disorders that are controlled by the excitation/relaxation rhythms imposed by the neural system such as cardiac rhythm and other disorders of the cardiovascular system; conditions related to proliferation of cells such as vasodilation or vasorestriction and blood pressure; cancer; cardiac arrhythmia; hypertension; congestive heart failure; conditions of the genital/urinary system; disorders of sexual function and fertility; adequacy of renal function; responsivity to anesthetics; mood disorders, such as

depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder, mood disorders due to a general medical condition, and substance-induced mood disorders; affective neurosis; depressive neurosis; anxiety neurosis; anxiety disorders including acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic attack, panic disorder, post-traumatic stress disorder, separation anxiety disorder, social phobia, specific phobia, substance-induced anxiety disorder and anxiety due to a general medical condition; acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, ischemic stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage; Huntington's Chorea; Huntington's disease and Tourette syndrome; Cushing's syndrome/disease; basophile adenoma; prolactinoma; hyperprolactinemia; hypophysis tumor/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric diskinesia; gastric ulcers; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic- adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; amyotrophic lateral sclerosis; multiple sclerosis; ocular damage; retinopathy; cognitive disorders; idiopathic and drug-induced Parkinson's disease; muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, seizure disorders, absence seisures, complex partial and generalized seizures; Lennox-Gastaut syndrome; cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnestic disorders or age related cognitive decline; schizophrenia or psychosis including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance-induced psychotic disorder; dissociative disorders including multiple personality syndromes and psychogenic amnesias; substance-related disorders, substance use, substance abuse, substance seeking, substance reinstatement, all types of psychological and physical addictions and addictive behaviors, reward-related behaviors (including substance-induced delirium, persisting dementia, persisting amnestic disorder, psychotic disorder or anxiety disorder; tolerance, addictive feeding, addictive feeding behaviors, binge/purge feeding behaviors, dependence, withdrawal or relapse from substances including alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, morphine, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics); appetite, taste, eating or drinking disorders; movement disorders, including akinesias and akinetic-rigid syndromes (including Parkinson's disease, drug-induced parkinsonism, postencephalitic

parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification), chronic fatigue syndrome, fatigue, including Parkinson's fatigue, multiple sclerosis fatigue, fatigue caused by a sleep disorder or a circadian rhythm disorder, medication-induced parkinsonism (such as neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor), Gilles de la Tourette's syndrome, epilepsy, and dyskinesias [including tremor (such as rest tremor, essential tremor, postural tremor and intention tremor), chorea (such as Sydenham's chorea, Huntington's disease, benign hereditary chorea, neuroacanthocytosis, symptomatic chorea, drug-induced chorea and hemiballism), myoclonus (including generalised myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics), restless leg syndrome and dystonia (including generalised dystonia such as iodiopathic dystonia, drug-induced dystonia, symptomatic dystonia and paroxymal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, spasmodic dysphonia, spasmodic torticollis, axial dystonia, dystonic writer's cramp and hemiplegic dystonia); neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration; epilepsy; seizure disorders; attention deficit/hyperactivity disorder (ADHD); conduct disorder; migraine (including migraine headache); headache; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; emesis, nausea, vomiting; gastric dyskinesia; gastric ulcers; Kallman's syndrome (anosmia); asthma; cancer; conditions associated with visceral pain such as irritable bowel syndrome, and angina; eating disorders; urinary incontinence; substance tolerance, substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.); psychosis; schizophrenia; anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder); mood disorders (including depression, mania, bipolar disorders); trigeminal neuralgia; hearing loss; tinnitus; neuronal damage including ocular damage; retinopathy; macular degeneration of the eye; emesis; brain edema; pain, including acute and chronic pain states, severe pain, intractable pain, inflammatory pain, neuropathic pain, post-traumatic pain, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain, neuropathic pain, post-traumatic pain, trigeminal neuralgia, migraine and migraine headache and other diseases related to general orexin system dysfunction.

Thus, in certain embodiments the present invention may provide methods for: enhancing the quality of sleep; augmenting sleep maintenance; increasing REM sleep; increasing stage 2 sleep; decreasing fragmentation of sleep patterns; treating insomnia and all types of sleep disorders; treating or controlling sleep disturbances associated with diseases such as neurological

disorders including neuropathic pain and restless leg syndrome; treating or controlling addiction disorders; treating or controlling psychoactive substance use and abuse; enhancing cognition; increasing memory retention; treating or controlling obesity; treating or controlling diabetes and appetite, taste, eating, or drinking disorders; treating or controlling hypothalamic diseases; treating or controlling depression; treating, controlling, ameliorating or reducing the risk of epilepsy, including absence epilepsy; treating or controlling pain, including neuropathic pain; treating or controlling Parkinson's disease; treating or controlling psychosis; treating or controlling dysthymic, mood, psychotic and anxiety disorders; treating or controlling depression, including major depression and major depression disorder; treating or controlling bipolar disorder; or treating, controlling, ameliorating or reducing the risk of schizophrenia, in a mammalian subject which comprises administering to the subject a compound of the present invention.

The subject compounds could further be of potential use in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein. The dosage of active ingredient in the compositions of this invention may be varied, however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The active ingredient may be administered to subjects (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. The dose will vary from subject to subject depending upon the nature and severity of disease, the subject's weight, special diets then being followed by a subject, concurrent medication, and other factors which those skilled in the art will recognize. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered to the subject, e.g., humans and elderly humans, to obtain effective antagonism of orexin receptors. The dosage range will generally be about 0.5 mg to 1.0 g. per subject per day which may be administered in single or multiple doses. In one embodiment, the dosage range will be about 0.5 mg to 500 mg per subject per day; in another embodiment about 0.5 mg to 200 mg per subject per day; and in yet another embodiment about 5 mg to 50 mg per subject per day. Pharmaceutical compositions of the present invention may be provided in a solid dosage formulation such as comprising about 0.5 mg to 500 mg active ingredient, or comprising about 1 mg to 250 mg active ingredient. The pharmaceutical composition may be provided in a solid dosage formulation comprising about 1 mg, 5 mg, 10 mg, 25 mg, 30 mg, 50 mg, 80 mg, 100 mg, 200 mg or 250 mg active ingredient. For oral administration, the compositions may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, such as 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, such as once or twice per day. The compounds may be administered before bedtime. For example, the compounds may be administered about 1Hour prior to bedtime, about 30 minutes prior to bedtime or immediately before bedtime.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of the present invention or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present invention is contemplated. However, the combination therapy may also include therapies in which the compound of the present invention and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the present invention. The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds.

Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is contemplated. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, such as about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used. In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered in combination with other compounds which are known in the art to be useful for enhancing sleep quality and

preventing and treating sleep disorders and sleep disturbances, including e.g., sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, antihistamines, benzodiazepines, barbiturates, cyclopyrrolones, GABA agonists, 5HT-2 antagonists including 5HT-2A antagonists and 5HT-2A/2C antagonists, histamine antagonists including histamine H3 antagonists, histamine H3 inverse agonists, imidazopyridines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, other orexin antagonists, orexin agonists, prokineticin agonists and antagonists, pyrazolopyrimidines, T-type calcium channel antagonists, triazolopyridines, and the like, such as: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, armodafinil, APD-125, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capromorelin, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, conazepam, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, EMD-281014, eplivanserin, estazolam, eszopiclone, ethchlorynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, gaboxadol, glutethimide, halazepam, hydroxyzine, ibutamoren, imipramine, indiplon, lithium, lorazepam, lormetazepam, LY-156735, maprotiline, MDL-100907, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, methyprylon, midaflur, midazolam, modafinil, nefazodone, NGD-2-73, nisobamate, nitrazepam, nortriptyline, ornortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, ramelteon, reclazepam, roletamide, secobarbital, sertraline, suproclone, TAK-375, temazepam, thioridazine, tiagabine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zopiclone, zolpidem, and salts thereof, and combinations thereof, and the like, or the compound of the present invention may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

In another embodiment, the subject compound may be employed in combination with other compounds which are known in the art, either administered separately or in the same pharmaceutical compositions, including, but are not limited to: insulin sensitizers including (i) PPARγ antagonists such as glitazones (e.g. ciglitazone; darglitazone; englitazone; isaglitazone (MCC-555); pioglitazone; rosiglitazone; troglitazone; tularik; BRL49653; CLX-0921; 5-BTZD), GW-0207, LG-100641, and LY-300512, and the like); (iii) biguanides such as metformin and phenformin; (b) insulin or insulin mimetics, such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente); Lys-Pro insulin, GLP-1 (73-7) (insulintropin); and GLP-1 (7-36)-NH_2); (c) sulfonylureas, such as acetohexamide; chlorpropamide; diabinese; glibenclamide; glipizide; glyburide; glimepiride; gliclazide; glipentide; gliquidone; glisolamide; tolazamide; and tolbutamide; (d) α-glucosidase inhibitors, such as acarbose, adiposine; camiglibose; emiglitate; miglitol; voglibose; pradimicin-Q; salbostatin; CKD-711; MDL-25,637; MDL-73,945; and MOR 14, and the like; (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (atorvastatin, itavastatin, fluvastatin,

lovastatin, pravastatin, rivastatin, rosuvastatin, simvastatin, and other statins), (ii) bile acid absorbers/sequestrants, such as cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran; Colestid®; LoCholest®, and the like, (ii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iii) proliferator-activater receptor α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), (iv) inhibitors of cholesterol absorption such as stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones such as ezetimibe, and the like, and (acyl CoA:cholesterol acyltransferase (ACAT)) inhibitors such as avasimibe, and melinamide, (v) anti-oxidants, such as probucol, (vi) vitamin E, and (vii) thyromimetics; (f) PPARα agonists such as beclofibrate, benzafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil; and other fibric acid derivatives, such as Atromid®, Lopid® and Tricor®, and the like, and PPARα agonists as described in WO 97/36579; (g) PPARδ agonists, such as those disclosed in WO97/28149; (h) PPAR α/δ agonists, such as muraglitazar, and the compounds disclosed in US 6,414,002; (i) anti-obesity agents, such as (1) growth hormone secretagogues, growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK-0677, SM-130686, CP-424,391, L-692,429, and L-163,255, and such as those disclosed in U.S. Patent Nos. 5,536,716, and 6,358,951, U.S. Patent Application Nos. 2002/049196 and 2002/022637, and PCT Application Nos. WO 01/56592 and WO 02/32888; (2) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; (3) cannabinoid receptor ligands, such as cannabinoid CB_1 receptor antagonists or inverse agonists, such as rimonabant, taranabant, AMT-251, and SR-14778 and SR 141716A (Sanofi Synthelabo), SLV-319 (Solvay), BAY 65-2520 (Bayer) and those disclosed in U.S. Patent Nos. 5,532,237, 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,624,941, 6,028,084, PCT Application Nos. WO 96/33159, WO 98/33765, WO98/43636, WO98/43635, WO 01/09120, WO98/31227, WO98/41519, WO98/37061, WO00/10967, WO00/10968, WO97/29079, WO99/02499, WO 01/58869, WO 01/64632, WO 01/64633, WO 01/64634, W002/076949, WO 03/007887, WO 04/048317, and WO 05/000809; (4) anti-obesity serotonergic agents, such as fenfluramine, dexfenfluramine, phentermine, and sibutramine; (5) β3-adrenoreceptor agonists, such as AD9677/TAK677 (Dainippon/Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, Trecadrine, Zeneca D7114, SR 59119A; (6) pancreatic lipase inhibitors, such as orlistat (Xenical®), Triton WR1339, RHC80267, lipstatin, tetrahydrolipstatin, teasaponin, diethylumbelliferyl phosphate, and those disclosed in PCT Application No. WO 01/77094; (7) neuropeptide Y1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A, and those disclosed in U.S. Patent No. 6,001,836, and PCT Patent Publication Nos. WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528; (8) neuropeptide Y5 antagonists, such as GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR226928, FR 240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104, and those disclosed in U.S. Patent Nos. 6,057,335; 6,043,246; 6,140,354; 6,166,038; 6,180,653; 6,191,160; 6,313,298; 6,335,345; 6,337,332; 6,326,375; 6,329,395; 6,340,683; 6,388,077; 6,462,053; 6,649,624; and 6,723,847, European Patent Nos. EP-01010691, and EP-

