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(54) **Title**: 4-FLUOROPIPERIDINE OREXIN RECEPTOR ANTAGONISTS

(57) **Abstract**: The present invention is directed to 4-fluoropiperidine compounds which are antagonists of orexin receptors, and which are useful in the treatment or prevention of neurological and psychiatric disorders and diseases in which orexin receptors are involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which orexin receptors are involved.

TITLE OF THE INVENTION

4-FLUOROPIPERIDINE OREXIN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

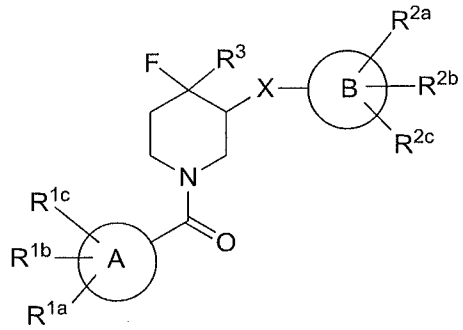
Orexin (hypocretin) neuropeptides are derived from a single gene (HCRT) encoding prepro-orexin that is processed into the mature 33 amino acid orexin A (OX-A) and orexin B (OX-B) peptides (Wong et al., Gen Comp Endocrinol, 2011, 171, 124-130). Both neuropeptides have overlapping endogenous specificity for two related G-protein coupled receptors found throughout mammals, orexin 1 and orexin 2 receptors (OX_1R and OX_2R, respectively) (Scammell and Winrow, Ann Rev Pharmacol Toxicol, 2011, 51, 243-266). OX-A has activity toward both OX_1R and OX_2R having binding affinities of 20 and 38 nM, respectively, while OX-B is relatively specific for OX_2R, exhibiting 36 nM affinity relative to 420 nM activity toward OX_1R (Sakurai et al., Cell, 1998, 92, 573-585). Orexin secreting neurons originate from the lateral and posterior areas of the hypothalamus and project to multiple brain regions to affect arousal and vigilance state changes associated with sleep/wake cycles (Scammell and Winrow, Ann Rev Pharmacol Toxicol, 2011, 51, 243-266), but also have the potential to influence behavior and physiology including feeding, metabolism and gastrointestinal function (Sakurai et al., Cell, 1998, 92, 573-585; Tsujino and Sakurai, Pharmacol Rev, 2009, 61, 162-176), reward pathways associated with addiction, learning and memory (Harris, et al., Trends Neurosci., 2006, 29, 571-577), anxiety behavior modulation (Suzuki et al., Brain Res, 2005, 1044, 116-121), depression and mood (Scott et al., Behav Brain Res, 2011222, 289-294) and the modulation of migraine and nociception (Akerman et al., Nat Rev Neurosci., 2011,12, 570-84; Mobarakeh et al., Peptides, 2005, 26, 767-777).

SUMMARY OF THE INVENTION

The present invention is directed to 4-fluoropiperidine compounds which are antagonists of orexin receptors, and which are useful in the treatment or prevention of neurological and psychiatric disorders and diseases in which orexin receptors are involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the 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, napthyl and heteroaryl;

B is selected from the group consisting of phenyl, napthyl and heteroaryl;

X is $-NR^4-$, -O- or $-CH_2-$,

wherein R^4 is selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6}alkyl,
(3) $-C_{3-6}$cycloalkyl, and
(4) $-CF_3$;

R^{1a}, R^{1b} and R^{1c} may be absent if the valency of A does not permit such substitution and are 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 or more substituents selected from R^{13},
(5) $-(C=O)_m-O_n-C_{3-6}$cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(6) $-(C=O)_m-C_{2-4}$alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(7) $-(C=O)_m-C_{2-4}$alkynyl, where the alkynyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(8) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(9) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{13},

(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^{14},

(c) C_{3-6}alkenyl, which is unsubstituted or substituted with R^{14},

(d) C_{3-6}alkynyl, which is unsubstituted or substituted with R^{14},

(e) C_{3-6}cycloalkyl which is unsubstituted or substituted with R^{14},

(f) phenyl, which is unsubstituted or substituted with R^{14}, and

(g) heterocycle, which is unsubstituted or substituted with R^{14},

(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^{2a}, R^{2b} and R^{2c} may be absent if the valency of B does not permit such substitution and are independently selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) -$(C=O)_m$-O_n-C_{1-6}alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(5) -$(C=O)_m$-O_n-C_{3-6}cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(6) -$(C=O)_m$-C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(7) -$(C=O)_m$-C_{2-4}alkynyl, where the alkynyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(8) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(9) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{13},
(10) -$(C=O)_m$-$NR^{10}R^{11}$,
(11) -$S(O)_2$-$NR^{10}R^{11}$,
(12) -$S(O)_q$-R^{12},
(13) -CO_2H,
(14) -CN, and
(15) -NO_2;

R^3 is selected from the group consisting of:
(1) hydrogen,
(2) halogen, and
(3) C_{1-6}alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{14},

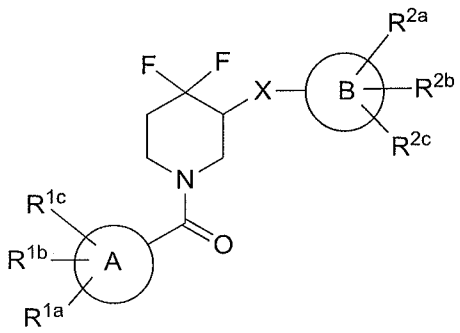
R^{13} is selected from the group consisting of:
(1) halogen,
(2) hydroxyl,
(3) -$(C=O)_m$-O_n-C_{1-6}alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{14},
(4) -O_n-(C_{1-3})perfluoroalkyl,
(5) -$(C=O)_m$-O_n-C_{3-6}cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{14},
(6) -$(C=O)_m$-C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{14},
(7) -$(C=O)_m$-C_{2-4}alkynyl, where the alkynyl is unsubstituted or substituted with one or more substituents selected from R^{14},
(8) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{14},
(9) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{14},
(10) -$(C=O)_m$-$NR^{10}R^{11}$,

(11) -S(O)$_2$-NR^{10}R^{11},
(12) -S(O)$_q$-R^{12},
(13) -CO$_2$H,
(14) -CN, and
(15) oxo;

R^{14} 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-C$_{1-6}$alkyl,
(8) phenyl,
(9) heterocycle,
(10) -CO$_2$H, and
(11) -CN;

or a pharmaceutically acceptable salt thereof.

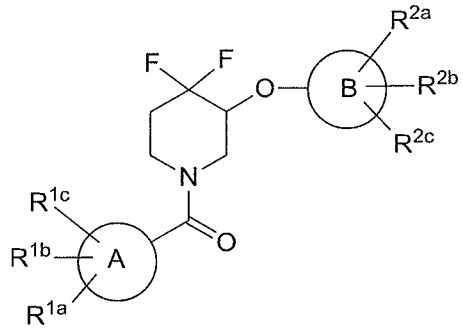
An embodiment of the present invention includes compounds of the formula Ia:



Ia

wherein A, B, R^{1a}, R^{1b}, R^{1c}, R^{2a}, R^{2b}, R^{2c} and X are defined herein; or a pharmaceutically acceptable salt thereof.

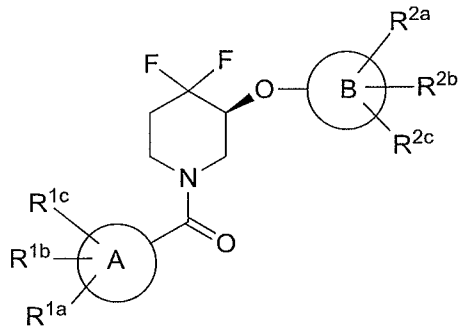
An embodiment of the present invention includes compounds of the formula Ib:



Ib

wherein A, B, R^{1a}, R^{1b}, R^{1c}, R^{2a}, R^{2b}, and R^{2c} are defined herein; or a pharmaceutically acceptable salt thereof.

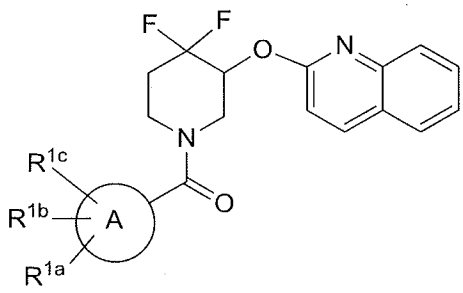
An embodiment of the present invention includes compounds of the formula Ib':



Ib'

wherein A, B, R^{1a}, R^{1b}, R^{1c}, R^{2a}, R^{2b}, and R^{2c} are defined herein; or a pharmaceutically acceptable salt thereof.

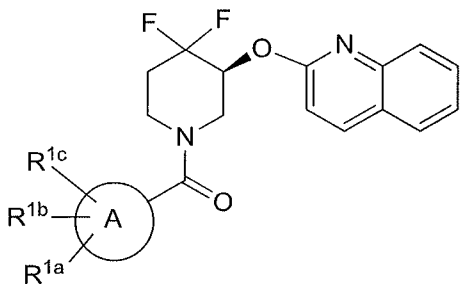
An embodiment of the present invention includes compounds of the formula Ic:



Ic

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

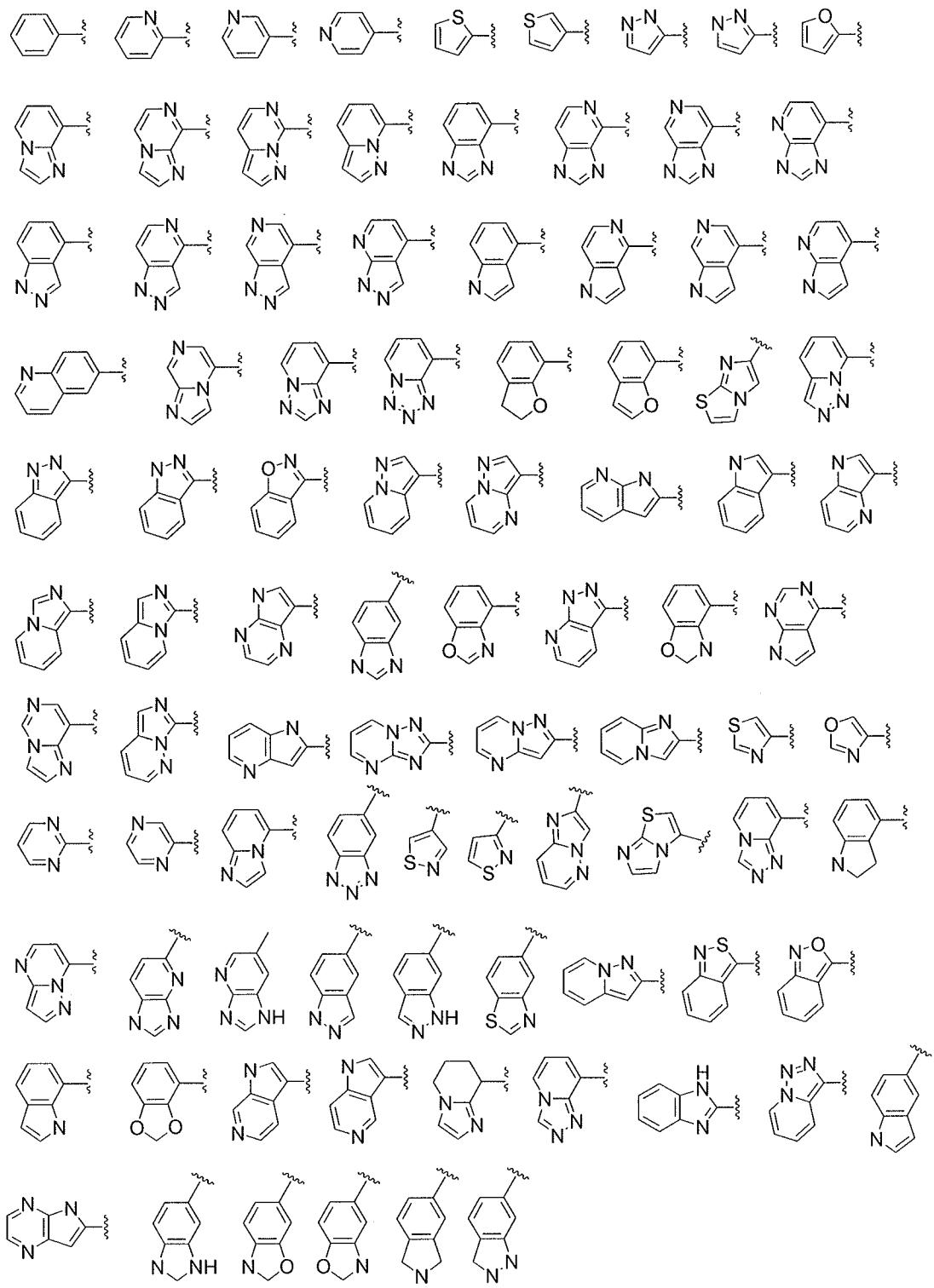
An embodiment of the present invention includes compounds of the formula Ic':



Ic'

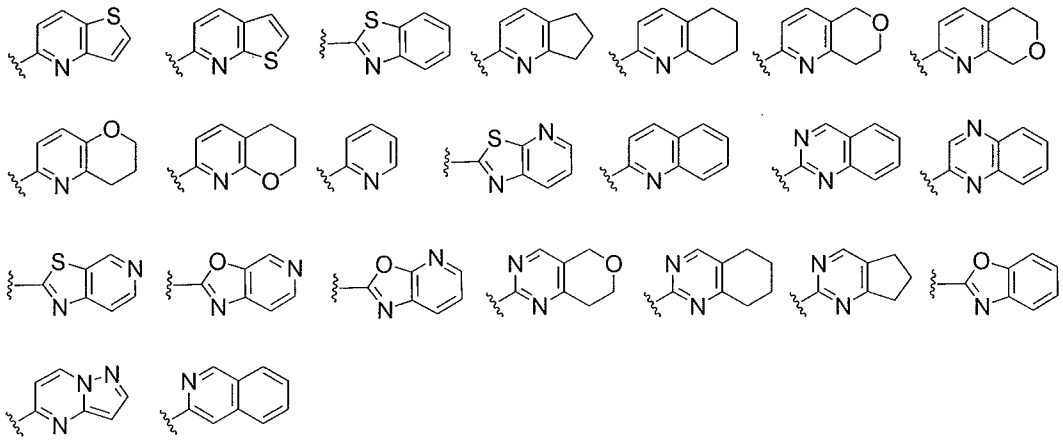
wherein A, R^{1a}, R^{1b}, and R^{1c} are defined herein; or a pharmaceutically acceptable salt thereof.