01044970; and PCT International Patent Publication Nos. WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/24768; WO 98/25907; WO 98/25908; WO 98/27063, WO 98/47505; WO 98/40356; WO 99/15516; WO 99/27965; WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/14376; WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/22592, WO 0248152, and WO 02/49648; WO 02/094825; WO 03/014083; WO 03/10191; WO 03/092889; WO 04/002986; and WO 04/031175; (9) melanin-concentrating hormone (MCH) receptor antagonists, such as those disclosed in WO 01/21577 and WO 01/21169; (10) melanin-concentrating hormone 1 receptor (MCH1R) antagonists, such as T-226296 (Takeda), and those disclosed in PCT Patent Application Nos. WO 01/82925, WO 01/87834, WO 02/051809, WO 02/06245, WO 02/076929, WO 02/076947, WO 02/04433, WO 02/51809, WO 02/083134, WO 02/094799, WO 03/004027; (11) melanin-concentrating hormone 2 receptor (MCH2R) agonist/antagonists; (12) orexin receptor antagonists, such as SB-334867-A, and those disclosed in patent publications herein; (13) serotonin reuptake inhibitors such as fluoxetine, paroxetine, and sertraline; (14) melanocortin agonists, such as Melanotan II; (15) Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, and ME-10145 (Melacure), CHIR86036 (Chiron); PT-141, and PT-14 (Palatin); (16) 5HT-2 agonists; (17) 5HT2C (serotonin receptor 2C) agonists, such as BVT933, DPCA37215, WAY161503, R-1065, and those disclosed in U.S. Patent No. 3,914,250, and PCT Application Nos. WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456, and WO 02/40457; (18) galanin antagonists; (19) CCK agonists; (20) CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771, JMV-180, A-71378, A-71623 and SR14613, and those discribed in U.S. Patent No. 5,739,106; (21) GLP-1 agonists; (22) corticotropin-releasing hormone agonists; (23) histamine receptor-3 (H3) modulators; (24) histamine receptor-3 (H3) antagonists/inverse agonists, such as hioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and O-[3-(1H-imidazol-4-yl)propanol]-carbamates; (25) β-hydroxy steroid dehydrogenase-1 inhibitors (β-HSD-1); (26) PDE (phosphodiesterase) inhibitors, such as theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast; (27) phosphodiesterase-3B (PDE3B) inhibitors; (28) NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; (29) ghrelin receptor antagonists, such as those disclosed in PCT Application Nos. WO 01/87335, and WO 02/08250; (30) leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); (31) leptin derivatives; (32) BRS3 (bombesin receptor subtype 3) agonists such as [D-Phe6,beta-Ala11,Phe13,Nle14]Bn(6-14) and [D-Phe6,Phe13]Bn(6-13)propylamide, and those compounds disclosed in Pept. Sci. 2002 Aug; 8(8): 461-75); (33) CNTF (Ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, PD170,292, and PD 149164 (Pfizer); (34) CNTF derivatives, such as axokine (Regeneron); (35) monoamine reuptake inhibitors, such as sibutramine; (36) UCP-1 (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-

2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-1-propenyl]benzoic acid (TTNPB), retinoic acid; (37) thyroid hormone β agonists, such as KB-2611 (KaroBioBMS); (38) FAS (fatty acid synthase) inhibitors, such as Cerulenin and C75; (39) DGAT1 (diacylglycerol acyltransferase 1) inhibitors; (40) DGAT2 (diacylglycerol acyltransferase 2) inhibitors; (41) ACC2 (acetyl-CoA carboxylase-2) inhibitors; (42) glucocorticoid antagonists; (43) acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001); (44) dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, TSL 225, TMC-2A/2B/2C, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, sitagliptin; and the compounds disclosed in US 6,699,871, WO 03/004498; WO 03/004496; EP 1 258 476; WO 02/083128; WO 02/062764; WO 03/000250; WO 03/002530; WO 03/002531; WO 03/002553; WO 03/002593; WO 03/000180; and WO 03/000181; (46) dicarboxylate transporter inhibitors; (47) glucose transporter inhibitors; (48) phosphate transporter inhibitors; (49) Metformin (Glucophage®); (50) Topiramate (Topimax®); (50) peptide YY, PYY 3-36, peptide YY analogs, derivatives, and fragments such as BIM-43073D, BIM-43004C (Olitvak, D.A. et al., Dig. Dis. Sci. 44(3):643-48 (1999)); (51) Neuropeptide Y2 (NPY2) receptor agonists such NPY3-36, N acetyl [Leu(28,31)] NPY 24-36, TASP-V, and cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY; (52) Neuropeptide Y4 (NPY4) agonists such as pancreatic peptide (PP), and other Y4 agonists such as 1229U91; (54) cyclooxygenase-2 inhibitors such as etoricoxib, celecoxib, valdecoxib, parecoxib, lumiracoxib, BMS347070, tiracoxib or JTE522, ABT963, CS502 and GW406381; (55) Neuropeptide Y1 (NPY1) antagonists such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A; (56) Opioid antagonists such as nalmefene (Revex ®), 3-methoxynaltrexone, naloxone, naltrexone; (57) 11β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitors such as BVT 3498, BVT 2733, and those disclosed in WO 01/90091, WO 01/90090, WO 01/90092, US 6,730,690 and US 2004-0133011; (58) aminorex; (59) amphechloral; (60) amphetamine; (61) benzphetamine; (62) chlorphentermine; (63) clobenzorex; (64) cloforex; (65) clominorex; (66) clortermine; (67) cyclexedrine; (68) dextroamphetamine; (69) diphemethoxidine, (70) N-ethylamphetamine; (71) fenbutrazate; (72) fenisorex; (73) fenproporex; (74) fludorex; (75) fluminorex; (76) furfurylmethylamphetamine; (77) levamfetamine; (78) levophacetoperane; (79) mefenorex; (80) metamfepramone; (81) methamphetamine; (82) norpseudoephedrine; (83) pentorex; (84) phendimetrazine; (85) phenmetrazine; (86) picilorex; (87) phytopharm 57; and (88) zonisamide., (89) neuromedin U and analogs or derivatives thereof, (90) oxyntomodulin and analogs or derivatives thereof, and (91) Neurokinin-1 receptor antagonists (NK-1 antagonists) such as the compounds disclosed in: U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, and 5,637,699.

In another embodiment, the subject compound may be employed in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine

oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; citalopram, duloxetine, fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranylcypromine and selegiline; moclobemide: venlafaxine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

In another embodiment, the subject compound may be employed in combination with anti-Alzheimer's agents; beta-secretase inhibitors, such as verubecestat; gamma-secretase inhibitors; growth hormone secretagogues; recombinant growth hormone; HMG-CoA reductase inhibitors; NSAID's including ibuprofen; vitamin E; anti-amyloid antibodies; CB-1 receptor antagonists or CB-1 receptor inverse agonists; antibiotics such as doxycycline and rifampin; N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine; cholinesterase inhibitors such as galantamine, rivastigmine, donepezil, and tacrine; growth hormone secretagogues such as ibutamoren, ibutamoren mesylate, and capromorelin; histamine H_3 antagonists; AMPA agonists; PDE IV inhibitors; $GABA_A$ inverse agonists; or neuronal nicotinic agonists.

In another embodiment, the subject compound may be employed in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

In another embodiment, the subject compound may be employed in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alentemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole.

In another embodiment, the subject compound may be employed in combination with acetophenazine, alentemol, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide, pramipexole, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene or trifluoperazine.

In another embodiment, the subject compound may be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone.

In another embodiment, the subject compound may be employed in combination with a nicotine agonist or a nicotine receptor partial agonist such as varenicline, opioid antagonists (e.g., naltrexone (including naltrexone depot), antabuse, and nalmefene), dopaminergic agents (e.g., apomorphine), ADD/ADHD agents (e.g., methylphenidate hydrochloride (e.g., Ritalin® and Concerta®), atomoxetine (e.g., Strattera®), a monoamine oxidase inhibitor (MAOI), amphetamines (e.g., Adderall®)) and anti-obesity agents, such as apo-B/MTP inhibitors, 11Beta-hydroxy steroid dehydrogenase-1 (11Beta-HSD type 1) inhibitors, peptide YY3-36 or analogs thereof, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, β3 adrenergic receptor agonists, dopamine receptor agonists, melanocyte-stimulating hormone receptor analogs, 5-HT2c receptor agonists, melanin concentrating hormone receptor antagonists, leptin, leptin analogs, leptin receptor agonists, galanin receptor antagonists, lipase inhibitors, bombesin receptor agonists, neuropeptide-Y receptor antagonists (e.g., NPY Y5 receptor antagonists), thyromimetic agents, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor antagonists, other orexin receptor antagonists, such as suvorexant, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors, human agouti-related protein antagonists, ghrelin receptor antagonists,

histamine 3 receptor antagonists or inverse agonists, and neuromedin U receptor agonists, and pharmaceutically acceptable salts thereof.

In another embodiment, the subject compound may be employed in combination with an anoretic agent such as aminorex, amphechloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; selective serotonin reuptake inhibitor (SSRI); halogenated amphetamine derivatives, including chlorphentermine, cloforex, clortermine, dexfenfluramine, fenfluramine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

In another embodiment, the subject compound may be employed in combination with an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, asprin, codiene, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the subject compound may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine.

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention may be effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing

the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Oily suspensions may be formulated by suspending the active ingredient in a suitable oil. Oil-in-water emulsions may also be employed. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Pharmaceutical compositions of the present compounds may be in the form of a sterile injectable aqueous or oleagenous suspension. The compounds of the present invention may also be administered in the form of suppositories for rectal administration. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention may be employed. The compounds of the present invention may also be formulated for administered by inhalation. The compounds of the present invention may also be administered by a transdermal patch by methods known in the art.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art (e.g. PCT Patent Publications WO2001/68609, WO2004/085403, WO2005/118548, WO2008/147518, WO2009/143033 and WO2010/048012) or as illustrated herein. The following abbreviations are used herein: Me: methyl; Et: ethyl; t-Bu: *tert*-butyl; Ar:

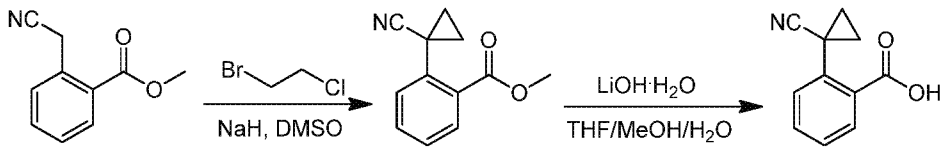
aryl; Ph: phenyl; BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Bn: benzyl; Ac: acetyl; Boc: tert-butyloxy carbonyl; BSA: bovine serum albumin; CbzCl: benzylchloroformate; CDI: carbonyl diimidazole; DCM: dichloromethane; DCE: dichloroethane; DEAD: diethylazodicarboxylate; DIPEA: N,N-diisopropylethylamine; DMF: N,N-dimethylformamide; DMSO: dimethylsulfoxide; CH_2Cl_2: dichloromethane; EDC: N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide; Et_3N: triethylamine; EtOAc: ethyl acetate; EtOH: ethanol; HCl: hydrogen chloride; HOAt: 1-hydroxy-7-aza-benzotriazole; HOBT: hydroxybenzotriazole hydrate; HPLC: high performance liquid chromatography; Hunig's base: N,N-diisopropylethylamine; MeOH: methanol; $MgSO_4$: magnesium sulfate; MTBE: methyl tert-butyl ether; $NaHCO_3$: sodium bicarbonate; NaOH: sodium hydroxide; NMM: N-methylmorpholine; PtO_2: platinum oxide; PyClu: 1-(chloro-1-pyrrolidinylmethylene)-pyrrolidinium hexafluorophosphate; rt: room temperature; $SOCl_2$: thionyl chloride; T3P: 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide; THF: tetrahydrofuran; TFA: trifluoracetic acid; X-Phos: 2-(dicyclohexyl-phosphino)-2',4',6'-triisopropylbiphenyl. The compounds of the present invention can be prepared in a variety of fashions.