An embodiment of the present invention includes compounds wherein A is selected from the group consisting of:



An embodiment of the present invention includes compounds wherein A is selected from the group consisting of: phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyrazolyl, thiazolyl, isothiazolyl, thiophenyl, benzimidazolyl, azabenzimidazolyl, benzimidazolonyl, indazolyl, dihydroindazolonyl, azaindazolyl, indolyl, indolonyl, dihydroisoindolonyl, azaindolyl, benzofuranyl, dihyrobenzofuranyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, imidazopyridinyl, tetrahydroimidazopyridinyl, imidazopyrazinyl, imidazopyridazinyl, imidazothiazolyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrrolopyrimidinyl, pyrrolopyrazinyl, triazolopyridinyl, triazolopyrimidinyl, and tetrazolopyridinyl. 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 pyrazolyl. An embodiment of the present invention includes compounds wherein A is thiazolyl. An embodiment of the present invention includes compounds wherein A is imidazopyridinyl. An embodiment of the present invention includes compounds wherein A is benzimidazolyl. An embodiment of the present invention includes compounds wherein A is azabenzimidazolyl. An embodiment of the present invention includes compounds wherein A is indazolyl.

An embodiment of the present invention includes compounds wherein B is selected from the group consisting of:



An embodiment of the present invention includes compounds wherein B is selected from the group consisting of:

(1) phenyl,

(2) quinoline,

(3) isoquinoline,

(4) benzoxazole,
(5) thienopyridine,
(6) pyridine,
(7) quinazoline,
(8) pyrimidine,
(9) benzothiazole, and
(10) quinoxaline.

An embodiment of the present invention includes compounds wherein B is quinoline. An embodiment of the present invention includes compounds wherein B is isoquinoline. An embodiment of the present invention includes compounds wherein B is pyridine. An embodiment of the present invention includes compounds wherein B is thienopyridine. An embodiment of the present invention includes compounds wherein B is benzothiazole. An embodiment of the present invention includes compounds wherein B is quinoxaline. An embodiment of the present invention includes compounds wherein B is quinazoline.

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, phenyl or napthyl,
(5) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,
(6) heteroaryl, wherein heteroaryl is selected from triazolyl, oxazolyl, pyrrolyl, imidazolyl, pyrazinyl, pyrazolyl, thiazolyl, oxadiazolyl, furanyl, tetrazolyl, thiophenyl, pyrrolidinyl, imidazolidinonyl, oxazolidinonyl, pyrrolidinonyl, pyridyl, and pyrimidinyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, -O-C_{1-6}alkyl, amino, or oxo,
(7) phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, or -O-C_{1-6}alkyl,
(8) -O-phenyl, which is unsubstituted or substituted with halogen, hydroxyl, C_{1-6}alkyl, or -O-C_{1-6}alkyl,
(9) -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,

(10) C_{3-6}cycloalkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,

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

(12) -CN.

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 or napthyl,

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

(6) heteroaryl, wherein heteroaryl is selected from triazolyl, oxazolyl, imidazolyl, pyrazolyl, thiazolyl, oxadiazolyl, tetrazolyl, imidazolidinonyl, oxazolidinonyl, pyrrolidinonyl, pyridyl, and pyrimidinyl, which is unsubstituted or substituted with halogen, hydroxyl or C_{1-6}alkyl,

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

(8) C_{3-6}cycloalkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl, and

(9) -CN.

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) triazolyl,

(6) oxazolyl,

(7) imidazolyl,

(8) pyrazolyl,

(9) thiazolyl,

(10) imidazolidinonyl,

(11) pyrimidinyl, and

(12) pyridyl.

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) halogen,

(3) trifluoromethyl,

(4) methyl,

(5) methoxy,

(6) triazolyl,

(7) oxazolyl,

(8) imidazolyl,

(9) pyrazolyl,

(10) thiazolyl,

(11) imidazolidinonyl,

(12) pyrimidinyl, and

(13) pyridyl.

An embodiment of the present invention includes compounds wherein R^{2a}, R^{2b} and R^{2c} 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 or napthyl,

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

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

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

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

(9) -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, and

(10) -CN.

An embodiment of the present invention includes compounds wherein R^{2a}, R^{2b} and R^{2c} 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, and
(6) -CN.

An embodiment of the present invention includes compounds wherein R^{2a}, R^{2b} and R^{2c} 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, and
(5) -CN.

An embodiment of the present invention includes compounds wherein R^{2c} is hydrogen, and R^{2a} and R^{2b} are independently selected from the group consisting of:

(1) hydrogen,
(2) chloro,
(3) fluoro,
(4) iodo,
(5) methoxy,
(6) -CN,
(7) methyl, and
(8) trifluoromethyl.

An embodiment of the present invention includes compounds wherein R^3 is fluoro. An embodiment of the present invention includes compounds wherein R^3 is hydrogen.

An embodiment of the present invention includes compounds wherein X is -O-. An embodiment of the present invention includes compounds wherein X is -NH-.

Specific 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_{1-8}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. A group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents. The term "heterocycle" as used herein includes both unsaturated and saturated heterocyclic moieties, wherein the unsaturated heterocyclic moieties (i.e. "heteroaryl") include azabenzimidazolyl, azaindazolyl,

azaindolyl, benzoimidazolyl, benzimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzothiophenyl, benzoxazepin, benzoxazolyl,benzoxazolonyl, benzisoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, dihyrobenzofuranyl, dihydroindazolonyl, dihydroisoindolonyl, dihydroindolyl, indolazinyl, indazolyl, indolonyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl,imidazopyridinyl, tetrahydroimidazopyridinyl, imidazopyrazinyl, imidazopyridazinyl, imidazothiazolyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrrolopyrimidinyl, pyrrolopyrazinyl, triazolopyridinyl, triazolopyrimidinyl, 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 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 subject compounds are useful in a method of antagonizing orexin receptor activity in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as antagonists of orexin receptor activity. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention. The present invention is directed to a compound of the present invention or a

pharmaceutically acceptable salt thereof for use in medicine. The present invention is further 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.

The subject treated in the present methods is generally a mammal, such as a human being, male or female. The term "therapeutically effective amount" means the amount of the subject compound 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. It is recognized that one skilled in the art may affect the neurological and psychiatric disorders by treating a patient presently afflicted with the disorders or by prophylactically treating a patient afflicted with the disorders with an effective amount of the 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 patient who 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 the individual in need thereof.

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 in relation to pharmaceutical composition, 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 pharmaceutical 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 may be 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 ug/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 ul assay buffer and then incubated for 60 min (37° C, 5% CO2) in 60 ul assay buffer containing 1 uM 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 ul assay buffer. 30 ul 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 ul, incubated for 5 min and finally 25 ul 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 Examples 1-265 herein had activity in the radioligand binding assay with a Ki of about 0.1 nM to 1,000 nM against the orexin-1 and/or the orexin-2 receptor. The final compounds of Examples 1-16, 18, 21, 29, 31, 34, 49, 58, 68, 69, 71, 75-76, 81, 85-88, 92, 93, 95-99, 101-130, 132-140, 142-146, 148, 150-153, 155, 156, 158-167, 179, 189, 191, 198, 199, 200, 203-206, 209, 230, 231, 234-237, 239-244, 246, 248-251, 262, and 264 had activity in the radioligand binding assay with a Ki of about 0.1 nM to 10 nM against the

orexin-1 and/or the orexin-2 receptor. All of the final compounds of Examples 1-265 herein had activity in the FLIPR assay with an IC50 of about 10 nM to 10,000 nM against the orexin-1 and/or the orexin-2 receptor. The final compounds of Examples 1, 3, 4, 7, 10, 11, 12, 14, 34, 36, 54, 60, 71, 72, 74, 75, 76, 81, 85, 88, 92, 93, 95-99, 101, 102, 104-110, 112-129, 132-140, 142, 143, 145, 146, 148, 150, 153, 155, 156, 158, 160, 162, 165, 166, 167, 198, 199, 230, 231, 233-237, 240, 242, 244, 248-251, and 264 had activity in the FLIPR assay with an IC50 of about 10 nM to 100 nM against the orexin-1 and/or the orexin-2 receptor. Such a result is indicative of the intrinsic activity of the compounds in use as antagonists of the orexin-1 receptor and/or the orexin-2 receptor.

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 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 occuring 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 tumour/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; dissociateive 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 specific embodiments the present invention provides 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 dperession disorder; treating or controlling bipolar disorder; or treating, controlling, ameliorating or reducing the risk of schizophrenia, in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of the present invention.

The subject compounds are further useful 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 patients (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 patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, 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 patient, 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 patient 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 patient per day; in another embodiment about 0.5 mg to 200 mg per patient per day; and in yet another embodiment about 5 mg to 50 mg per patient 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 patient 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 1 hour 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 includes 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 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 conbination 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, include, 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; 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, 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 acceptble 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 acceptble 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 are 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.

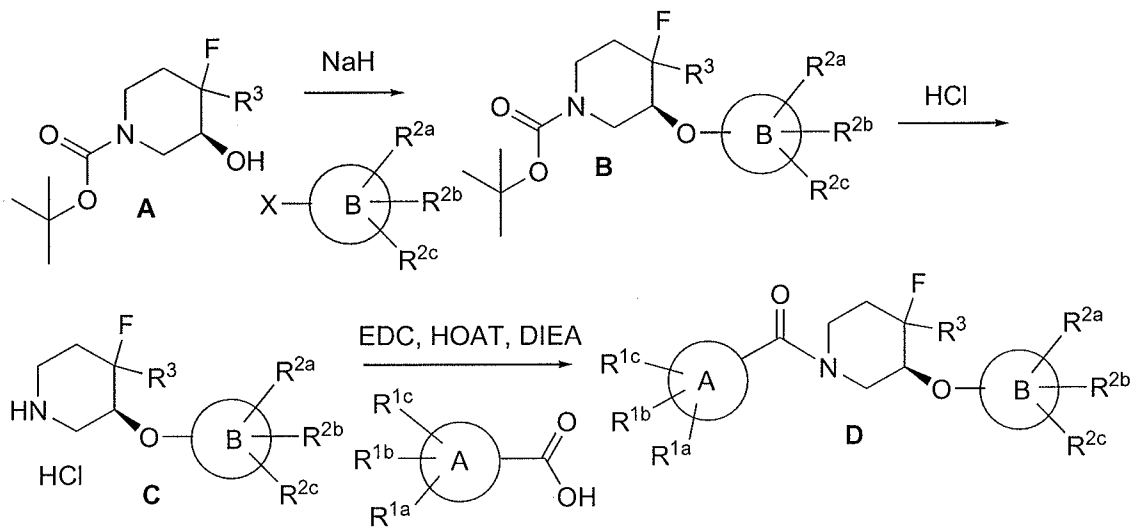
Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents 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 WO01/68609, WO2004/085403, WO2005/118548, WO 2008/147518, WO 2010/048012) or as illustrated herein. The following abbreviations are used herein: Me: methyl; Et: ethyl; t-Bu: *tert*-butyl; Ar: aryl; Ph: phenyl; Bn: benzyl; Ac: acetyl; THF: tetrahydrofuran; DEAD: diethylazodicarboxylate; DIPEA: N,N-diisopropylethylamine; NMM: N-methylmorpholine; DMSO: dimethylsulfoxide; EDC: N-(3-

Dimethylaminopropyl)-N'-ethylcarbodiimide; HOBT: hydroxybenzotriazole hydrate; Boc: tert-butyloxy carbonyl; Et_3N: triethylamine; DCM: dichloromethane; DCE: dichloroethane; BSA: bovine serum albumin; TFA: trifluoracetic acid; DMF: N,N-dimethylformamide; MTBE: methyl tert-butyl ether; $SOCl_2$: thionyl chloride; CDI: carbonyl diimidazole; PyClu: 1-(chloro-1-pyrrolidinylmethylene)-pyrrolidinium hexafluorophosphate; rt: room temperature; HPLC: high performance liquid chromatography. 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.

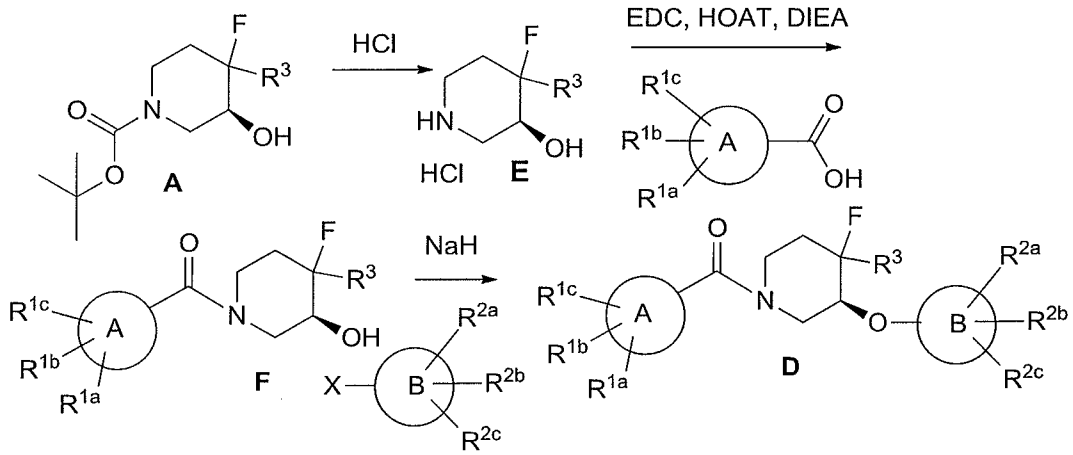
REACTION SCHEME 1



Compounds of the invention are prepared as outlined in Scheme 1. Protected 3-hydroxypiperidine **A** is alkylated with a 2-halohetercycle using NaH as the base to provide **B**. Some examples 2-halohetercycles are 2-chloroquinolines or 2-fluoroquinolines. Alternative alkylating agents, such as 2-chloropyridines or 2-fluoropyridines, are used to provide general structures **B**. Standard deprotection conditions, *e.g.* HCl, is used to produce **C**. Other acids,

such as TFA, may also be used to effect the deprotection. Intermediate **C** is reacted with a carboxylic acid under standard EDC-HOAT coupling conditions to provide **D**. Other standard coupling conditions may be employed in the synthesis of such amides, such as use of an alternative coupling reagent like PyBOP or HATU, or activation of the carboxylic acid as an acid anhydride or acid chloride.

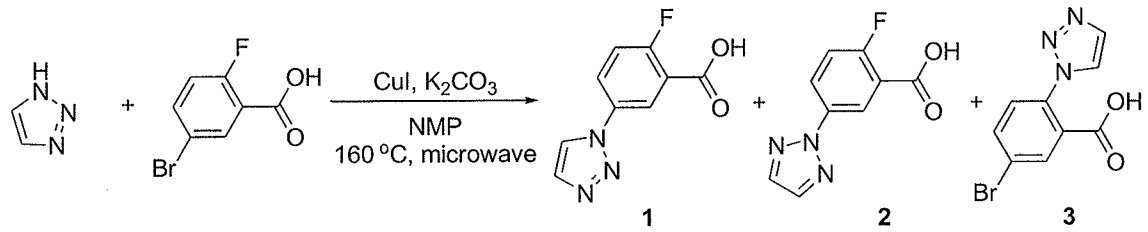
REACTION SCHEME 2



Alternatively, compounds of the invention are prepared as outlined in Scheme 2. Standard deprotection conditions of **A**, *e.g.* HCl, is used to produce **E**. Intermediate **E** can be reacted with a carboxylic acid under standard EDC-HOAT coupling conditions to provide **F**. Other standard coupling conditions may be employed in the synthesis of such amides, such as use of an alternative coupling reagent like PyBOP or HATU, or activation of the carboxylic acid as an acid anhydride or acid chloride. Intermediate **F** is alkylated with a 2-haloheterocycle using NaH as the base to provide **D**. Some examples of 2-halohetercoycles are 2-chloroquinolines or 2-fluoroquinolines. Alternative alkylating agents, such as 2-chloropyridines or 2-fluoropyridines, may also be used to provide general structures **D**.

The carboxylic acids (RCO_2H) and alkylating agents (*e.g.* 2-chloropyridines) used to prepare the compounds of the present invention are readily available or they may be obtained from commercial sources or synthesized by methodology familiar to those skilled in the art and as described in the chemical literature. Synthetic routes to the examples not previously disclosed are outlined in the experimental section below.

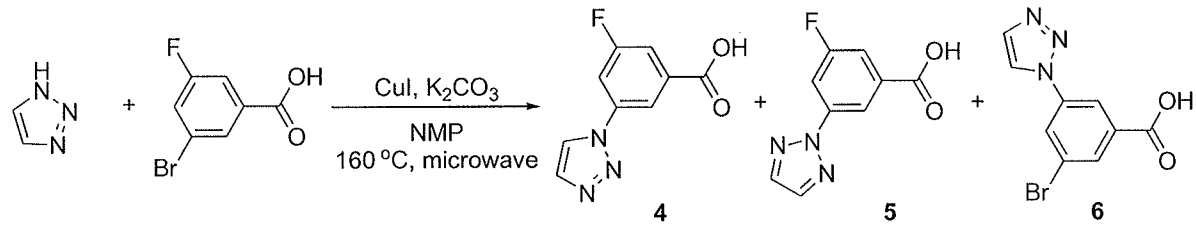
INTERMEDIATES 1, 2, 3



2-Fluoro-5-(1*H*-1,2,3-triazol-1-yl)benzoic acid, 2-fluoro-5-(2*H*-1,2,3-triazol-2-yl)benzoic acid, and 5-bromo-2-(1*H*-1,2,3-triazol-1-yl)benzoic acid

A solution of 1,2,3-triazole (63.1 mg, 0.913 mmol), 5-bromo-2-fluorobenzoic acid (100 mg, 0.457 mmol), copper(I) iodide (8.70 mg, 0.046 mmol), and potassium carbonate (126 mg, 0.913 mmol) in NMP (2 mL) was heated to 160 °C under microwave radiation for 3 h. The reaction mixture was filtered and purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compounds in order of elution: 2-fluoro-5-(1*H*-1,2,3-triazol-1-yl)benzoic acid [MS: m/z = 208 (M + 1)], 5-bromo-2-(1*H*-1,2,3-triazol-1-yl)benzoic acid [MS: m/z = 268, 270 (M + 1)], and 2-fluoro-5-(2*H*-1,2,3-triazol-2-yl)benzoic acid [MS: m/z = 208 (M + 1)].

INTERMEDIATES 4, 5, 6

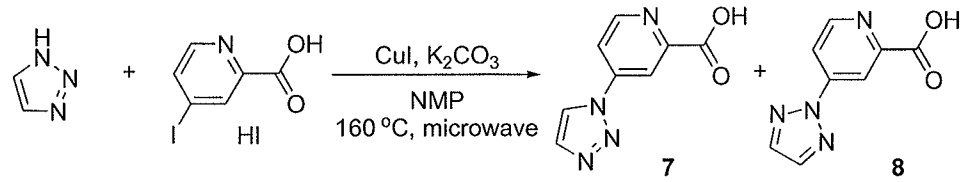


3-Fluoro-5-(1*H*-1,2,3-triazol-1-yl)benzoic acid, 3-fluoro-5-(2*H*-1,2,3-triazol-2-yl)benzoic acid, and 3-bromo-5-(1*H*-1,2,3-triazol-1-yl)benzoic acid

A solution of 1,2,3-triazole (63.1 mg, 0.913 mmol), 5-bromo-2-fluorobenzoic acid (100 mg, 0.457 mmol), copper(I) iodide (8.70 mg, 0.046 mmol), and potassium carbonate (126 mg, 0.913 mmol) in NMP (2 mL) was heated to 160 °C under microwave radiation for 13 h. The reaction mixture was filtered and purified by HPLC using a reversed phase C18 column and

eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compounds in order of elution: 3-fluoro-5-(1*H*-1,2,3-triazol-1-yl)benzoic acid [MS: m/z = 208 (M + 1)], 3-bromo-5-(1*H*-1,2,3-triazol-1-yl)benzoic acid [MS: m/z = 268, 270 (M + 1)], and 3-fluoro-5-(2*H*-1,2,3-triazol-2-yl)benzoic acid [MS: m/z = 208 (M + 1)].

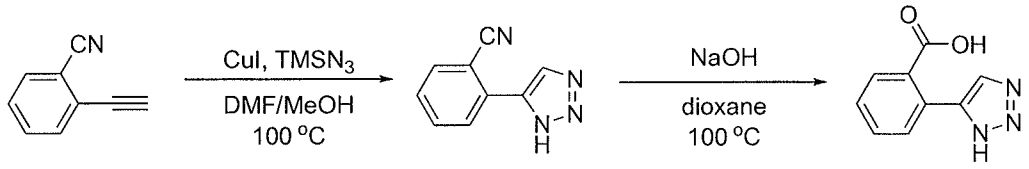
INTERMEDIATES 7, 8



4-(1*H*-1,2,3-Triazol-1-yl)pyridine-2-carboxylic acid and 4-(2*H*-1,2,3-triazol-2-yl)pyridine-2-carboxylic acid

A solution of 1,2,3-triazole (55.0 mg, 0.796 mmol), 4-iodopyridine-2-carboxylic acid hydroiodide (150 mg, 0.398 mmol), copper(I) iodide (7.58 mg, 0.040 mmol), and potassium carbonate (165 mg, 1.19 mmol) in NMP (2 mL) was heated to 160 °C under microwave radiation for 7 h. The reaction mixture was filtered and purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compounds in order of elution: 4-(1*H*-1,2,3-triazol-1-yl)pyridine-2-carboxylic acid [MS: m/z = 191 (M + 1)]and 4-(2*H*-1,2,3-triazol-2-yl)pyridine-2-carboxylic acid [MS: m/z = 191 (M + 1)].

INTERMEDIATE 9



2-(1*H*-1,2,3-Triazol-4-yl)benzonitrile

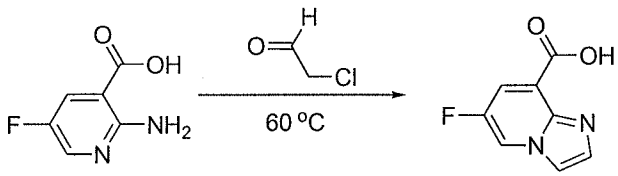
A solution of 2-ethynylbenzonitrile (500 mg, 3.93 mmol), copper(I) iodide (37.4 mg, 0.197 mmol), and trimethylsilyl azide (1.04 mL, 7.87 mmol) in DMF (9 mL) and MeOH (0.9 mL) was heated to 100 °C for 22 h. The reaction mixture was poured onto water (50 mL) and

extracted with EtOAc (3 x 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound. MS: m/z = 171 (M + 1).

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

A solution of 2-(1*H*-1,2,3-triazol-4-yl)benzonitrile (669 mg, 3.93 mmol), and 10M sodium hydroxide (1.97 mL, 19.7 mmol) in dioxane (10 mL) was heated to 100 °C for 18 h. The reaction mixture was concentrated *in vacuo*, dissolved in water (5 mL), and purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compound. MS: m/z = 190 (M + 1).

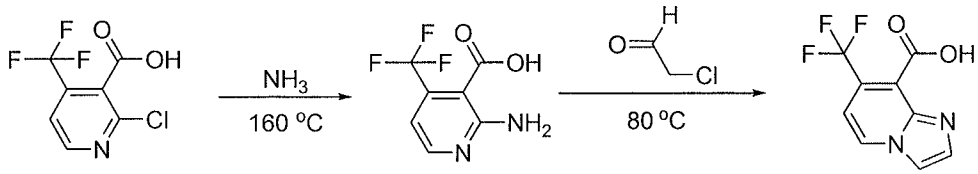
INTERMEDIATE 10



6-Fluoroimidazo[1,2-a]pyridine-8-carboxylic acid

A mixture of 2-amino-5-fluoronicotinic acid (100 mg, 0.641 mmol) and 50% aq. chloroacetaldehyde (0.107 mL, 0.833 mmol) was heated to 60 °C for 2 h. The reaction mixture was concentrated *in vacuo* to yield the title compound. MS: m/z = 181 (M + 1).