In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATES

Intermediate A

2-(1-Cyanocyclopropyl)benzoic acid



A1 A2 Int A

Step 1: Methyl 2-(1-cyanocyclopropyl)benzoate (A2)

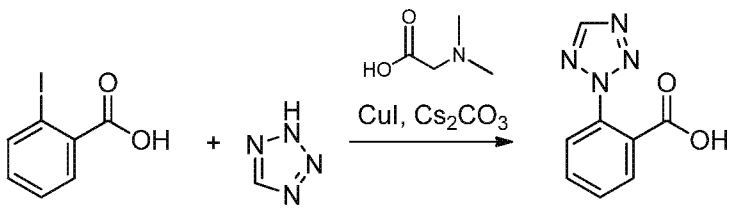
To a solution of NaH (1.1 g, 26.2 mmol) in DMSO (20 mL) was added compound A1 (2 g, 11.4 mmol); after stirring at RT under nitrogen for 1 h, 1-bromo-2-chloroethane (1.8 g, 12.6 mmol) was added and the mixture stirred at RT for 2 h. The mixture was quenched with ice water (10 mL) and extracted with EtOAc (10 mL×3). The organic layers were combined, dried, and concentrated *in vacuo* to give the crude compound, which was purified by silica gel column chromatography (4.8% EtOAc in petroleum ether) to give the title compound as a solid. MS (ESI) m/e (M+H+) was detected.

Step 2: 2-(1-Cyanocyclopropyl)benzoic acid

A solution of compound A2 in THF/MeOH/H_2O (3:1:1, 16 mL) was treated with lithium hydroxide in water (3 mL). The mixture was stirred overnight at RT. The THF and MeOH were removed *in vacuo* and the resulting solution acidified to pH ~1 with 1 N HCl to give a white crystalline precipitate. The crystals were isolated by filtration, washed with water, and dried *in vacuo* affording intermediate A as a solid. MS (ESI) m/e ($M+H^+$): 187.9.

Intermediate B

2-(2*H*-Tetrazol-2-yl)benzoic acid.

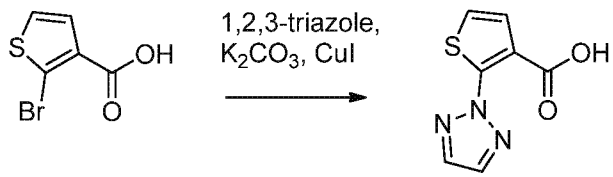


Intermediate B

To a 20 mL microwave tube was charged 2-iodobenzoic acid (1.85 g, 7.46 mmol), cesium carbonate (4.06 g, 12.5 mmol), copper(I) iodide (0.128 g, 0.671 mmol), and DMA (8.0 mL). *N,N'*-Dimethylglycine (0.131 g, 1.27 mmol) and tetrazole (1.29 g, 18.4 mmol) were added, and the solution was irradiated at 100 °C for 1 h. The reaction was diluted with water and 1 *N* aqeous sodium hydroxide and washed with EtOAc. The aqueous fraction was acidified with conc. HCl and extracted 2x with EtOAc. The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography [0-85% (1% acetic acid in EtOAc) in hexanes], providing the title compound. ^{1}H NMR (400 MHz, CD_3OD): δ 7.72-7.84 (m, 3 H), 8.07 (dd, J = 7.6, 1.6 Hz, 1 H), 8.90 (s, 1 H) ppm. LRMS m/z (M+H) 191.1 found, 191.2.

Intermediate C

2-(2*H*)-1,2,3-Triazol-2-yl)thiophene-3-carboxylic acid



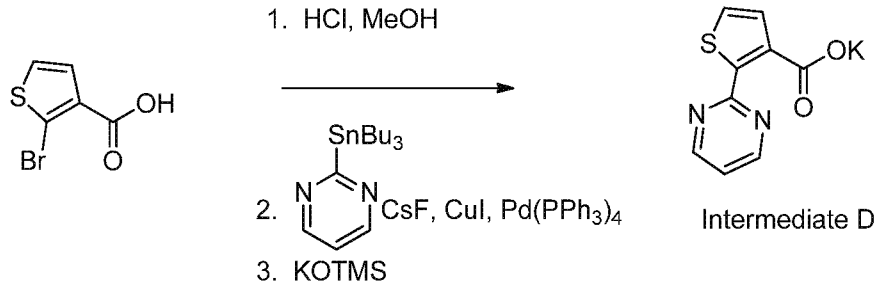
Intermediate C

A solution of 2-bromo-3-thiophene carboxylic acid (1.50 g, 7.24 mmol), 1*H*-1,2,3-triazole (0.600 g, 8.69 mmol), potassium carbonate (2.00 g, 14.5 mmol), and copper iodide (0.138 g, 0.724 mmol) in DMF (36.2 mL) was purged subsurface with nitrogen and heated at 75 °C for 96 h. The reaction was diluted with water, washed with ether, and acidified with conc. HCl. The acidic aqueous solution was extracted 3x with EtOAc and the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The

crude material was purified by silica gel column chromatography [0-70% (1% acetic acid in EtOAc) in hexanes], providing the title compound as a solid. LRMS m/z (M+H) 196.2 found, 196.1 required.

Intermediate D

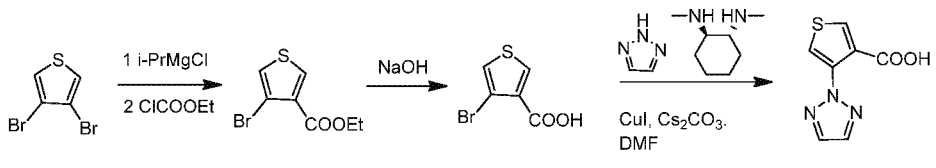
Potassium 2-(pyrimidin-2-yl)thiophene-3-carboxylate.



A solution of 2-bromo-3-thiophene carboxylic acid (3.35 g, 16.2 mmol) in methanol (50 mL) was cooled to 0 °C and saturated with gaseous HCl. The solution was heated at 60 °C overnight, then concentrated *in vacuo*. The residue was redissolved in EtOAc, washed with saturated, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*, providing methyl 2-bromothiophene-3-carboxylate as a oil. LRMS m/z (M+H) 221.1 found, 221.0 required. A solution of methyl 2-bromothiophene-3-carboxylate (1.74 g, 7.87 mmol), 2-(tributylstannyl)pyrimidine (4.36 g, 11.81 mmol), cesium fluoride (4.78 g, 31.5 mmol), and copper(I) iodide (0.450 g, 2.36 mmol) in DMF (16 mL) in a pressure vessel was purged subsurface with nitrogen and treated with palladium tetrakis (0.455 g, 0.394 mmol). The mixture was sealed and heated at 120 °C overnight. The reaction was partitioned between EtOAc and water and filtered through celite. The organic layer was washed with saturated, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0-30% EtOAc in hexanes), providing methyl 2-(pyrimidin-2-yl)thiophene-3-carboxylate as a solid. LRMS m/z (M+H) 221.2 found, 221.1 required. A solution of methyl 2-(pyrimidin-2-yl)thiophene-3-carboxylate (0.695 g, 3.16 mmol) and potassium trimethylsilanolate (0.506 g, 3.94 mmol) in THF (16 mL) was stirred at RT overnight, then diluted with ether and filtered through a glass frit. The solids were washed with ether and concentrated, providing the title compound as a solid. LRMS m/z (M+H) 207.3 found, 207.1 required.

Intermediate E

4-[1,2,3]Triazol-2-yl-thiophene-3-carboxylic acid



Step 1: 4-Bromo-thiophene-3-carboxylic acid ethyl ester (E1)

To a solution of 3,4-dibromothiophene (30 g, 0.12 mol) in THF (200 mL) at 0 °C was added i-PrMgCl (2.0 M solution in THF, 77 mL, 0.15 mol), keeping the temperature below 5 °C. The resulting mixture was stirred at 0-5 °C for 5 h and then ethyl chloroformate (14.4 mL, 0.15 mol) was added dropwise at < 10 °C and the resulting mixture was warmed to RT, stirred overnight, and quenched with saturated, aqueous NH_4Cl. Most of the THF was then removed *in vacuo*, water was added, and the mixture was extracted with EtOAc (80 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, the filtrate concentrated *in vacuo*, and the crude product was purified by silica gel column chromatography (petroleum ether:EtOAc =300:1) to provide the title compound as a oil.

Step 2: 4-Bromo-thiophene-3-carboxylic acid (E2)

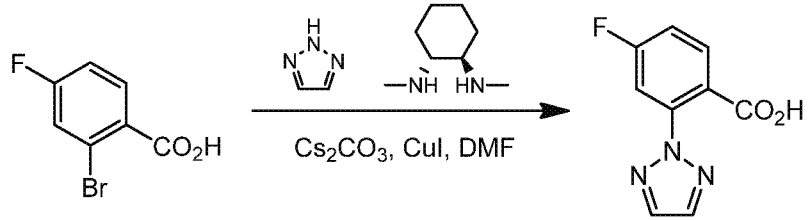
To a solution of the product from Step 1 (10 g, 43 mmol) in methanol (60 mL) was added sodium hydroxide (3.4 g, 86 mmol) and water (1 mL) and the mixture was stirred at RT overnight. The mixture was concentrated *in vacuo*. The residue was diluted with water (30mL) and extracted with EtOAc (25 mL x 4). The pH of aqueous layer was adjusted to ~3 with 1 N HCl and extracted with EtOAc (25 mL x 4). The combined extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compoud as a solid. LRMS m/z (M+H) 206.9, 208.9 found, 206.9, 208.9 required.

Step 3: 4-[1,2,3]Triazol-2-yl-thiophene-3-carboxylic acid (Intermediate E)

To a mixture of the product from Step 2 (7.9 g, 38 mmol), Cs_2CO_3 (24.8 g,76 mmol), and CuI (2.88 g, 7.6 mmol) in DMF (200 mL) was added 2*H*-[1,2,3]triazole (5.24 g,76 mmol) and *N*,*N*'-dimethyl-cyclohexane-1,2-diamine (0.9 g, 6.5 mmol) and the mixture was stirred at 110 °C overnight. The cooled mixture was adjusted to ~pH 12 with 1 N sodium hydroxide and extracted with EtOAc (50 mL x 3). The aqueous layer was adjusted to ~pH 4 with 1 N HCl and extracted with EtOAc (50 mLx4). The extracts were dried over Na_2SO_4, filtered, the filtrate concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (petroleum ether:EtOAc = 10:1) to provide the title compound. LRMS m/z (M+H) 196.0 found, 196.0 required.

Intermediate F

4-Fluoro-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid

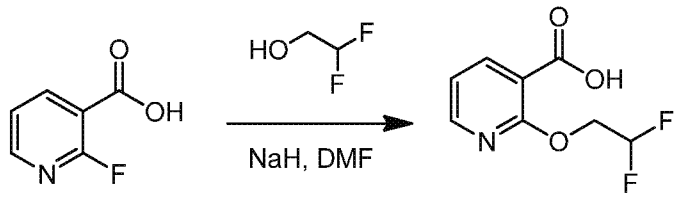


Intermediate F

To a mixture of 2-bromo-4-fluorobenzoic acid (30 g, 137 mmol), cesium carbonate (89.26 g, 274 mmol), and CuI (5.27 g, 27.4 mmol) in DMF (200 mL) was added *N,N'*-dimethylcyclohexane-1,2-diamine (3.7 mL,23.3 mmol) and 1*H*-1,2,3-triazole (18.92 g, 274 mmol). The resulting mixture was stirred at 110 °C overnight, cooled, concentrated *in vacuo*, and diluted with water (150 mL). The aqueous layer was washed with EtOAc (300 mL x 3). The aqueous layer was acidified with 2 N HCl and extracted with EtOAc (300 mL x 4). The combined organic layers were washed with brine (150 mL x 3), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether:EtOAc = 100:1 ~ 5:1) to provide the title compound as a solid. LRMS m/z (M+H) 208.0 found, 208.0 required.