INTERMEDIATE 11



2-Amino-4-(trifluoromethyl)nicotinic acid

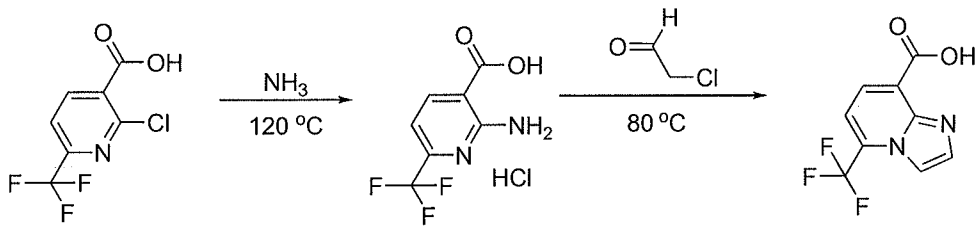
A mixture of 2-chloro-4-(trifluoromethyl)nicotinic acid (1.00 g, 4.43 mmol) and 7M ammonia in MeOH (15.0 mL, 105 mmol) in a steel pressure bomb was heated to 120 °C for 18 h and 160 °C for 20 h. The reaction mixture was concentrated *in vacuo*, then dissolved in 10% HCl (5 mL) and purified directly by HPLC using a reversed phase

C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compound. MS: m/z = 207 (M + 1).

7-(Trifluoromethyl)imidazo[1,2-a]pyridine-8-carboxylic acid

A mixture of 2-amino-4-(trifluoromethyl)nicotinic acid (74.0 mg, 0.359 mmol) and 50% aq. chloroacetaldehyde (0.093 mL, 0.718 mmol) was heated to 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* to yield the title compound. MS: m/z = 231 (M + 1).

INTERMEDIATE 12



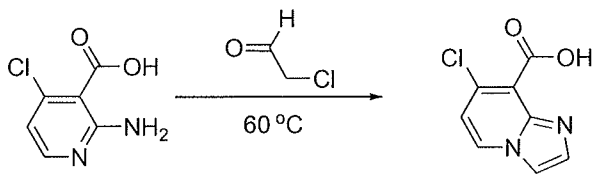
2-Amino-6-(trifluoromethyl)nicotinic acid hydrochloride

A mixture of 2-chloro-6-(trifluoromethyl)nicotinic acid (1.00 g, 4.43 mmol) and 7M ammonia in MeOH (20.0 mL, 140 mmol) in a steel pressure bomb was heated to 120 °C for 64 h. The reaction mixture was concentrated *in vacuo*, then added 10% HCl (5 mL) and the resulting solid was filtered, washed with 10% HCl (2 x 5 mL) and dried to yield the title compound. MS: m/z = 207 (M + 1).

5-(Trifluoromethyl)imidazo[1,2-a]pyridine-8-carboxylic acid

A mixture of 2-amino-6-(trifluoromethyl)nicotinic acid (114 mg, 0.470 mmol) and 50% aq. chloroacetaldehyde (0.121 mL, 0.940 mmol) was heated to 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* to yield the title compound. MS: m/z = 231 (M + 1).

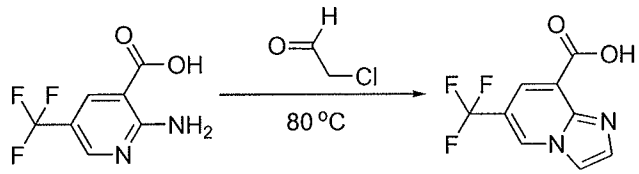
INTERMEDIATE 13



7-Chloroimidazo[1,2-a]pyridine-8-carboxylic acid

A mixture of 2-amino-4-chloronicotinic acid hydrochloride (153 mg, 0.732 mmol) and 50% aq. chloroacetaldehyde (0.369 mL, 2.86 mmol) was heated to 60 °C for 26 h. The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compound. MS: m/z = 197 (M + 1).

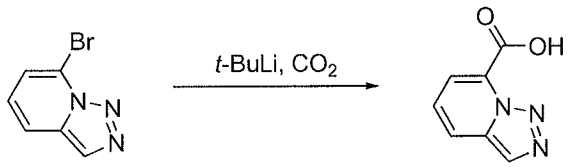
INTERMEDIATE 14



6-(Trifluoromethyl)imidazo[1,2-a]pyridine-8-carboxylic acid

A mixture of 2-amino-5-trifluoronicotinic acid hydrochloride (100 mg, 0.485 mmol) and 50% aq. chloroacetaldehyde (0.125 mL, 0.970 mmol) was heated to 80 °C for 18 h. The reaction mixture was concentrated *in vacuo* to yield the title compound. MS: m/z = 231 (M + 1).

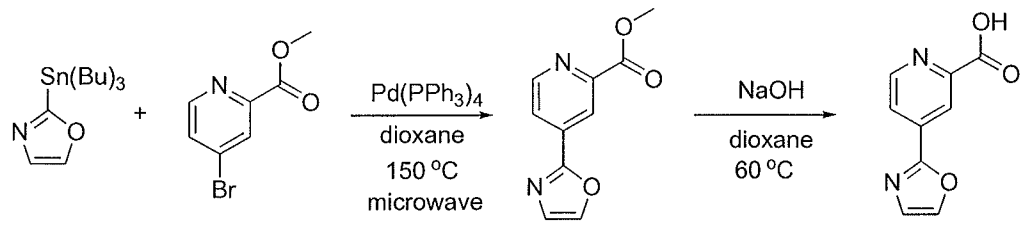
INTERMEDIATE 15



[1,2,3]Triazolo[1,5-*a*]pyridine-7-carboxylic acid

To a solution of 7-bromo[1,2,3]triazolo[1,5-a]pyridine (172 mg, 0.869 mmol) in THF (2 mL) at -78 °C was added *tert*-butyllithium (1.12 mL, 1.91 mmol, 1.7 M) and the solution was stirred for 1 h. The reaction mixture was poured onto crushed dried ice and allowed to warm to ambient temperature. The resulting yellow solid was filtered, washed with THF (2 x 3 mL), and dried to yield the title compound. MS: m/z = 164 (M + 1).

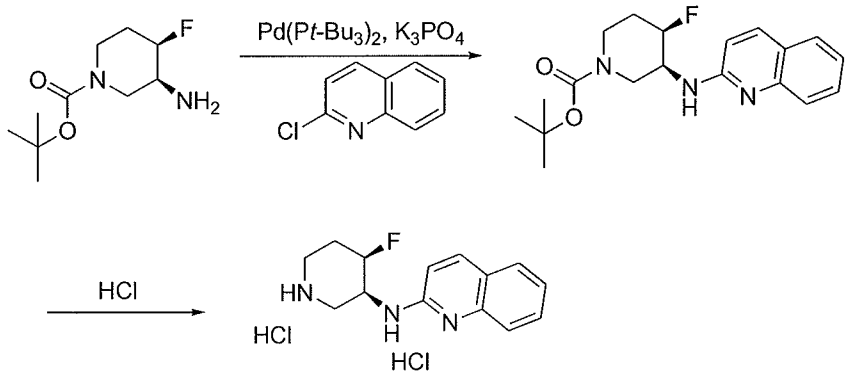
INTERMEDIATE 16



4-(1,3-Oxazol-2-yl)pyridine-2-carboxylic acid

A solution of methyl 4-bromopicolinate (100 mg, 0.463 mmol), 2-(tributylstannyl)oxazole (249 mg, 0.694 mmol), and tetrakis(triphenylphosphine)palladium (26.7 mg, 0.023 mmol) in dioxane (2 mL) was heated to 150 °C under microwave radiation for 15 min. To the reaction mixture was added 10M sodium hydroxide (0.140 mL, 1.40 mmol) and the solution was heated to 60 °C for 18 h. The reaction mixture was concentrated *in vacuo*, dissolved in water (3 mL), filtered, and purified by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compound. MS: m/z = 191 (M + 1).

INTERMEDIATE 17



tert-Butyl (3*S*,4*R*)-4-fluoro-3-(quinolin-2-ylamino)piperidine-1-carboxylate

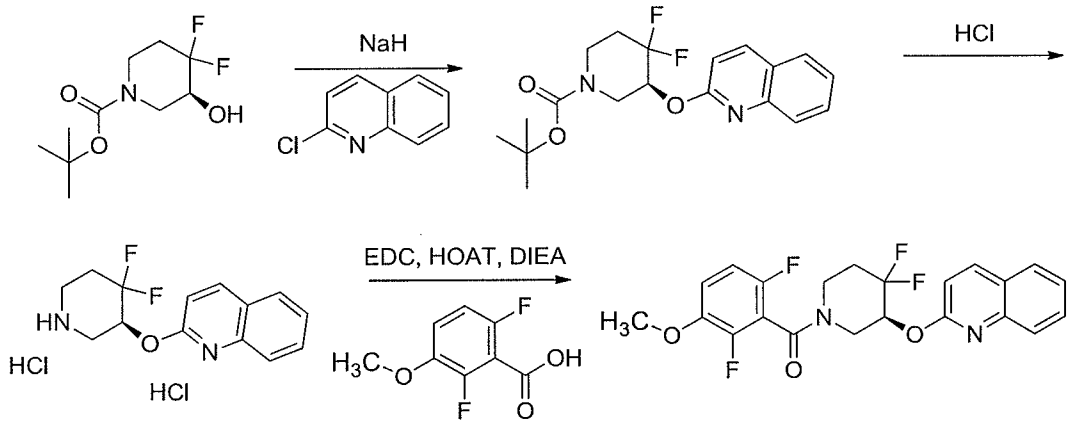
A solution of methyl 2-chloroquinoline (15.0 mg, 0.092 mmol), *tert*-butyl (3*S*,4*R*)-3-amino-4-fluoropiperidine-1-carboxylate (31.1 mg, 0.101 mmol), bis(tri-*tert*-butylylphosphine)palladium (1.8 mg, 0.0037 mmol), and tripotassium phosphate (58.4 mg, 0.275 mmol) in DMA (0.2 mL) was heated to 100 °C for 20 h. The reaction mixture was filtered, and purified by HPLC using a reversed phase C18 column and eluting with a gradient of

H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compound. MS: m/z = 346 (M + 1).

N-[(3*S*,4*R*)-4-Fluoropiperidin-3-yl]quinolin-2-amine dihydrochloride

4M HCl in dioxane (0.724 mL, 2.90 mmol) was added to *tert*-butyl (3*S*,4*R*)-4-fluoro-3-(quinolin-2-ylamino)piperidine-1-carboxylate (10 mg, 0.029 mmol) and the solution was stirred at ambient temperature for 2 h. The reaction mixture was concentrated *in vacuo* to provide the title compound as a white solid. MS: m/z = 246 (M + 1).

EXAMPLE 1



tert-Butyl (3*S*)-4,4-difluoro-3-(quinolin-2-yloxy)piperidine-1-carboxylate

Sodium hydride (2.36 g, 59.0 mmol) was added to a solution of *tert*-butyl (3*S*)-4,4-difluoro-3-hydroxypiperidine-1-carboxylate (7.00 g, 29.5 mmol) in DMSO (10 mL) and the solution was stirred at ambient temperature for 0.5 h. 2-Chloroquinoline (5.79 g, 35.4 mmol) was added and the solution was stirred for 18 h. The reaction mixture was poured onto water (500 mL) and extracted with Et_2O (3 x 150 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified directly by column chromatography on silica gel, eluting with Hex:EtOAc 100:0 --> 80:20 to provide the title compound as a white solid. MS: m/z = 365 (M + 1).

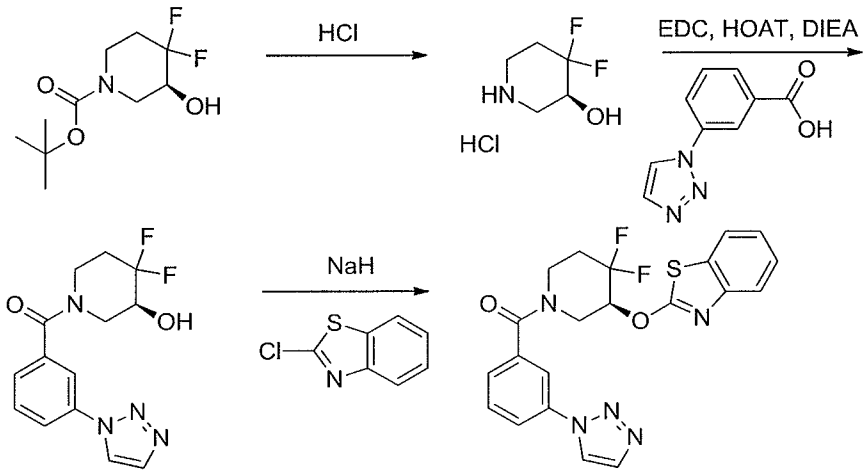
2-{[(3*S*)-4,4-Difluoropiperidin-3-yl]oxy}quinoline dihydrochloride

4M HCl in dioxane (70.7 mL, 283 mmol) was added to *tert*-butyl (3*S*)-4,4-difluoro-3-(quinolin-2-yloxy)piperidine-1-carboxylate (10.3 g, 28.3 mmol) and the suspension was stirred at ambient temperature for 72 h. The reaction mixture was concentrated *in vacuo* to provide the title compound as a white solid. MS: m/z = 265 (M + 1).

(3*S*)-(4,4-Difluoro-3-(quinolin-2-yloxy)piperidin-1-yl)(2,6-difluoro-3-methoxyphenyl)methanone

A solution of EDC (6.82 mg, 0.036 mmol), HOAT (4.84 mg, 0.036 mmol), DIEA (0.026 mL, 0.148 mmol), 2,6-difluoro-3-methoxybenzoic acid (7.25 mg, 0.039 mmol) was stirred in DMF (0.5 mL) for 0.5 h, followed by the addition of 2-{[(3*S*)-4,4-difluoropiperidin-3-yl]oxy}quinoline dihydrochloride (10.0 mg, 0.030 mmol). The solution was stirred for 6 h at ambient temperature, then purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compound as the trifluoroacetate salt.MS: m/z = 435 (M + 1); HRMS: m/z = 435.1308 (M+1); calculated m/z = 435.1326 (M+1) for $C_{22}H_{19}F_4N_2O_3$.

EXAMPLE 2



(3*S*)-4,4-Difluoropiperidin-3-ol hydrochloride

4M HCl in dioxane (19.6 mL, 78 mmol) was added to *tert*-butyl (3*S*)-4,4-difluoro-3-(quinolin-2-yloxy)piperidine-1-carboxylate (6.19 g, 26.1 mmol) and the suspension was stirred

at ambient temperature for 1 h. The resulting white solid was filtered, washed with dioxane (2 x 20 mL), and dried provide the title compound as a white solid.

(*S*)-(3-(1*H*-1,2,3-Triazol-1-yl)phenyl)(4,4-difluoro-3-hydroxypiperidin-1-yl)methanone

A solution of EDC (970 mg, 5.06 mmol), HOAT (689 g, 5.06 mmol), DIEA (3.68 mL, 21.1 mmol), and 3-(1*H*-1,2,3-triazol-1-yl)benzoic acid (798 mg, 4.22 mmol) was stirred in DMF (5 mL) for 0.5 h, followed by the addition of (3*S*)-4,4-difluoropiperidin-3-ol hydrochloride (732 mg, 4.22 mmol) in DMF (0.5 mL). The solution was stirred for 16 h at ambient temperature, then filtered and concentrated *in vacuo*. The crude was purified by column chromatography on silica gel, eluting with DCM:EtOAc 100:0 --> 0:100 to provide the title compound as a white solid. MS: m/z = 309 (M + 1).

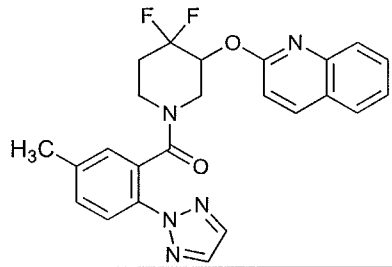
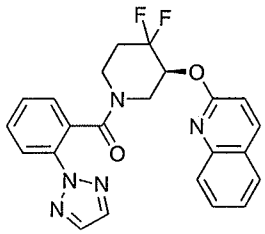
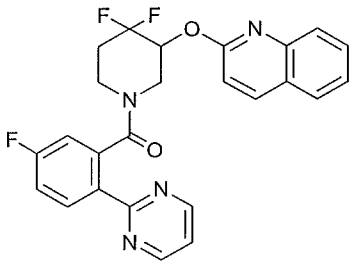
(*S*)-(3-(1*H*-1,2,3-Triazol-1-yl)phenyl)(3-(benzo[d]thiazol-2-yloxy)-4,4-difluoropiperidin-1-yl)methanone

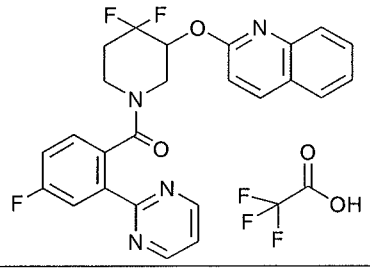
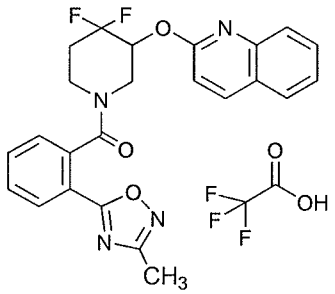
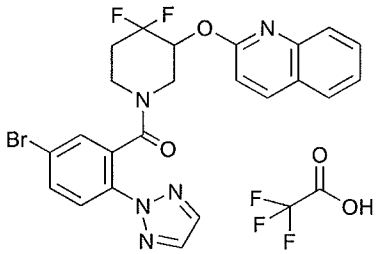
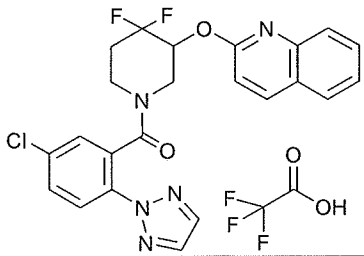
Sodium hydride (5.19 mg, 0.130 mmol) was added to a solution of (*S*)-(3-(1*H*-1,2,3-triazol-1-yl)phenyl)(4,4-difluoro-3-hydroxypiperidin-1-yl)methanone (20.0 mg, 0.065 mmol) in DMSO (1 mL) and the solution was stirred at ambient temperature for 0.5 h. 2-chlorobenzothiazole (13.0 mg, 0.078 mmol) was added and the solution was stirred for 16 h at ambient temperature. The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1 The desired fractions were concentrated to yield the title compound as the trifluoroacetate salt. MS: m/z = 442 (M + 1); HRMS: m/z = 442.1133 (M+1); calculated m/z = 442.1144 (M+1) for $C_{21}H_{18}F_2N_5O_2S_1$.

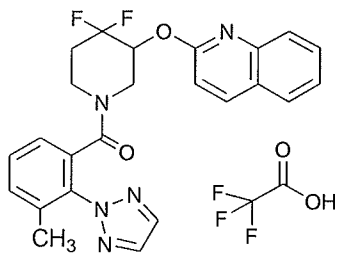
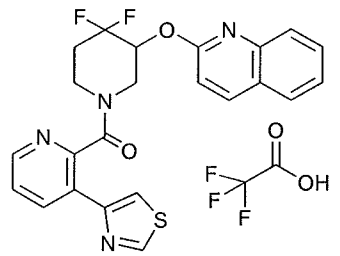
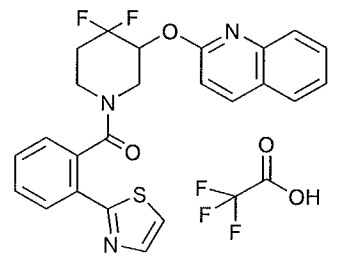
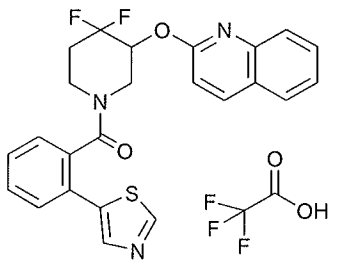
TABLE 1

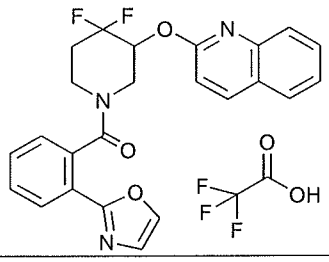
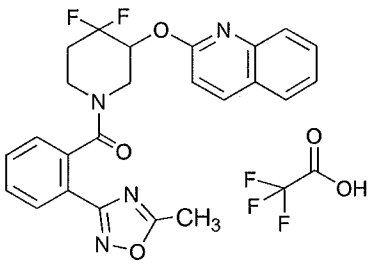
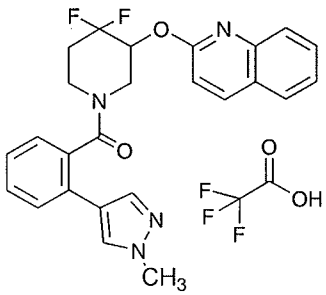
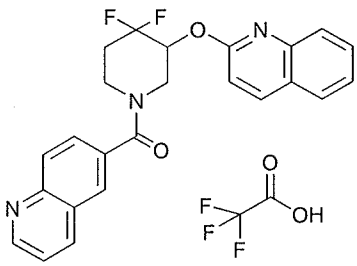
The following compounds were prepared using the foregoing methodology and general procedure described in Example 1, but substituting the appropriate acid for 2,6-difluoro-3-methoxybenzoic acid (Step 3) and the appropriate alkylating agent for 2-chloroquinoline (Step 1), as described in the foregoing Reaction Schemes and Examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in

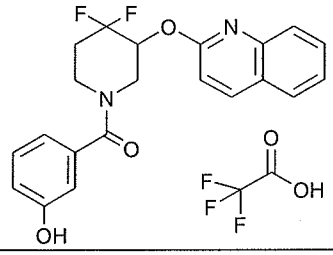
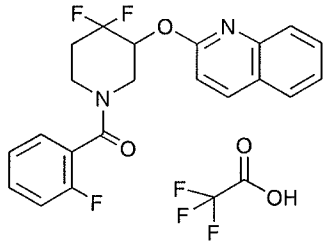
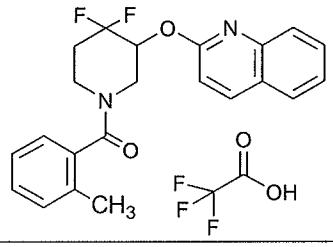
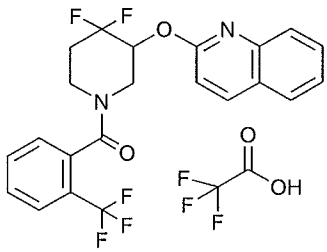
the art of organic synthesis from commercially available reagents using conventional reactions without undue experimentation.

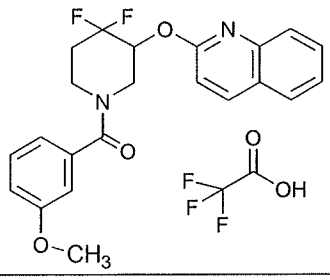
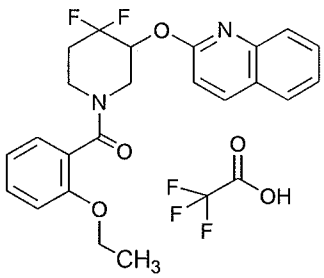
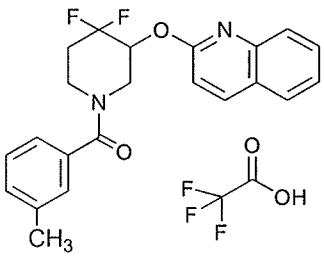
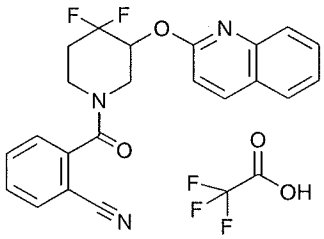
Example	Structure	Name	MS (M+1)
3		2-[(4,4-difluoro-1-{[5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline	450
4		2-[(3S)-(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline	436
5		2-({4,4-difluoro-1-[(5-fluoro-2-pyrimidin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline	465

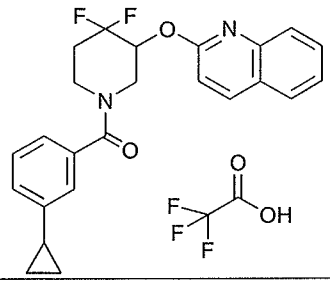
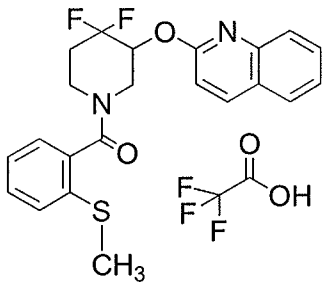
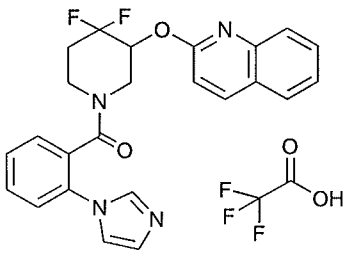
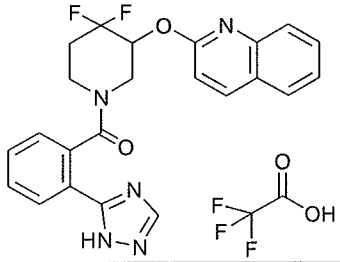
6		2-({4,4-difluoro-1-[(4-fluoro-2-pyrimidin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	465
7		2-[(4,4-difluoro-1-{[2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	451
8		2-[(1-{[5-bromo-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl)oxy]quinoline trifluoroacetate	514, 516
9		2-[(1-{[5-chloro-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl)oxy]quinoline trifluoroacetate	470

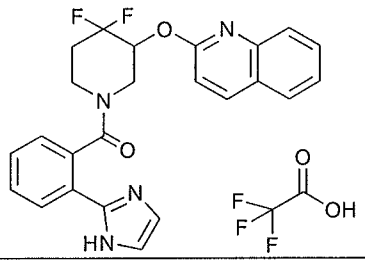
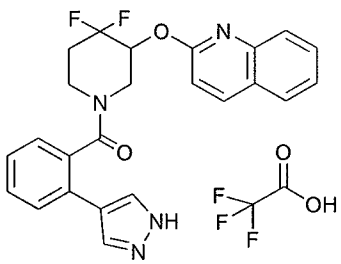
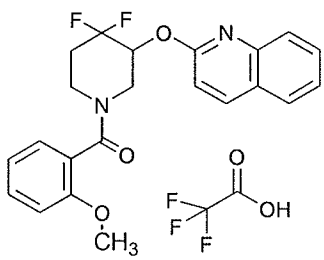
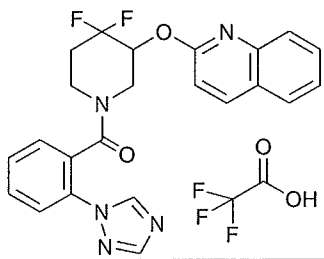
10		2-[(4,4-difluoro-1-{[3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	450
11		2-[(4,4-difluoro-1-{[3-(1,3-thiazol-4-yl)pyridin-2-yl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	453
12		2-[(4,4-difluoro-1-{[2-(1,3-thiazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	452
13		2-[(4,4-difluoro-1-{[2-(1,3-thiazol-5-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	452