Intermediate G

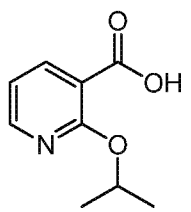
2-(2,2-Difluoroethoxy)nicotinic acid



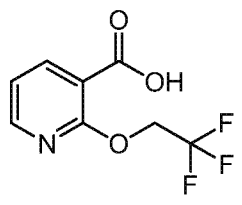
Intermediate G

To a suspension of 2,2-difluoroethanol (492 mg, 6.0 mmol) in DMF (10 mL) at 0 °C was added NaH (180 mg, 4.5 mmol) and the mixture was stirred at 0 °C for 0.5 h. A suspension of 2-fluoronicotinic acid (423 mg, 3.0 mmol) and NaH (180 mg, 4.5 mmol) in DMF (5mL) was added dropwise at 0 °C and the resulting mixture was stirred at RT overnight. The mixture was diluted with water, acidified to pH~3 with 1 N HCl, and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product which was used without further purification. LRMS m/z (M+H) 204.1 found, 204.0 required.

The following intermediates were made as described above, replacing 2,2-difluoroethanol with the appropriate alcohol.

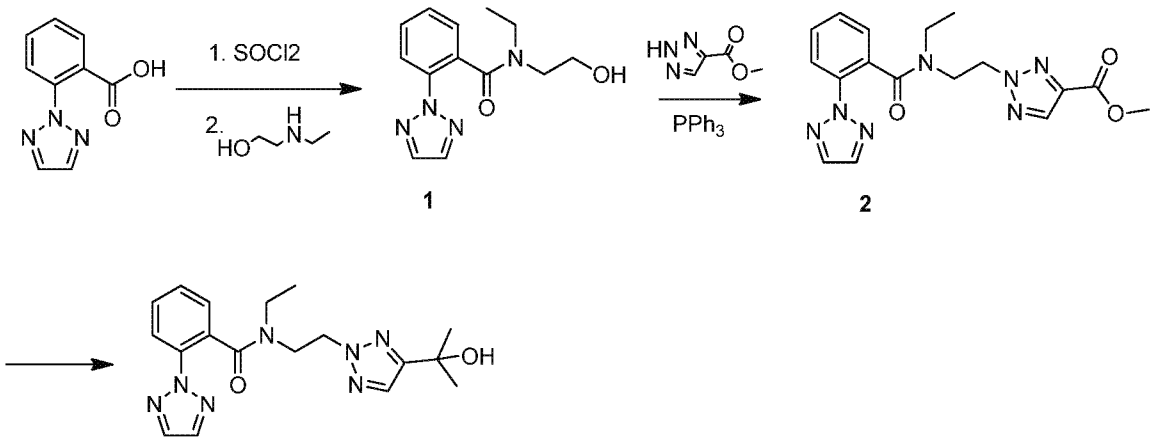


Intermediate H



Intermediate J

EXAMPLE 1



Example 1

N-Ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide

Step 1: *N*-Ethyl-*N*-(2-hydroxyethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide (1)

A solution of 2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (2.10 g, 11.2 mmol) in $SOCl_2$ (30 mL) was stirred at 80°C for 2 h. After cooling to RT, the mixture was concentrated *in vacuo*. To a mixture of 2-(ethylamino)ethanol (997 mg, 11.2 mmol) and DIEA (4.30 g, 336. mmol) in DCM (15 mL) at 0 °C was added dropwise the above residue. The resulting mixture was stirred at RT for 3 h, then quenched with water (50 mL) and extracted with EtOAc (80 mL x 3). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50% EtOAc in petroleum ether) to give the title compound as a oil. LRMS m/z (M+H) 261.3 found, 261.1 required.

Step 2: Methyl 2-(2-(*N*-ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamido)ethyl)-2*H*-1,2,3-triazole-4-carboxylate (2)

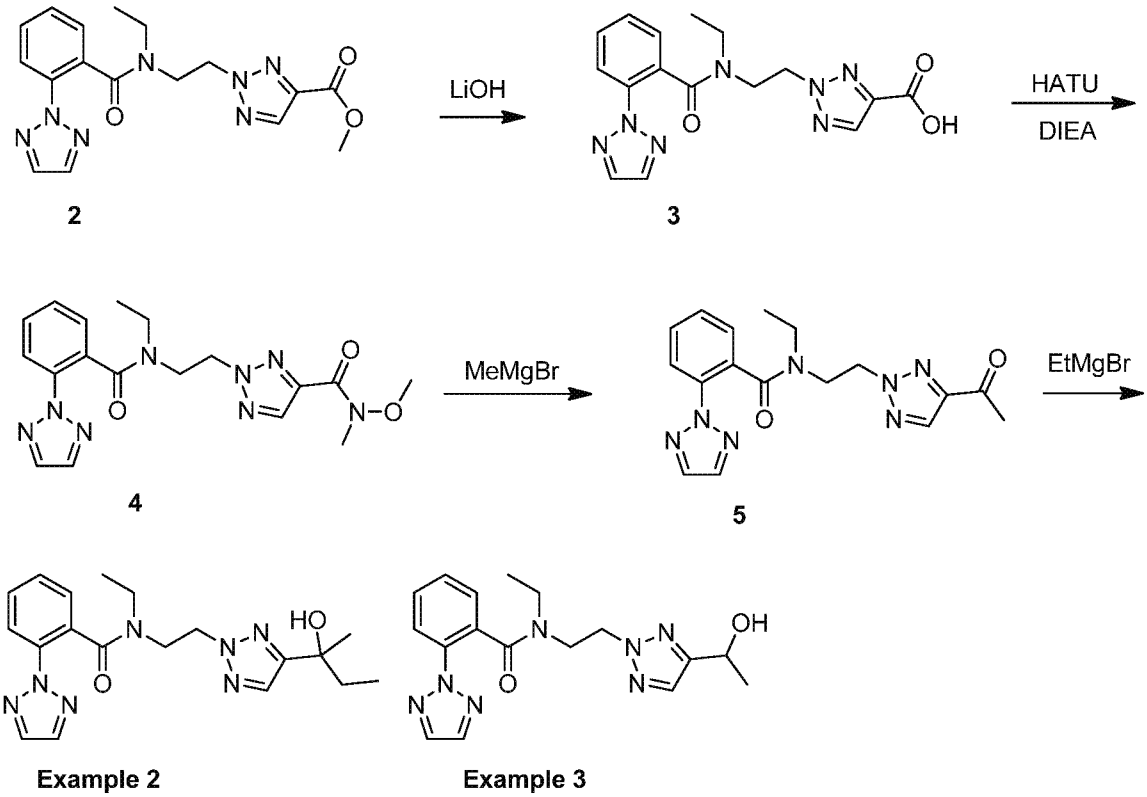
To a solution of the product from Step 1 (800 mg, 3.07 mmol), methyl 2*H*-1,2,3-triazole-4-carboxylate (469 mg, 3.69 mmol), and triphenylphosphine (967 mg, 3.69 mmol) in THF (5 mL) was added a solution of (*E*)-di-*tert*-butyl diazene-1,2-dicarboxylate (920 mg, 4.00 mmol) in THF (4 mL) dropwise. The resulting mixture was stirred at RT overnight, then quenched with water and extracted with EtOAc (100 mL x 3). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50% EtOAc in petroleum ether) to give the title compound as a solid. LRMS m/z (M+H) 370.1 found, 370.2 required.

Step 3: *N*-Ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide

To a solution of the product from Step 2 (100 mg, 0.27 mmol) in THF (3 mL) was added MeMgBr (3 M in ether, 0.27 mL, 0.81 mmol) at 0 °C under N_2. The mixture was stirred at the same temperature for 2 h. The mixture was quenched with saturated, aqueous NH_4Cl and

extracted with EtOAc (20 mL x 3). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by prep-HPLC to give the title compound as a oil. LRMS m/z (M-OH) 352.2 found, 370.2 required.

EXAMPLE 2 AND EXAMPLE 3



N-Ethyl-*N*-(2-(4-(2-hydroxybutan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide and *N*-Ethyl-*N*-(2-(4-(1-hydroxyethyl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide

Step 1: 2-(2-(*N*-ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamido)ethyl)-2*H*-1,2,3-triazole-4-carboxylic acid (3):

To a solution of compound 2 (1.0 g, 2.71 mmol, Example 1, Step 2) in MeOH (10 mL) and water (5 mL) was added LiOH (hydrate, 0.34 g, 8.12 mmol). The resulting mixture was stirred at RT overnight. The mixture was concentrated *in vacuo* to remove most of the MeOH. The aqueous mixture was diluted with water (20 mL) and adjusted to ~pH 3 with 1 N HCl and extracted with DCM (20 mL x 3). The combined organic layers were concentrated *in vacuo* to give the title compound as a solid. LRMS m/z (M+H) 356.1 found, 356.1 required.

Step 2: 2-(2-(*N*-Ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamido)ethyl)-*N*-methoxy-*N*-methyl-2*H*-1,2,3-triazole-4-carboxamide (4):

To a solution of the product from Step 1 (900 mg, 2.53 mmol) in DCM (10 mL) was

added HATU (1252 mg, 3.29 mmol) TEA (1.412 ml, 10.13 mmol). The mixture was stirred at RT for 30 mins and then N,O-dimethylhydroxylamine (201 mg, 3.29 mmol) was added. The mixture was stirred at RT for 5 h, then quenched with water (50 mL) and extracted with EtOAc (50 mL×3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (66% EtOAc in petroleum ether) to give the title compound as a solid. LRMS m/z (M+H) 399.1 found, 399.2 required.

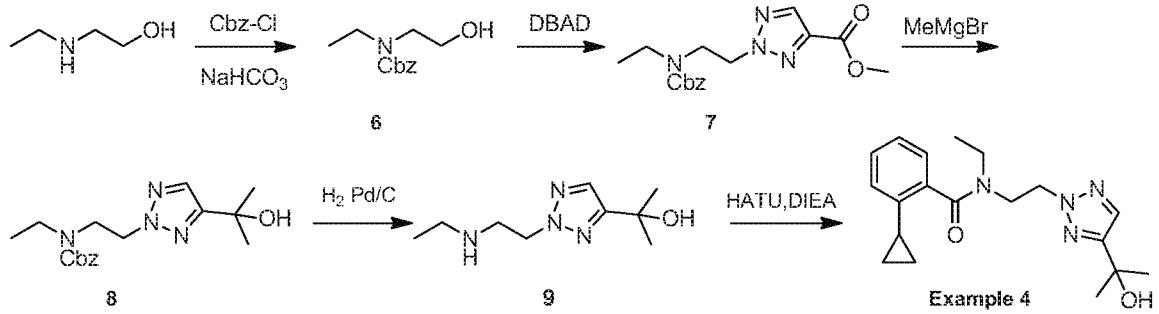
Step 3: *N*-(2-(4-Acetyl-2*H*-1,2,3-triazol-2-yl)ethyl)-*N*-ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamide (5):

To a solution of the product from Step 2 (1 g, 2.510 mmol) in dry THF (2 mL) at -70 °C was added CH3MgBr (3 M in ether, 2.5 mL, 7.53 mmol) dropwise. The mixture was stirred at -70 °C for 3 h, then quenched with water (20 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over $MgSO_4$ and filtered. Concentrated *in vacuo*. The residue was purified by prep-HPLC to give the title compound as a solid. LRMS m/z (M+H) 354.1 found, 354.2 required.

Step 4: *N*-Ethyl-*N*-(2-(4-(2-hydroxybutan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide (Example 2) & *N*-Ethyl-*N*-(2-(4-(2-hydroxybutan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide (Example 3)

To a solution of the product from Step 3 (100 mg, 0.283 mmol) in dry THF (3 mL) at -70 °C was added a solution of EtMgBr (37.7 mg, 0.283 mmol) dropwise. The mixture was stirred at -70 °C for 3 h. The mixture was quenched with water (20 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over $MgSO_4$ and filtered. Concentrated *in vacuo*. The residue was purified by prep-HPLC to give Example **2** and Example **3** as solids. Example 2: LRMS m/z (M-OH) 366.4 (M-OH) found, 384.2 required. Example 3: LRMS m/z (M-OH) 338.1, 356.1 (M+H) found, 356.2 required.