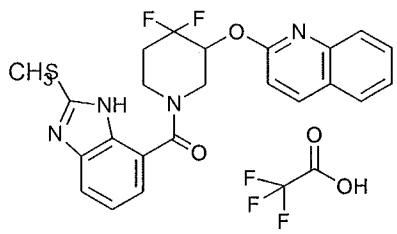
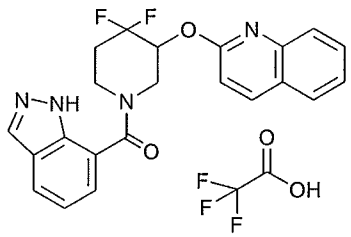
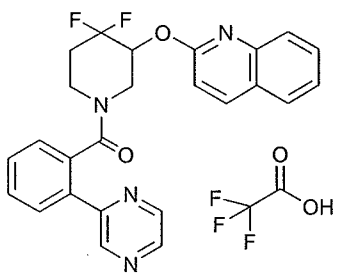
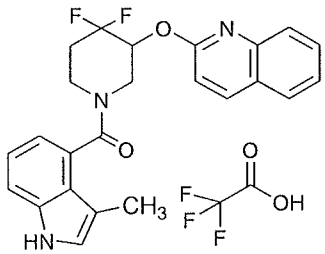
14		2-[(4,4-difluoro-1-{[2-(1,3-oxazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	436
15		2-[(4,4-difluoro-1-{[2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	451
16		2-[(4,4-difluoro-1-{[2-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	449
17		2-{[4,4-difluoro-1-(quinolin-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	420

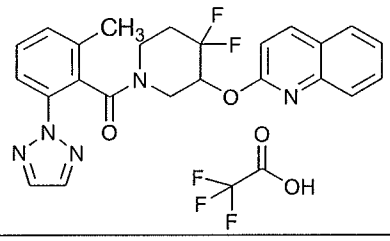
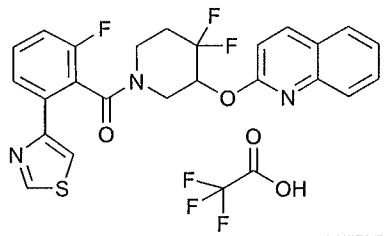
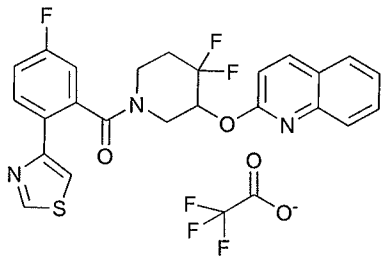
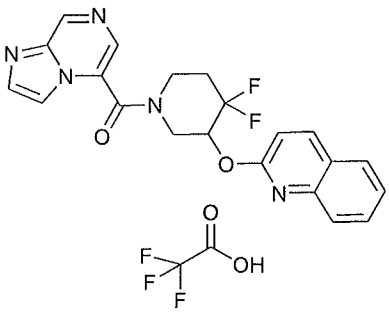
18		3-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}phenol trifluoroacetate	385
19		2-({4,4-difluoro-1-[(2-fluorophenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	387
20		2-({4,4-difluoro-1-[(2-methylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	383
21		2-[(4,4-difluoro-1-{[2-(trifluoromethyl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	437

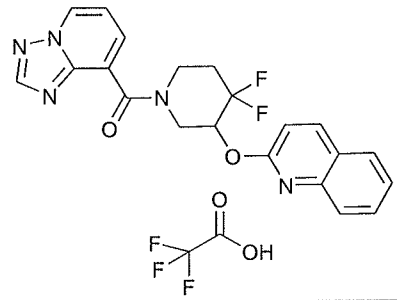
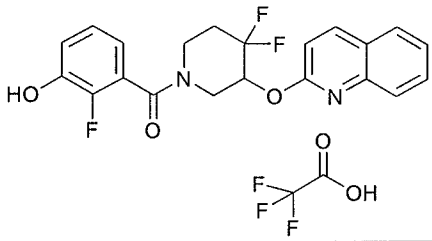
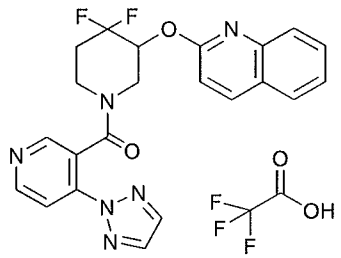
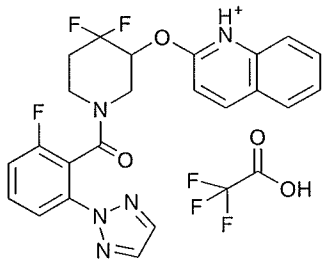
22		2-({4,4-difluoro-1-[(3-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	399
23		2-({1-[(2-ethoxyphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline trifluoroacetate	413
24		2-({4,4-difluoro-1-[(3-methylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	383
25		2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}benzonitrile trifluoroacetate	394

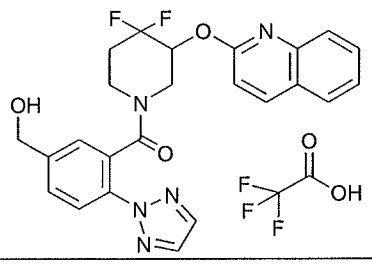
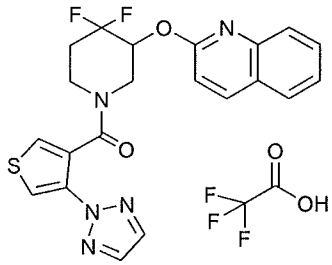
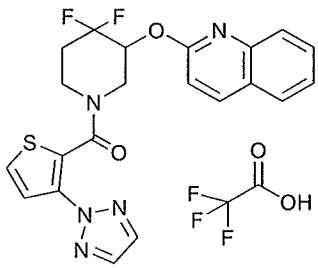
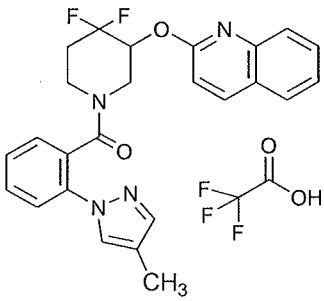
26		2-({1-[(3-cyclopropylphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline trifluoroacetate	409
27		2-[(4,4-difluoro-1-{[2-(methylsulfanyl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	415
28		2-[(4,4-difluoro-1-{[2-(1H-imidazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	435
29		2-[(4,4-difluoro-1-{[2-(1H-1,2,4-triazol-5-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	436

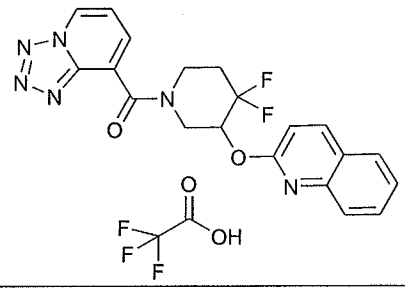
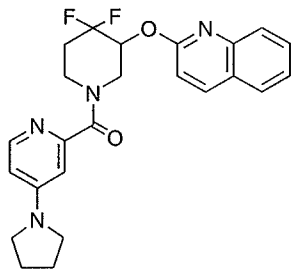
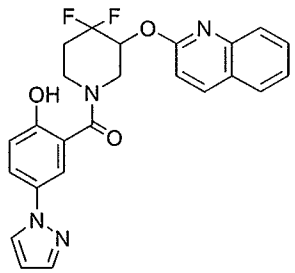
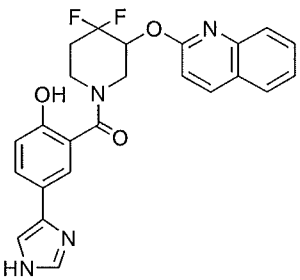
30		2-[(4,4-difluoro-1-{[2-(1H-imidazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	435
31		2-[(4,4-difluoro-1-{[2-(1H-pyrazol-4-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	435
32		2-({4,4-difluoro-1-[(2-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	399
33		2-[(4,4-difluoro-1-{[2-(1H-1,2,4-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	436

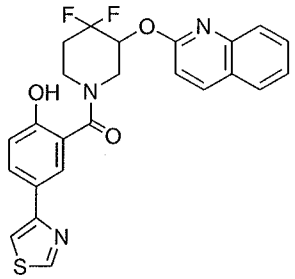
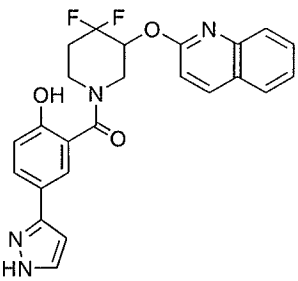
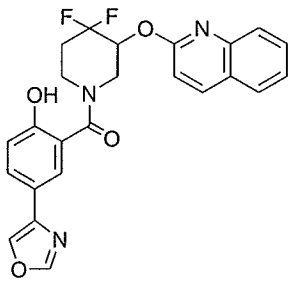
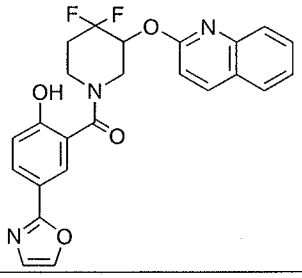
34		2-[(4,4-difluoro-1-{[2-(methylsulfanyl)-1H-benzimidazol-7-yl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	455
35		2-{[4,4-difluoro-1-(1H-indazol-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
36		2-({4,4-difluoro-1-[(2-pyrazin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	447
37		2-({4,4-difluoro-1-[(3-methyl-1H-indol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	422

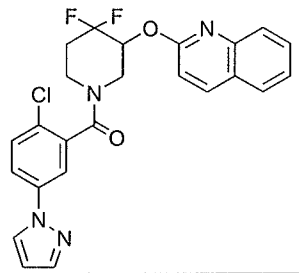
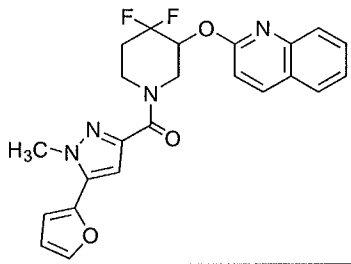
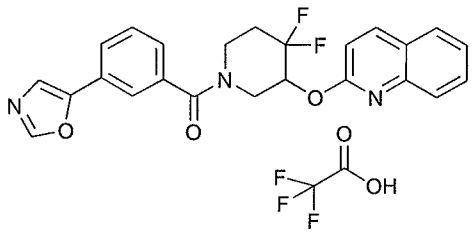
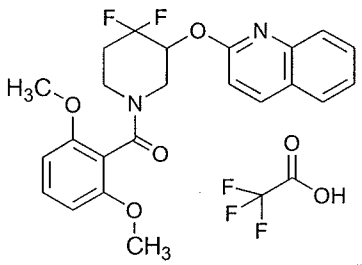
38		2-[(4,4-difluoro-1-{[2-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-piperidin-3-yl)oxy]quinoline trifluoroacetate	450
39		2-[(4,4-difluoro-1-{[2-fluoro-6-(1,3-thiazol-4-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	470
40		2-[(4,4-difluoro-1-{[5-fluoro-2-(1,3-thiazol-4-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	470
41		2-{[4,4-difluoro-1-(imidazo[1,2-a]pyrazin-5-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410

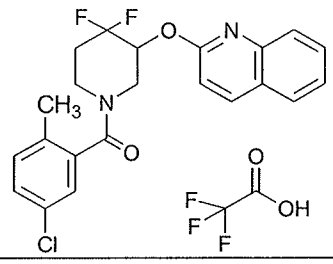
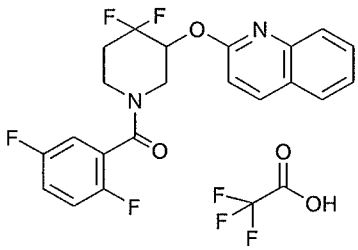
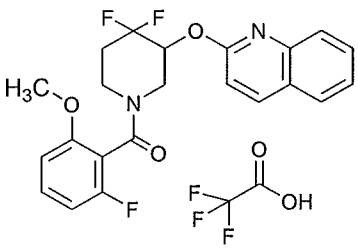
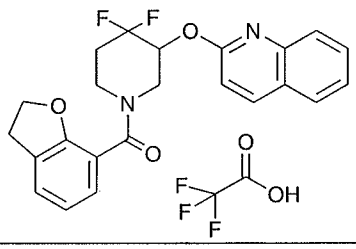
42		2-{[4,4-difluoro-1-([1,2,4]triazolo[1,5-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
43		3-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-2-fluorophenol trifluoroacetate	403
44		2-[(4,4-difluoro-1-{[4-(2H-1,2,3-triazol-2-yl)pyridin-3-yl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	437
45		2-[(4,4-difluoro-1-{[2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-piperidin-3-yl)oxy]quinoline trifluoroacetate	454

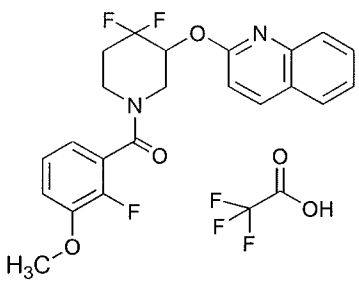
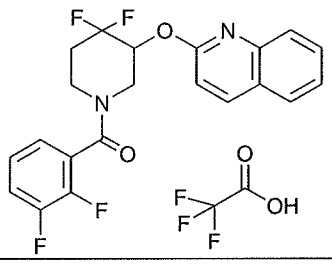
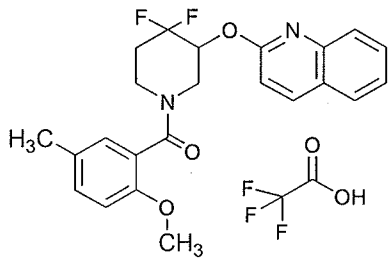
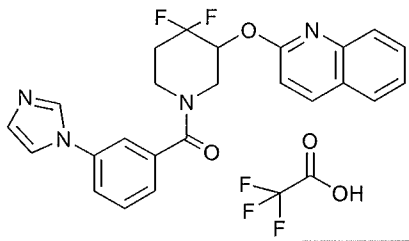
46		[3-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(2H-1,2,3-triazol-2-yl)phenyl]methanol trifluoroacetate	466
47		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)thiophen-3-yl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	442
48		2-[(4,4-difluoro-1-{[3-(2H-1,2,3-triazol-2-yl)thiophen-2-yl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	442
49		2-[(4,4-difluoro-1-{[2-(4-methyl-1H-pyrazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	449

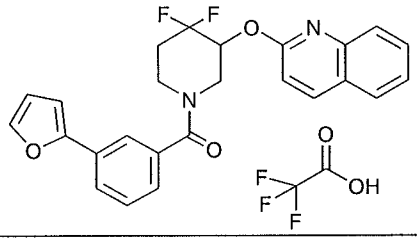
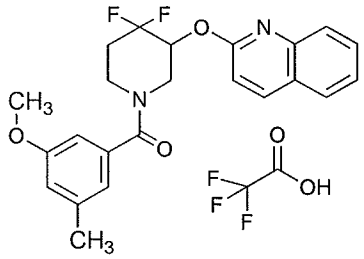
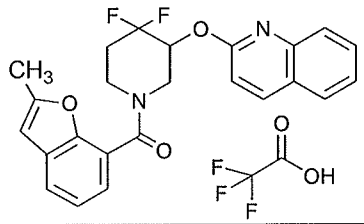
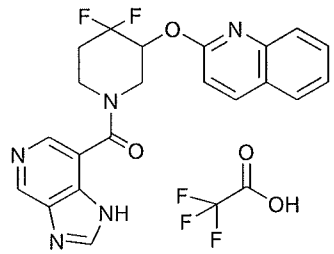
50		2-{[4,4-difluoro-1-(tetrazolo[1,5-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	411
51		2-({4,4-difluoro-1-[(4-pyrrolidin-1-ylpyridin-2-yl)carbonyl]piperidin-3-yl}oxy)quinoline	439
52		2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1H-pyrazol-1-yl)phenol	451
53		2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1H-imidazol-4-yl)phenol	451

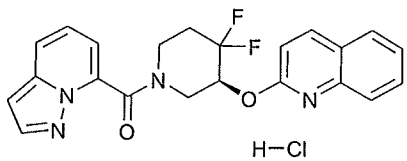
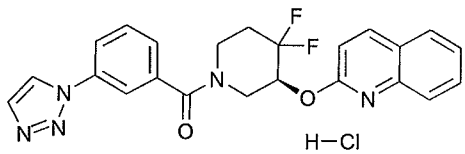
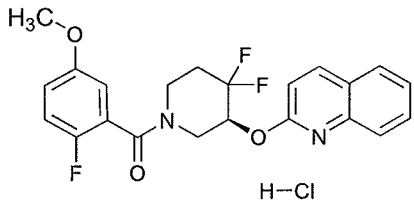
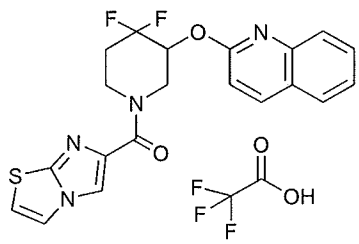
54		2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1,3-thiazol-4-yl)phenol	468
55		2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1H-pyrazol-3-yl)phenol	451
56		2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1,3-oxazol-4-yl)phenol	452
57		2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1,3-oxazol-2-yl)phenol	452

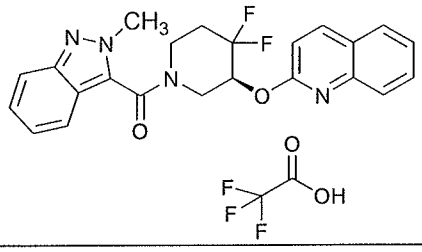
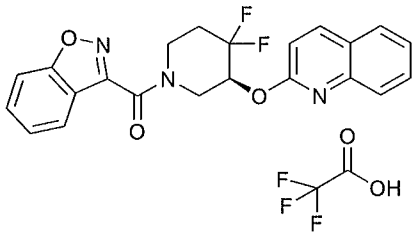
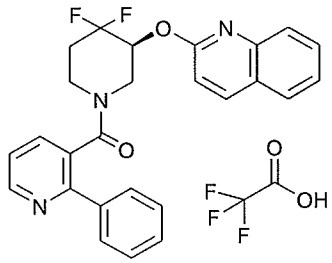
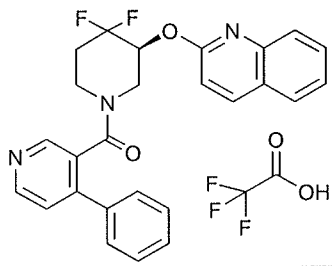
58		2-[(1-{[2-chloro-5-(1H-pyrazol-1-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl)oxy]quinoline	469
59		2-({4,4-difluoro-1-[(5-furan-2-yl-1-methyl-1H-pyrazol-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline	439
60		2-[(4,4-difluoro-1-{[3-(1,3-oxazol-5-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	436
61		2-({1-[(2,6-dimethoxyphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline trifluoroacetate	429

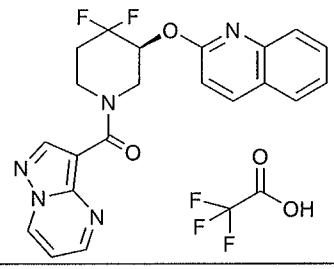
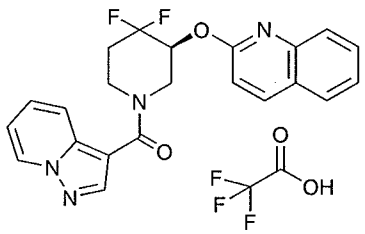
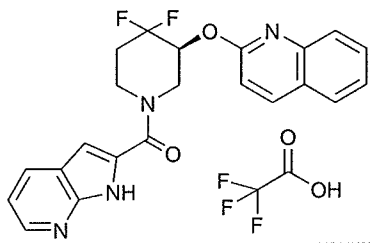
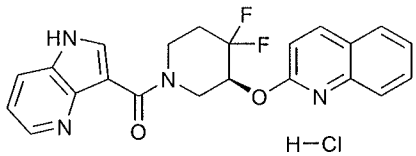
62		2-({1-[(5-chloro-2-methylphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline trifluoroacetate	417
63		2-({1-[(2,5-difluorophenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline trifluoroacetate	405
64		2-({4,4-difluoro-1-[(2-fluoro-6-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	417
65		2-{[1-(2,3-dihydro-1-benzofuran-7-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline trifluoroacetate	411

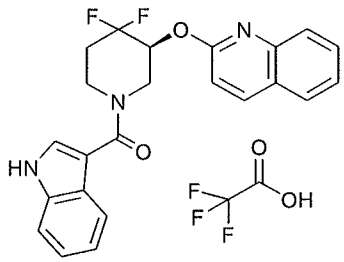
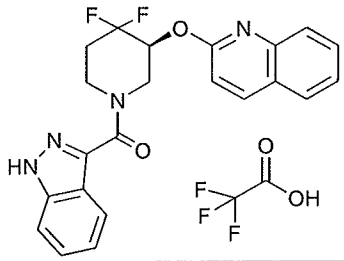
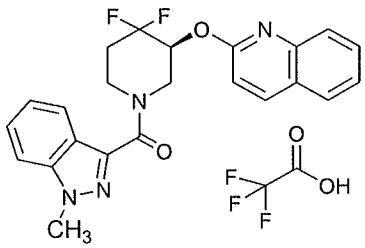
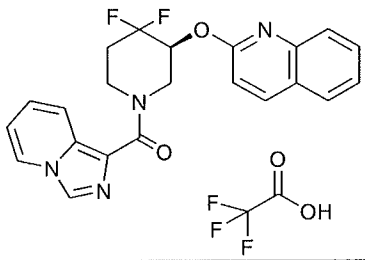
66		2-({4,4-difluoro-1-[(2-fluoro-3-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	417
67		2-({1-[(2,3-difluorophenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline trifluoroacetate	405
68		2-({4,4-difluoro-1-[(2-methoxy-5-methylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	413
69		2-[(4,4-difluoro-1-{[3-(1H-imidazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	435

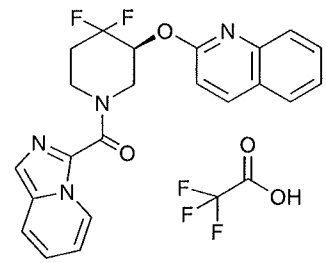
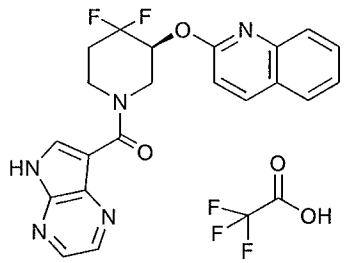
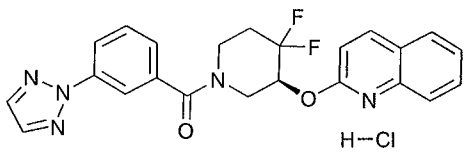
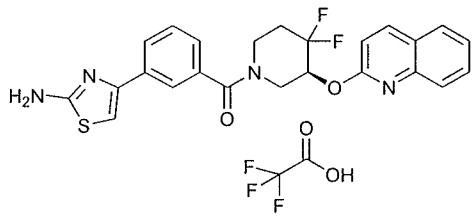
70		2-({4,4-difluoro-1-[(3-furan-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	435
71		2-({4,4-difluoro-1-[(3-methoxy-5-methylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	413
72		2-({4,4-difluoro-1-[(2-methyl-1-benzofuran-7-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	423
73		2-{[4,4-difluoro-1-(1H-imidazo[4,5-c]pyridin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410

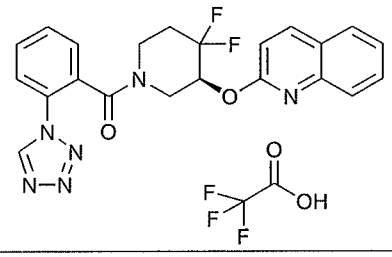
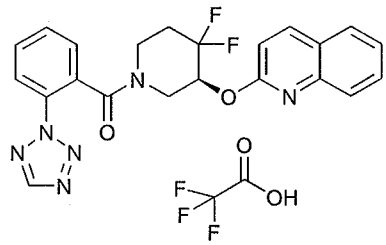
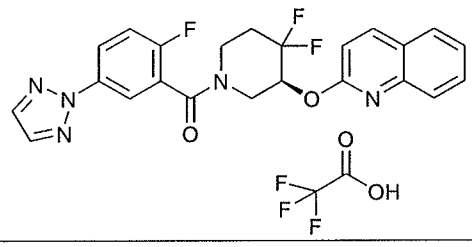
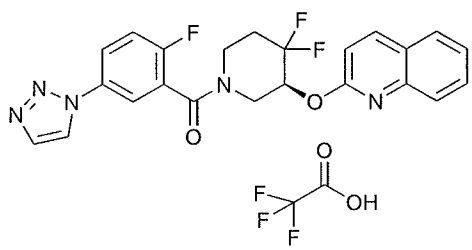
74	 H–Cl	2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyridin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline hydrochloride	409
75	 H–Cl	2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline hydrochloride	436
76	 H–Cl	2-({(3S)-4,4-difluoro-1-[(2-fluoro-5-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline hydrochloride	417
77		2-{[4,4-difluoro-1-(imidazo[2,1-b][1,3]thiazol-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	415