EXAMPLE 4



2-Cyclopropyl-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)benzamide

Step 1: Benzyl ethyl(2-hydroxyethyl)carbamate (6):

To a solution of 2-(ethylamino)ethanol (5.0 g, 56.1 mmol) in THF/water (30 ml/30 mL) was added $NaHCO_3$ (9.42 g, 112 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 mins and then Cbz-Cl (10.5 g, 61.7 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at RT overnight, then quenched with water (20 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10%-30% EtOAc in petroleum ether), providing the title compound as a oil. LRMS m/z (M+H) 224.1 found, 224.1 required.

Step 2: Methyl 2-(2-(((benzyloxy)carbonyl)(ethyl)amino)ethyl)-2*H*-1,2,3-triazole-4-carboxylate (7):

To a solution of the product from Step 1 (9.5 g, 42.5 mmol), methyl 2*H*-1, 2, 3-triazole-4-carboxylate (6.49 g, 51.1 mmol), and PPh_3 (16.7 g, 63.8 mmol) in THF (100 mL) was added a solution of DIAD (19.6 g, 85.0 mmol) in THF dropwise at 0 °C under N_2. The resulting mixture was stirred at RT overnight. Water was added to quench the reaction and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10%-50% EtOAc in petroleum ether), providing the title compound as a oil. LRMS m/z (M+H) 333.1 found, 333.1 required.

Step 3: Benzyl ethyl(2-(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)carbamate (8):

To a solution of the product from Step 2 (3.0 g, 9.03 mmol) in THF (30 mL) was added MeMgBr (3 M in ether , 5.3 mL, 15.9 mmol) dropwise at 0 °C. The mixture was stirred at RT for 3 h, then quenched with saturated, aqueous NH_4Cl and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10%-30% EtOAc in petroleum ether) to give the title compound as a oil. LRMS m/z (M+H) 333.1 found, 333.1 required.

Step 4: 2-(2-(2-(ethylamino)ethyl)-2H-1,2,3-triazol-4-yl)propan-2-ol (9):

To a solution of the product from Step 3 (2.0 g, 6.02 mmol) in THF (20 mL) was added Pd/C (10 wt%, 192 mg). The mixture was stirred at RT under a hydrogen balloon overnight, filtered, and concentrated *in vacuo* to give the title compound as a oil. LRMS m/z (M+H) 199.1 found, 199.1 required.

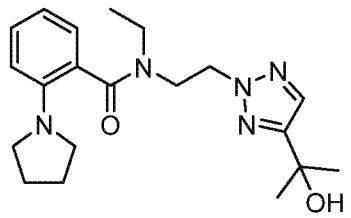
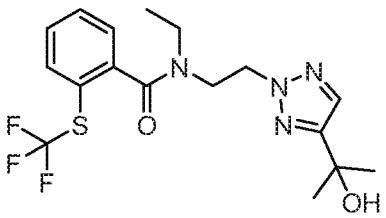
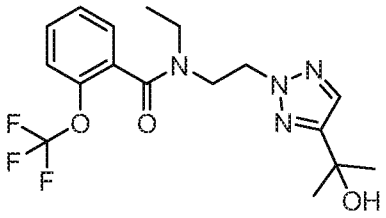
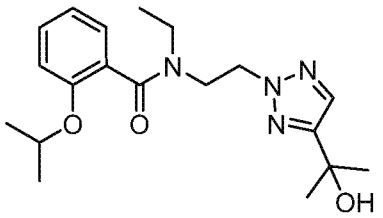
Step 5: 2-Cyclopropyl-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)benzamide (10)

To a solution of the product from Step 4 (67.3 mg, 0.34 mmol) in DCM (3 mL) was added DIEA (120 mg, 0.93 mmol), HATU (129 mg, 0.34 mmol), and 2-cyclopropylbenzoic acid (50 mg, 0.31mmol). The resulting mixture was stirred at RT overnight, then quenched with

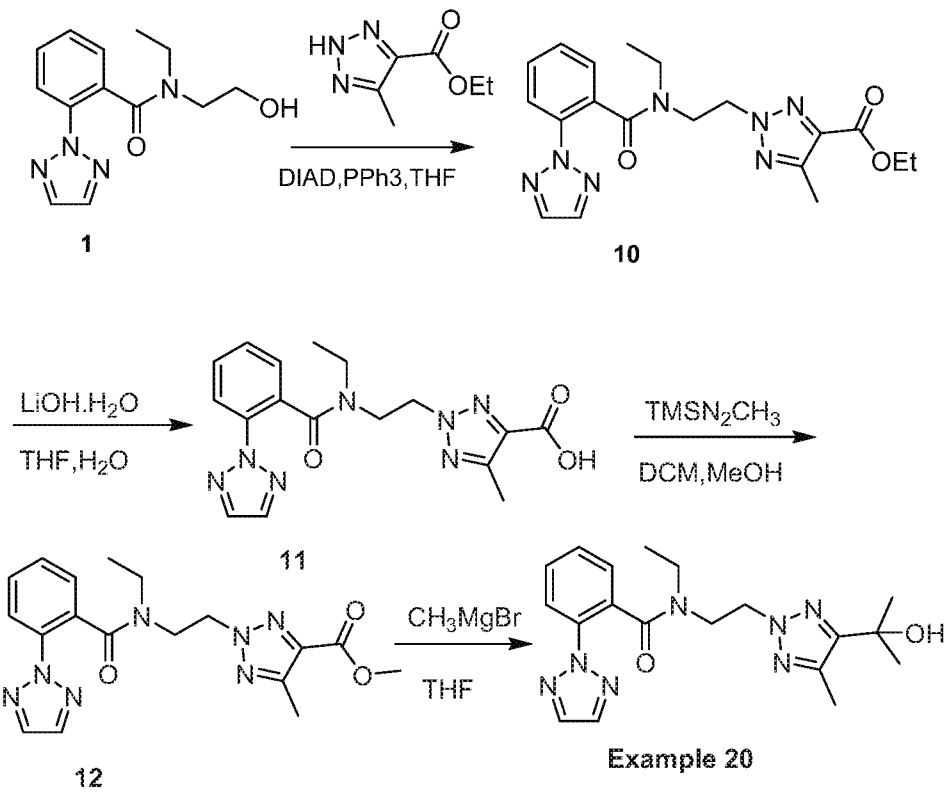
water (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by prep-HPLC to give title compound as a oil. LRMS m/z (M+H) 325.4 (M-OH) found, 343.2 required.

TABLE 1

The following compounds were prepared according to the general procedure provided in Example 4 and procedures herein. The starting materials are either prepared as described in the intermediates section, commercially available, or may be prepared from commercially available reagents using conventional reactions well known in the art.

Ex.	Structure	Name	Mass [M+H]
5		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(pyrrolidin-1-yl)benzamide	Calc'd (M+Na+MeCN) 435.2, found 435.3
11		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-((trifluoromethyl)thio)benzamide	Calc'd 403.1, found 403.2
12		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(trifluoromethoxy)benzamide	Calc'd (M+Na) 409.1, found (M-OH) 369.2 (M+Na) 409.2
18		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)ethyl)-2-isopropoxybenzamide	Calc'd 361.2, found 361.2

EXAMPLE 20



1 10 11 12 Example 20

N-Ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide

Step 1: Ethyl 2-(2-(*N*-ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamido)ethyl)-5-methyl-2*H*-1,2,3-triazole-4-carboxylate (10)

To a solution of compound 1 (263 mg, 1.01 mmol, Step 1 in Example 1), ethyl 5-methyl-2*H*-1,2,3-triazole-4-carboxylate (130 mg, 0.839 mmol), and PPh_3 (442 mg, 1.68 mmol) in dry THF (5 mL) was added DIAD (440 mg, 7.29 mmol) at 0 °C. The mixture was stirred at RT for 4 h. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (0~50% EtOAc in petroleum ether) to give the title compound as a solid. LCMS m/z (M+H) 398.2 found, 398.2 required.

Step 2: 2-(2-(*N*-Ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamido)ethyl)-5-methyl-2*H*-1,2,3-triazole-4-carboxylic acid (2)

To a solution of the product from Step 1 (250 mg, 0.630 mmol) in THF (8 mL) and H_2O (2 mL) was added LiOH (hydrate, 277 mg, 6.30 mmol). The mixture was stirred at RT for 1.5 h, then concentrated *in vacuo* to remove THF and the aqueous layer was extracted with DCM (15 mL x 2). The combined aqueous phase was adjusted to pH 3~4 with 4 N HCl and extracted with EtOAc (15 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound as a oil. LCMS m/z (M+H) 370.1 found, 370.2 required.

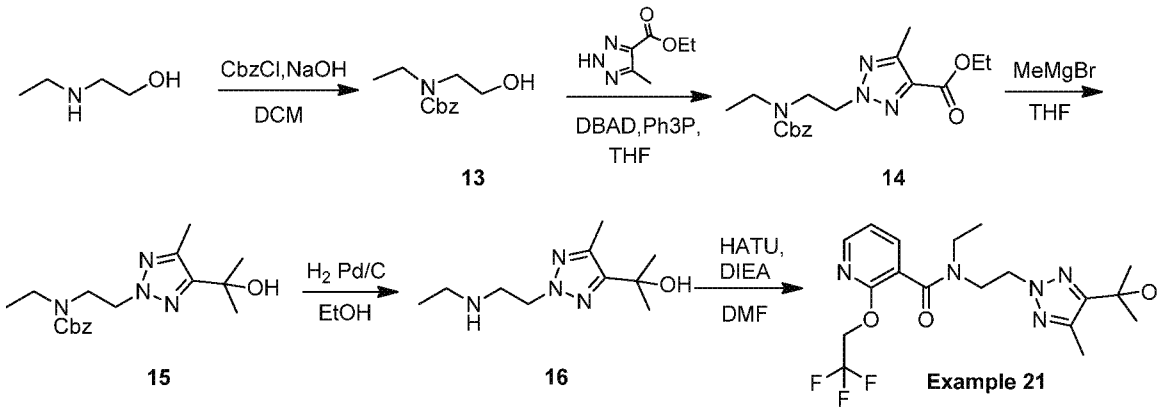
Step 3: Methyl 2-(2-(*N*-ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamido)ethyl)-5-methyl-2*H*-1,2,3-triazole-4-carboxylate (3)

To a solution of the product from Step 2 (200 mg, 0.542 mmol) in DCM (8 mL) and MeOH (2 mL) was added $TMSCH_2N_2$ (2 M in n-hexane, 0.5 mL, 1.08 mmol) dropwise at 0 °C. The reaction mixture was stirred at RT for 2 h. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (0~50% EtOAc in petroleum ether) to give the title compound as a solid. LCMS m/z (M+H) 384.2 found, 384.2 required.

Step 4: *N*-Ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide

To a solution of MeMgBr (3 M in ether, 0.2 mL, 0.628 mmol) in THF (1 mL) was added a solution of the product from Step 3 (60 mg, 0.157 mmol) in THF (2 mL) dropwise at -20 °C under N_2. The mixture was stirred at 0 °C for 2 h, then quenched with saturated, aqueous NH_4Cl and extracted with EtOAc (20 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* and the residue was purified by prep-HPLC to give the title compound as a oil. LCMS m/z (M-OH) 366.2 (M+Na) 406.2 found, 384.2 required.

EXAMPLE 21



N-Ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2,2,2-trifluoroethoxy)nicotinamide

Step 1: Benzyl ethyl(2-hydroxyethyl)carbamate (13)

To a solution of 2-(ethylamino)ethanol (17.8 g, 0.2 mol) in THF (300 mL) and 1 N aqueous NaOH (300 mL, 0.3 mol) at 0 °C was added CbzCl (40.8 g, 0.24 mol) dropwise. The resulting mixture was stirred at RT overnight. EtOAc (100 mL) was added and the organic layer was separated. The organic fraction was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (33% EtOAc in petroleum ether) to give the title compound as a oil. LRMS m/z (M+H) 224.2 found, 224.2 required.

Step 2: Ethyl 2-(2-(((benzyloxy)carbonyl)(ethyl)amino)ethyl)-5-methyl-2*H*-1,2,3-triazole-4-carboxylate (14)

To a solution of the product from Step 1 (5.35 g, 0.024 mol), ethyl 5-methyl-2*H*-1,2,3-triazole-4-carboxylate (3.1 g, 0.02 mol), and PPh3(10.5 g, 0.04 mol) in THF (50 mL) at 0 °C was added DBAD (9.2 g, 0.04 mol). The resulting mixture was stirred at RT under N_2 for 16 h, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (33% EtOAc in petroleum ether) to give the titled compound as a oil. LRMS m/z (M+H) 361.2 found, 361.2 required.

Step 3: Benzyl ethyl(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)carbamate (15)

To a solution of the product from Step 2 (2.6 g, 7.2 mmol) in THF (40 mL) at -10 °C was added MeMgBr solution (3 M in ether, 16 mL, 48 mmol). The resulting mixture was stirred at -10 °C ~ -5 °C for 2 h, then quenched with 15 mL of water and extracted with EtOAc (50 mL). The organic phase was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50% EtOAc in petroleum ether) to give the title compound as a colorless oil. LRMS m/z (M+H) 369.3 found, 369.3 required.

Step 4: 2-(2-(2-(Ethylamino)ethyl)-5-methyl-2*H*-1,2,3-triazol-4-yl)propan-2-ol (16)

To a solution of the product from Step 3 (1.9 g, 5.46 mmol) in EtOH (50 mL) was added Pd/C (10 wt%, 0.19 g). The resulting mixture was under a hydrogen balloon for 16 h and then filtered and concentrated *in vacuo* to afford the target compound as a oil, which was used without further purification. LRMS m/z (M+H) 213.2 found, 213.2 required.

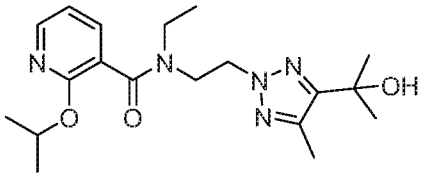
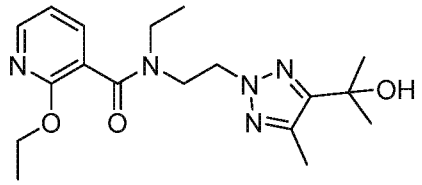
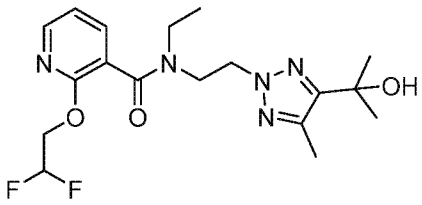
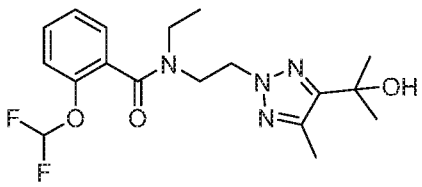
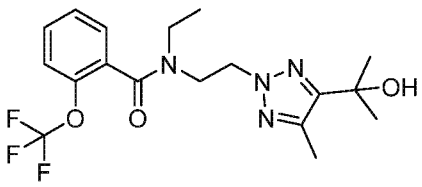
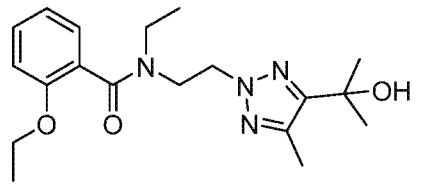
Step 5: *N*-Ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2,2,2-trifluoroethoxy)nicotinamide (Example 21)

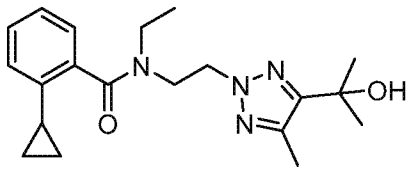
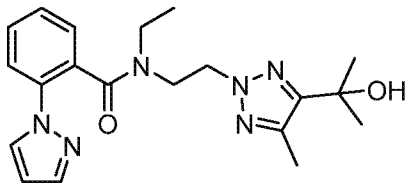
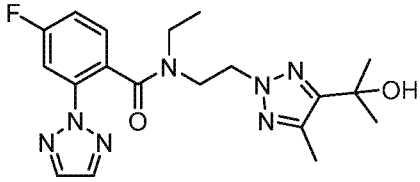
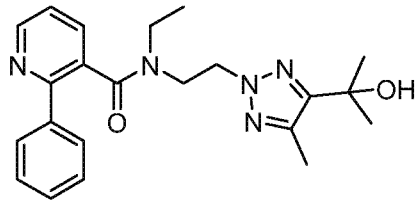
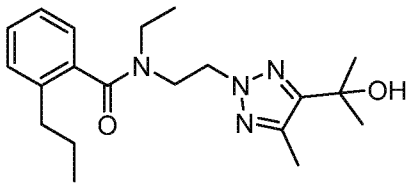
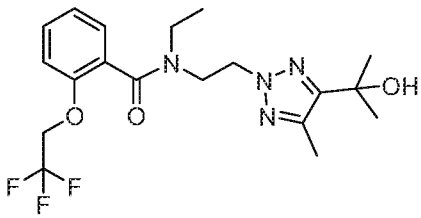
A mixture of 2-(2,2,2-trifluoroethoxy)nicotinic acid (50 mg ,0.21 mmol), HATU (80 mg, 0.21 mmol), and DIEA (74 mg, 0.57 mmol) in DMF (2 mL) was stirred at RT for 10 mins, then the product from Step 4 (30 mg, 0.14 mmol) was added. The resulting mixture was stirred at RT for an additional 16 h and then filtered. The filtrate was purified by prep-HPLC to afford the title compound as a oil.

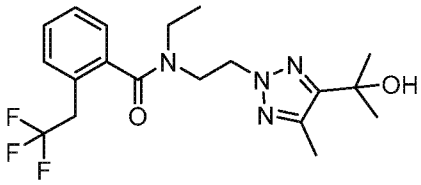
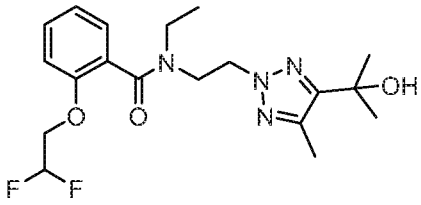
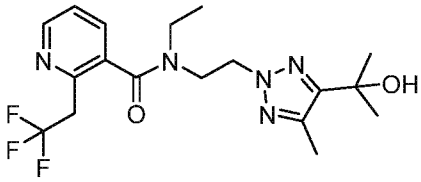
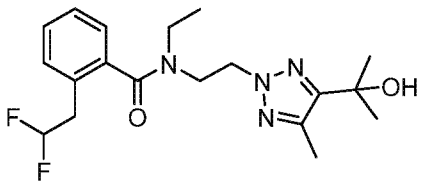
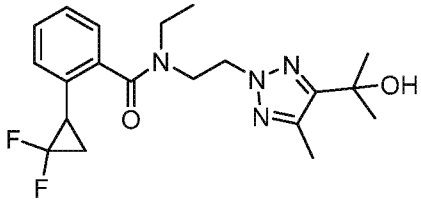
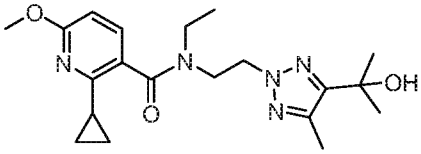
TABLE 2

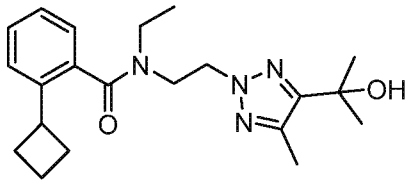
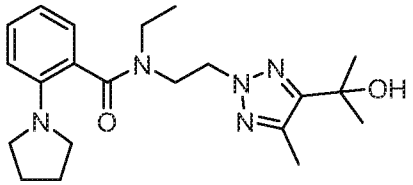
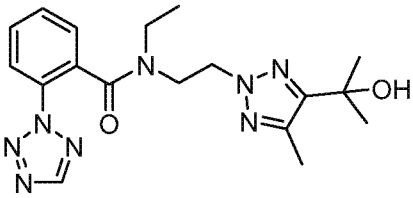
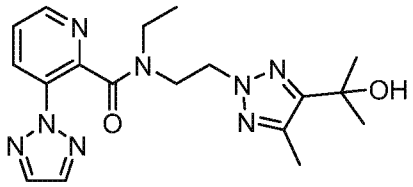
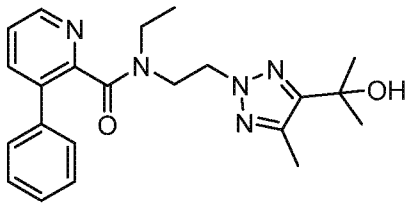
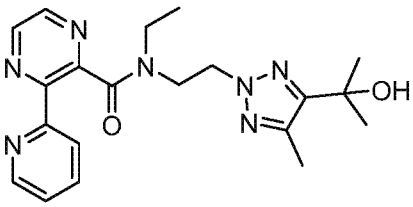
The following compounds were prepared according to the general procedure provided in Example 21 and procedures herein. The starting materials are either prepared as described in the intermediates section, commercially available, or may be prepared from commercially available reagents using conventional reactions well known in the art.

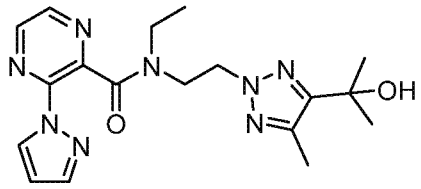
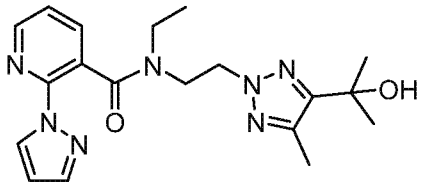
Ex.	Structure	Name	Mass

22		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-isopropoxynicotinamide	Calc'd (M+Na) 398.2, found (M-OH) 358.2 (M+Na) 398.2
23		2-ethoxy-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)nicotinamide	Calc'd (M+Na) 384.2, found (M-OH) 344.2, (M+Na) 384.2
24		2-(2,2-difluoroethoxy)-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)nicotinamide	Calc'd (M+Na) 420.2, found (M-OH) 380.2, (M+Na) 420.1
25		2-(difluoromethoxy)-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)benzamide	Calc'd (M+Na) 405.2, found (M-OH) 365.2, (M+Na) 405.1
26		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(trifluoromethoxy)benzamide	Calc'd (M+Na) 423.2, found (M-OH) 383.2, (M+Na) 423.1
27		2-ethoxy-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)benzamide	Calc'd (M+Na) 383.2, found (M-OH) 343.2, (M+Na) 383.2

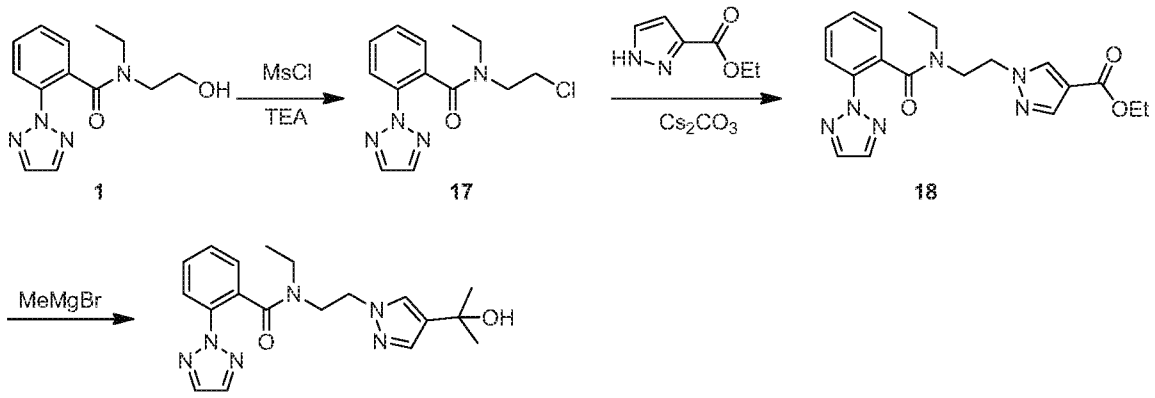
28		2-cyclopropyl-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)benzamide	Calc'd (M+Na) 379.2, found (M-OH) 339.1, (M+Na) 379.1
29		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(1*H*-pyrazol-1-yl)benzamide	Calc'd (M+Na) 405.2, found (M-OH) 365.1, (M+Na) 405.1
30		*N*-ethyl-4-fluoro-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide	Calc'd (M+Na) 424.2, found (M-OH) 384.1, (M+Na) 424.1
31		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-phenylnicotinamide	Calc'd (M+H) 394.2, found (M+H) 394.2
32		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-propylbenzamide	Calc'd (M+Na) 381.2, found (M-OH) 341.2, (M+Na) 381.2
33		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2,2,2-trifluoroethoxy)benzamide	Calc'd (M+Na) 437.2, found (M-OH) 397.1, (M+Na) 437.1

34		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2,2,2-trifluoroethyl)benzamide	Calc'd (M+Na) 421.2, found (M-OH) 381.1, (M+Na) 421.1
35		2-(2,2-difluoroethoxy)-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)benzamide	Calc'd (M+Na) 419.2, found (M-OH) 379.1, (M+Na) 419.1
36		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2,2,2-trifluoroethyl)nicotinamide	Calc'd (M+Na) 422.2, found (M-OH) 382.1, (M+Na) 422.1
37		2-(2,2-difluoroethyl)-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)benzamide	Calc'd (M+Na) 403.2, found (M-OH) 363.1, (M+Na) 403.1
38		2-(2,2-difluorocyclopropyl)-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)benzamide	Calc'd (M+Na) 415.2, found (M-OH) 375.1, (M+Na) 415.1
39		2-cyclopropyl-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-6-methoxynicotinamide	Calc'd (M+Na) 410.2, found (M-OH) 370.2, (M+Na) 410.1

40		2-cyclobutyl-*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)benzamide	Calc'd (M+Na) 393.2, found (M-OH) 353.2, (M+Na) 393.1
41		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(pyrrolidin-1-yl)benzamide	Calc'd (M+H) 386.2, found (M+H) 386.2
42		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(2*H*-tetrazol-2-yl)benzamide	Calc'd (M+Na) 407.2, found (M-OH) 367.2, (M+Na) 407.2
43		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-3-(2*H*-1,2,3-triazol-2-yl)picolinamide	Calc'd (M+Na) 407.2, found (M-OH) 367.2, (M+Na) 407.1
44		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-3-phenylpicolinamide	Calc'd (M+H) 394.2, found (M+H) 394.2
45		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-3-(pyridin-2-yl)pyrazine-2-carboxamide	Calc'd (M+H) 396.2, found (M+H) 396.1

47		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-3-(1*H*-pyrazol-1-yl)pyrazine-2-carboxamide	Calc'd (M+Na) 407.2, found (M-OH) 367.2, (M+Na) 407.2
48		*N*-ethyl-*N*-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2*H*-1,2,3-triazol-2-yl)ethyl)-2-(1*H*-pyrazol-1-yl)nicotinamide	Calc'd (M+Na) 406.2, found (M-OH) 366.1, (M+Na) 406.1

EXAMPLE 49



N-Ethyl-*N*-{2-[4-(1-hydroxy-1-methylethyl)-1*H*-pyrazol-1-yl]ethyl}-2-(2*H*-1,2,3-triazol-2-yl)benzamide

Step 1: N-(2-Chloroethyl)-*N*-ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamide (17)

To a solution of compound 1 (700 mg, 2.69 mmol, example 1, Step 1) in DCM (5 mL) was added TEA (1.2 mL, 8.07 mmol) at 0 °C. The mixture was stirred at the same temperature for 10 mins, then methanesulfonyl chloride (670 mg, 5.85 mmol) was added. The resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated, aqueous NH_4Cl and extracted with DCM (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound as a oil. LRMS m/z (M+H) 279.1 found, 279.1 required.

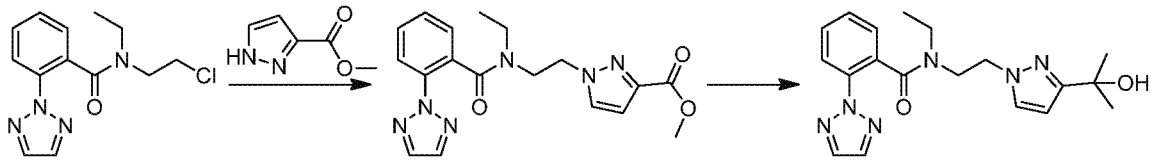
Step 2: Ethyl 1-(2-(*N*-ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamido)ethyl)-1*H*-pyrazole-4-carboxylate (18)

A mixture of the product from Step 1 (150 mg, 0.538 mmol), methyl 1*H*-pyrazole-3-carboxylate (102 mg, 0.807 mmol), and Cs_2CO_3 (351 mg, 1.076 mmol) in DMF (2 mL) was stirred at 80 °C overnight. After cooling to RT, the mixture was diluted with water and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* and the residue was purified by prep-TLC (50% EtOAc in petroleum ether) to give the title as a oil. LRMS m/z (M+H) 383.2 found, 383.1 required.

Step 3: *N*-Ethyl-*N*-{2-[4-(1-hydroxy-1-methylethyl)-1*H*-pyrazol-1-yl]ethyl}-2-(2*H*-1,2,3-triazol-2-yl)benzamide

To a solution of the product from Step 2 (100 mg, 0.261 mmol) in THF (2 mL) was added MeMgBr (3 M in ether, 0.5 mL, 1.5 mmol) at 0 °C dropwise. The resulting mixture was stirred at RT for 1 h, then quenched with saturated, aqueous NH4Cl and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by prep-HPLC to give the title compound as a oil. LRMS m/z (M+H) 351.1 (M-OH) found, 369.2 required.

EXAMPLE 50



17 19 Example 50

N-Ethyl-*N*-{2-[3-(1-hydroxy-1-methylethyl)-1*H*-pyrazol-1-yl]ethyl}-2-(2*H*-1,2,3-triazol-2-yl)benzamide

Step 1: Methyl 1-(2-(*N*-ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamido)ethyl)-1*H*-Pyrazole-3-carboxylate (19)

A mixture of *N*-(2-chloroethyl)-*N*-ethyl-2-(2*H*-1,2,3-triazol-2-yl)benzamide (150 mg, 0.538 mmol, Example 21, Step 1), methyl 1*H*-pyrazole-3-carboxylate (102 mg, 0.807 mmol), and Cs_2CO_3 (351 mg, 1.076 mmol) in DMF (2 mL) was stirred at 80 °C overnight. After cooling to RT, the mixture was diluted with water and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (50% EtOAc in petroleum ether) to give the title compound as a oil. LRMS m/z (M+H) 369.2 found, 369.1 required.

Step 2: *N*-Ethyl-*N*-{2-[3-(1-hydroxy-1-methylethyl)-1*H*-pyrazol-1-yl]ethyl}-2-(2*H*-1,2,3-triazol-2-yl)benzamide

To a solution of the product from Step 1 (100 mg, 0.271 mmol) in THF (2 mL) was added MeMgBr (3 M in ether, 0.5 mL, 1.5 mmol) at 0 °C dropwise. The resulting mixture was stirred at RT for 1 h, then quenched with saturated, aqueous NH_4Cl and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by prep-HPLC to give the title compound as a oil. LRMS m/z (M+H) 351.2 (M-OH) found, 369.2 required.

TABLE 3

The following table shows representative data for the compounds of the Examples as orexin receptor antagonists as determined by the assays described herein.

Example	hOX2R FLIPR IC_{50} (nM)	hOX1R FLIPR IC_{50} (nM)
1	58	>10,000
2	65	>10,000
3	373	>10,000
4	47	>10,000
5	41	>10,000
11	34	>10,000
12	247	>10,000
18	145	>10,000
20	12	2855
21	21	>10,000
22	61	>10,000
23	58	>10,000
24	44	>10,000
25	35	>10,000
26	19	>10,000
27	27	>10,000
28	13	1561
29	28	>10,000
30	10	5539
31	33	>10,000
32	32	2207
33	52	>10,000
34	37	>10,000
35	35	>10,000
36	270	>10,000

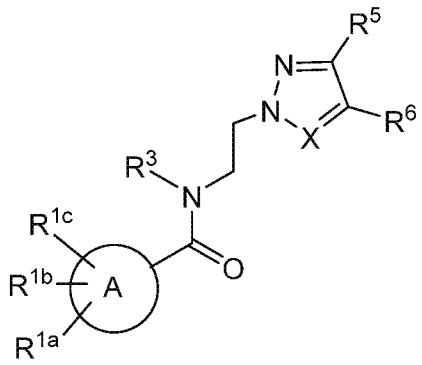
37	10	>10,000
38	10	1481
39	14	2843
40	13	1174
41	15	2103
42	29	>10,000
43	180	>10,000
44	106	>10,000
45	87	>10,000
47	239	>10,000
48	13	7521
49	35	>10,000
50	23	>10,000

As indicated by the data herein, the compounds of the present examples provide greater functional selectivity for the orexin-2 receptor over the orexin-1 receptor. The distinction in potency between the orexin-2 receptor and the orexin-1 receptor in the whole cell FLIPR functional assay provides enhanced predictive value for determining in vivo efficacy. Increasing the functional selectivity for the orexin-2 receptor reduces the potential for dual receptor antagonism in vivo. Such greater functional selectivity may provide benefits over other orexin receptor antagonists that are known in the art.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention.

CLAIMS

1. A compound of the formula I:



I

wherein:

A is selected from the group consisting of phenyl, naphthyl and heteroaryl;

X is N or CH;

each of R^{1a}, R^{1b} and R^{1c} is independently selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) $-(C=O)_m-O_n-C_{1-6}$alkyl, where m is 0 or 1, n is 0 or 1 (wherein if m is 0 or n is 0, a bond is present) and where the alkyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(5) $-(C=O)_m-O_n-C_{3-6}$cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(6) $-(C=O)_m-C_{2-4}$alkenyl, where the alkenyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(7) $-(C=O)_m-C_{2-4}$alkynyl, where the alkynyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(8) $-(C=O)_m-O_n$-phenyl or $-(C=O)_m-O_n$-naphthyl, where the phenyl or naphthyl is unsubstituted or substituted with one to three substituents independently selected from R^4,

(9) $-(C=O)_m-O_n$-heterocycle, where the heterocycle is unsubstituted or substituted with one to three substituents independently selected from R^4,

(10) $-(C=O)_m-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from the group consisting of:

(a) hydrogen,

(b) C_{1-6}alkyl, which is unsubstituted or substituted with R^4,

(c) C_{3-6}alkenyl, which is unsubstituted or substituted with R^4,

(d) C_{3-6}alkynyl, which is unsubstituted or substituted with R^4,

(e) C_{3-6}cycloalkyl which is unsubstituted or substituted with R^4,

(f) phenyl, which is unsubstituted or substituted with R^4, and

(g) heterocycle, which is unsubstituted or substituted with R^4,

(11) $-S(O)_2-NR^{10}R^{11}$,

(12) $-S(O)_q-R^{12}$, where q is 0, 1 or 2 and where R^{12} is selected from the definitions of R^{10} and R^{11},

(13) $-CO_2H$,

(14) -CN, and

(15) $-NO_2$;

R^3 is selected from hydrogen and C_{1-6}alkyl;

R^4 is selected from the group consisting of:

(1) hydroxyl,

(2) halogen,

(3) C_{1-6}alkyl,

(4) $-C_{3-6}$cycloalkyl,

(5) $-O-C_{1-6}$alkyl,

(6) $-O(C=O)-C_{1-6}$alkyl,

(7) $-NH_2$,

(8) $-NH-C_{1-6}$alkyl,

(9) $-NO_2$,

(10) phenyl,

(11) heterocycle,

(12) $-CO_2H$, and

(13) -CN;

R^5 is selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C_{1-6}alkyl, which is unsubstituted or substituted with halogen or hydroxyl,

(4) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with halogen, and

(5) $-(C=O)-O-C_{1-6}$alkyl;

R^6 is selected from the group consisting of:

(1) hydrogen,

(2) halogen,

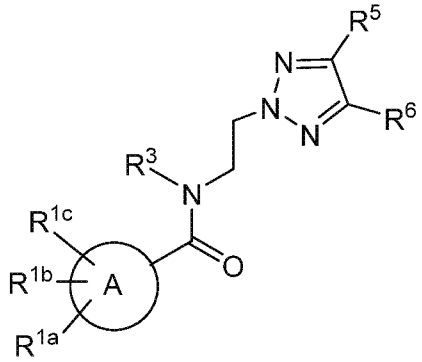
(3) C_{1-6}alkyl, which is unsubstituted or substituted with halogen or hydroxyl,

(4) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with halogen, and

(5) $-(C=O)-O-C_{1-6}$alkyl;

or a pharmaceutically acceptable salt thereof.

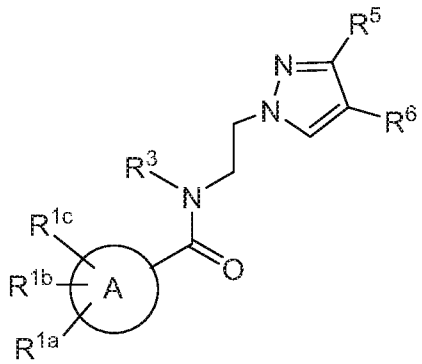
2. The compound of Claim 1 of the formula Ia:



Ia

or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1 of the formula Ic:



Ic

or a pharmaceutically acceptable salt thereof.

4. The compound of any of Claims 1-3 or a pharmaceutically acceptable salt thereof wherein R^{1a}, R^{1b} and R^{1c} are independently selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,

(5) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,

(6) -CN, and

(7) heteroaryl, wherein heteroaryl is selected from imidazolyl, indolyl, oxazolyl, pyridyl, pyrrolyl, pyrimidinyl, tetrazolyl, and triazolyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl or-NO_2.

5. The compound of any of Claims 1-4 or a pharmaceutically acceptable salt thereof wherein R^3 is ethyl.

6. The compound of any of Claims 1-5 or a pharmaceutically acceptable salt thereof wherein R^5 is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) $-C(CH_3)_2OH$,
(4) $-CH(OH)CF_3$,
(5) $-CH(OH)CH_3$,
(6) $-C(OH)(CH_3)CH_2CH_3$,
(7) $-C(OH)(CF_3)CH_3$, and
(8) $-C(=O)OCH_3$.

7. The compound of any of Claims 1-5 or a pharmaceutically acceptable salt thereof wherein R^5 is selected from the group consisting of: methyl and $-C(CH_3)_2OH$.

8. The compound of any of Claims 1-5 or a pharmaceutically acceptable salt thereof wherein R^6 is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) $-C(CH_3)_2OH$,
(4) $-CH(OH)CF_3$,
(5) $-CH(OH)CH_3$,
(6) $-C(OH)(CH_3)CH_2CH_3$,
(7) $-C(OH)(CF_3)CH_3$, and
(8) $-C(=O)OCH_3$.

9. The compound of any of Claims 1-5 or a pharmaceutically acceptable salt thereof wherein R^6 is selected from the group consisting of: methyl and $-C(CH_3)_2OH$.

10. A compound which is selected from the group consisting of:
N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-2H-1,2,3-triazol-2-yl)ethyl)-2-(2H-1,2,3-triazol-2-yl)benzamide;
N-ethyl-N-(2-(4-(2-hydroxybutan-2-yl)-2H-1,2,3-triazol-2-yl)ethyl)-2-(2H-1,2,3-triazol-2-yl)benzamide;
N-ethyl-N-(2-(4-(1-hydroxyethyl)-2H-1,2,3-triazol-2-yl)ethyl)-2-(2H-1,2,3-triazol-2-yl)benzamide;
2-cyclopropyl-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-2H-1,2,3-triazol-2-yl)ethyl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-2H-1,2,3-triazol-2-yl)ethyl)-2-(pyrrolidin-1-yl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-2H-1,2,3-triazol-2-yl)ethyl)-2-((trifluoromethyl)thio)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-2H-1,2,3-triazol-2-yl)ethyl)-2-(trifluoromethoxy)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-2H-1,2,3-triazol-2-yl)ethyl)-2-isopropoxybenzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(2H-1,2,3-triazol-2-yl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(2,2,2-trifluoroethoxy)nicotinamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-isopropoxynicotinamide;

2-ethoxy-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)nicotinamide

2-(2,2-difluoroethoxy)-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)nicotinamide;

2-(difluoromethoxy)-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(trifluoromethoxy)benzamide;

2-ethoxy-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)benzamide;

2-cyclopropyl-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(1H-pyrazol-1-yl)benzamide;

N-ethyl-4-fluoro-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(2H-1,2,3-triazol-2-yl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-phenylnicotinamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-propylbenzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(2,2,2-trifluoroethoxy)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(2,2,2-trifluoroethyl)benzamide;

2-(2,2-difluoroethoxy)-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(2,2,2-trifluoroethyl)nicotinamide;

2-(2,2-difluoroethyl)-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)benzamide;

2-(2,2-difluorocyclopropyl)-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)benzamide;

2-cyclopropyl-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-6-methoxynicotinamide;

2-cyclobutyl-N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(pyrrolidin-1-yl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(2H-tetrazol-2-yl)benzamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-3-(2H-1,2,3-triazol-2-yl)picolinamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-3-phenylpicolinamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-3-(pyridin-2-yl)pyrazine-2-carboxamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-3-(1H-pyrazol-1-yl)pyrazine-2-carboxamide;

N-ethyl-N-(2-(4-(2-hydroxypropan-2-yl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-2-(1H-pyrazol-1-yl)nicotinamide;

N-ethyl-N-{2-[4-(1-hydroxy-1-methylethyl)-1H-pyrazol-1-yl]ethyl}-2-(2H-1,2,3-triazol-2-yl)benzamide; and

N-ethyl-N-{2-[3-(1-hydroxy-1-methylethyl)-1H-pyrazol-1-yl]ethyl}-2-(2H-1,2,3-triazol-2-yl)benzamide;

or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition which comprises an inert carrier and a compound of any of Claims 1-10 or a pharmaceutically acceptable salt thereof.

12. A compound of any of Claims 1-10 or a pharmaceutically acceptable salt thereof for use in therapy.

13. A compound of any of Claims 1-10, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a sleep disorder.

14. A method for enhancing the quality of sleep in a mammalian subject which comprises administering to the patient an effective amount of the compound of any of Claims 1-10 or a pharmaceutically acceptable salt thereof.

15. A method for treating insomnia in a mammalian subject which comprises administering to the patient an effective amount of the compound of any of Claims 1-10 or a pharmaceutically acceptable salt thereof.

16. A method for treating or controlling obesity in a mammalian subject which comprises administering to the patient an effective amount of the compound of any of Claims 1-10 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/094590

A. CLASSIFICATION OF SUBJECT MATTER

C07D 249/04(2006.01)i; C07D 231/12(2006.01)i; C07D 231/16(2006.01)i; C07D 231/18(2006.01)i; C07D 231/20(2006.01)i; C07D 231/28(2006.01)i; A61K 31/415(2006.01)i; A61K 31/4152(2006.01)i; A61K 31/4155(2006.01)i; A61K 31/4192(2006.01)i; A61P 25/20(2006.01)i; A61P 25/00(2006.01)i; A61P 3/04(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 249/-; C07D 231/-; A61K 31/-; A61P 25/-; A61P 3/-

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT,CNKI,WPI,EPODOC,ISI Web of Knowledge,STN(REGISTRY,MARPAT): merck,orexin,azole,triazole,diazole, searching the formula

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007078113 A1 (SK CORPORATION ET AL.) 12 July 2007 (2007-07-12) description, page 42, compound 40, page 50, compound 89, page 55, compound 136, claims 10-11	1(part), 2, 6(part), 8(part), 11-13(part), 16(part)
X	CN 103608347 A (ASTELLAS PHARMA INC.) 26 February 2014 (2014-02-26) description, page 148, compound 751, paragraph [0055]	1(part), 3(part), 11-13(part)
X	REGISTRY. *STN Columbus*, 11 August 2013 (2013-08-11), RN(1448136-93-3, 1448135-58-7 et al.)	1(part), 3-4(part), 8(part), 12-13(part)
X	REGISTRY. *STN Columbus*, 09 August 2013 (2013-08-09), RN(1448126-55-3, 1448123-50-9 et al.)	1(part), 3-4(part), 8(part), 12-13(part)

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 September 2015	**22 September 2015**
Name and mailing address of the ISA/CN **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **CHEN,Xi** Telephone No. **(86-10)82246724**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REGISTRY. *STN Columbus,* 06 July 2006 (2006-07-06), RN 890714-09-7	1(par), 3(part), 6(part), 12-13(part)
X	WO 2007061763 A2 (MERCK & CO., INC. ET AL.) 31 May 2007 (2007-05-31) abstract, description, page 1, line 35 to page 5, line 24, page 14, lines 10-25, table 1	1(part), 2, 3-9(part), 11-16(part)
E	WO 2014210159 A1 (PROTEOSTASIS THERAPEUTICS, INC.) 31 December 2014 (2014-12-31) claims 71-72, compound 115	1(part), 2, 6(part), 8(part), 11-13(part)
A	JP 2014015452 A (TAISHO PHARMACEUTICAL CO., LTD.) 30 January 2014 (2014-01-30) claim 1, abstract	1(part), 2, 3-9(part), 10, 11-16(part)
A	CN 103443094 A (TAISHO PHARMACEUTICAL CO., LTD.) 11 December 2013 (2013-12-11) claims 1-9, abstract	1(part), 2, 3-9(part), 10, 11-16(part)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/094590

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

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

1. ☑ Claims Nos.: **14-16**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 14-16 are directed to a method for treatment of diseases, the search has been carried out and based on the use of claimed compound for manufacturing medicaments having the alleged effects.

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

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2014/094590

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2007078113	A1	12 July 2007	KR	1394245	B1	14 May 2014
				EP	1971600	A1	24 September 2008
				US	7915297	B2	29 March 2011
				EP	1971600	B1	21 August 2013
				JP	5246499	B2	24 July 2013
				US	2009131336	A1	21 May 2009
				JP	2009522255	A	11 June 2009
				KR	2007007238	A	04 July 2007
CN	103608347	A	26 February 2014	TW	201311685	A	16 March 2013
				EA	201391769	A1	30 April 2014
				KR	20140040774	A	03 April 2014
				US	2014088080	A1	27 March 2014
				MX	2013014082	A	21 March 2014
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				IL	229513	D0	30 January 2014
				EP	2716642	A1	09 April 2014
				JP	WO2012165399	A1	23 February 2015
				EP	2716642	A4	03 December 2014
				WO	2012165399	A1	06 December 2012
				CA	2836202	A1	06 December 2012
WO	2007061763	A2	31 May 2007	US	2009088452	A1	02 April 2009
				EP	1954276	A2	13 August 2008
				JP	2009516742	A	23 April 2009
				WO	2007061763	A3	13 December 2007
				AU	2006316321	A1	31 May 2007
				CA	2629192	A1	31 May 2007
WO	2014210159	A1	31 December 2014	None			
JP	2014015452	A	30 January 2014	None			
CN	103443094	A	11 December 2013	RU	2013132930	A	27 January 2015
				EP	2653469	A1	23 October 2013
				CA	2821893	A1	21 June 2012
				MX	2013006715	A	26 August 2013
				SG	191103	A1	30 August 2013
				NZ	611865	A	28 November 2014
				KR	20140000703	A	03 January 2014
				AU	2011342049	A1	04 July 2013
				TW	201307320	A	16 February 2013
				US	2013281465	A1	24 October 2013
				EP	2653469	A4	07 May 2014
				WO	2012081692	A1	21 June 2012