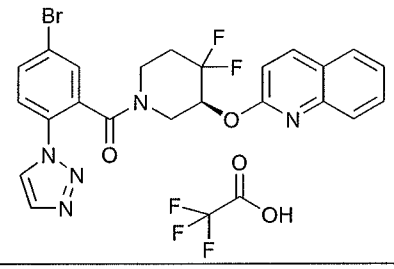
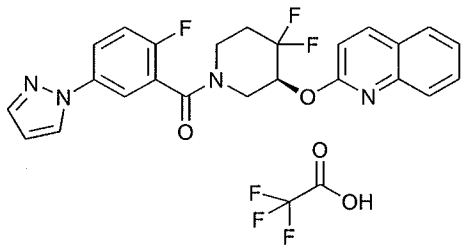
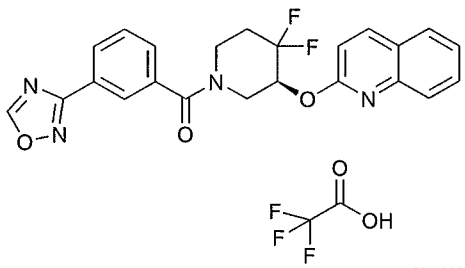
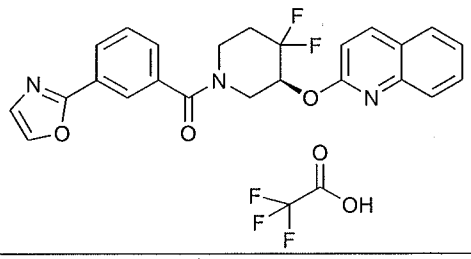
78		2-({(3S)-4,4-difluoro-1-[(2-methyl-2H-indazol-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	423
79		2-{[(3S)-1-(1,2-benzisoxazol-3-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline trifluoroacetate	410
80		2-({(3S)-4,4-difluoro-1-[(2-phenylpyridin-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	446
81		2-({(3S)-4,4-difluoro-1-[(4-phenylpyridin-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	446

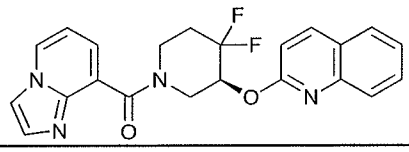
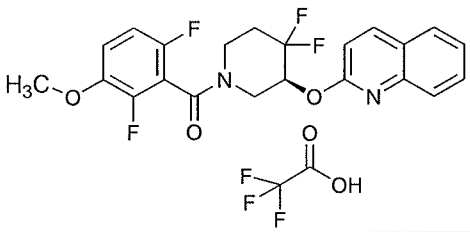
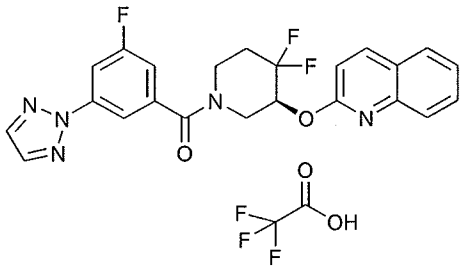
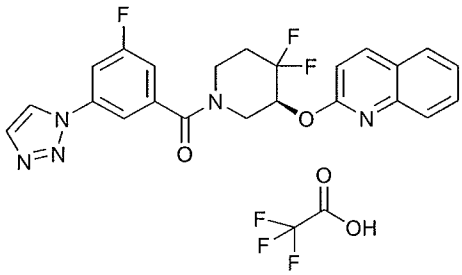
82		2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyrimidin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
83		2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
84		2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[2,3-b]pyridin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
85		2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[3,2-b]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline hydrochloride	409

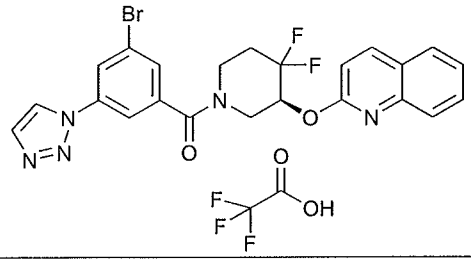
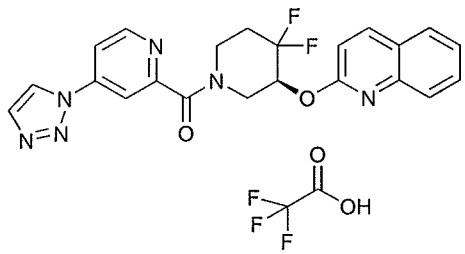
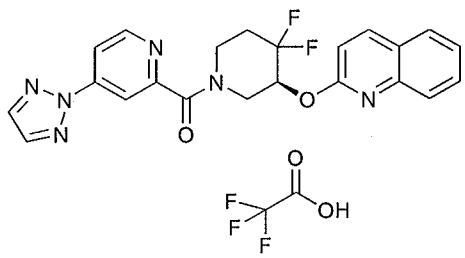
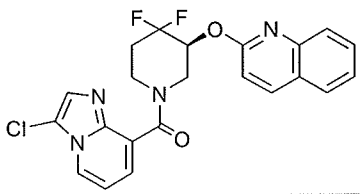
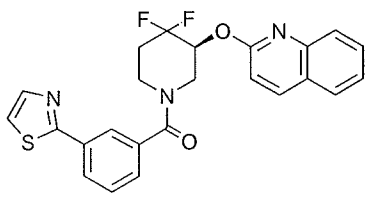
86		2-{[(3S)-4,4-difluoro-1-(1H-indol-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	408
87		2-{[(3S)-4,4-difluoro-1-(1H-indazol-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
88		2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-indazol-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	423
89		2-{[(3S)-4,4-difluoro-1-(imidazo[1,5-a]pyridin-1-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409

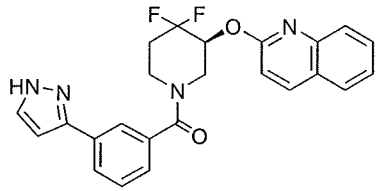
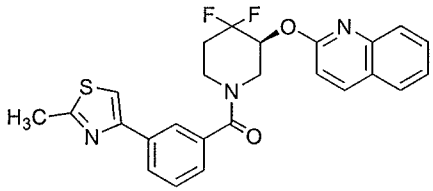
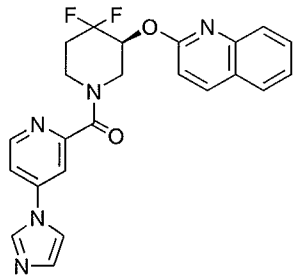
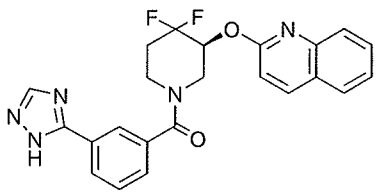
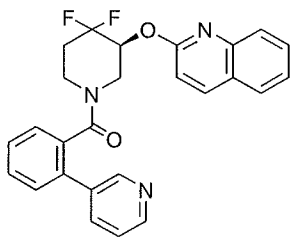
90		2-{[(3S)-4,4-difluoro-1-(imidazo[1,5-a]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
91		2-{[(3S)-4,4-difluoro-1-(5H-pyrrolo[2,3-b]pyrazin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
92		2-{[(3S)-4,4-difluoro-1-{[3-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline hydrochloride	436
93		4-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}phenyl)-1,3-thiazol-2-amine trifluoroacetate	467

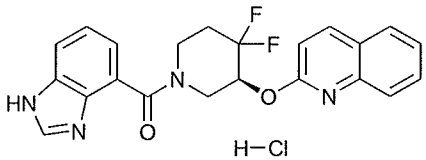
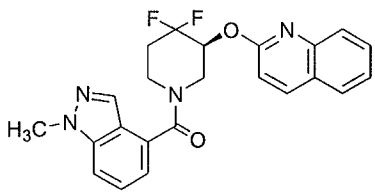
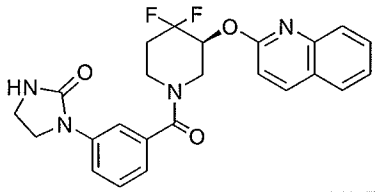
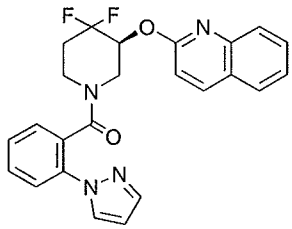
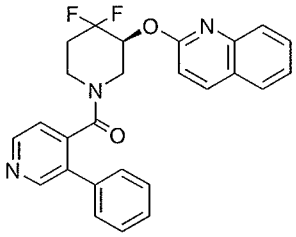
94		2-{[(3S)-4,4-difluoro-1-{[2-(1H-tetrazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	437
95		2-{[(3S)-4,4-difluoro-1-{[2-(2H-tetrazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	437
96		2-{[(3S)-4,4-difluoro-1-{[2-fluoro-5-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-piperidin-3-yl]oxy}quinoline trifluoroacetate	454
97		2-{[(3S)-4,4-difluoro-1-{[2-fluoro-5-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}-piperidin-3-yl]oxy}quinoline trifluoroacetate	454

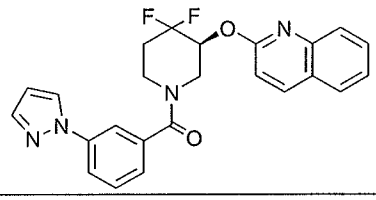
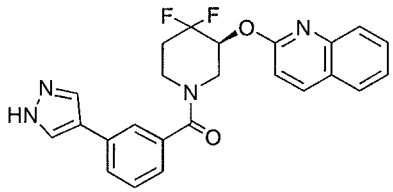
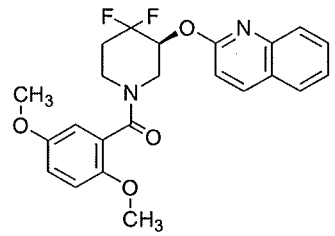
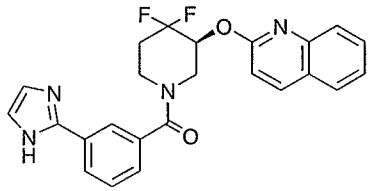
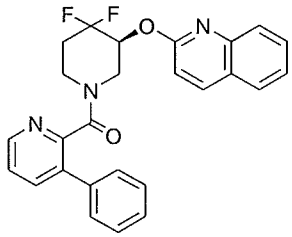
98		2-{[(3S)-1-{[5-bromo-2-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl]oxy}quinoline trifluoroacetate	514. 516
99		2-{[(3S)-4,4-difluoro-1-{[2-fluoro-5-(1H-pyrazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	453
100		2-{[(3S)-4,4-difluoro-1-{[3-(1,2,4-oxadiazol-3-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	437
101		2-{[(3S)-4,4-difluoro-1-{[3-(1,3-oxazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	436

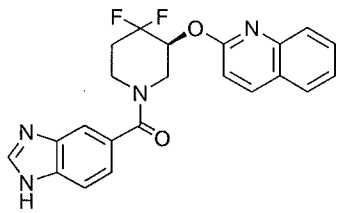
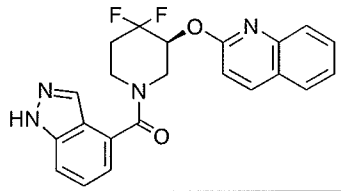
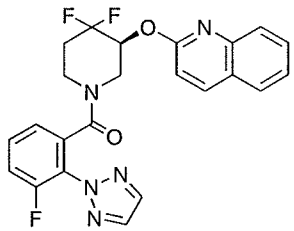
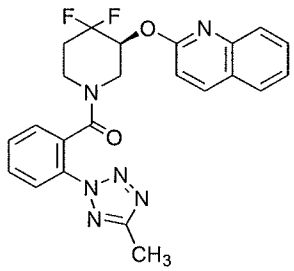
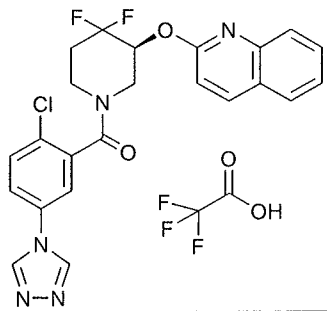
102		(3S)-(4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone	409
102		2-({(3S)-1-[(2,6-difluoro-3-methoxyphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline trifluoroacetate	435
103		2-{[(3S)-4,4-difluoro-1-{[3-fluoro-5-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-piperidin-3-yl]oxy}quinoline trifluoroacetate	454
104		2-{[(3S)-4,4-difluoro-1-{[3-fluoro-5-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}-piperidin-3-yl]oxy}quinoline trifluoroacetate	454

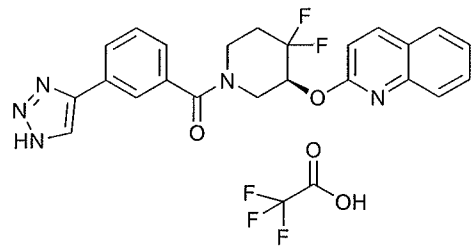
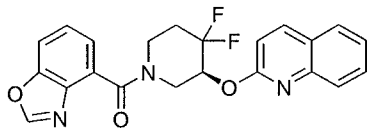
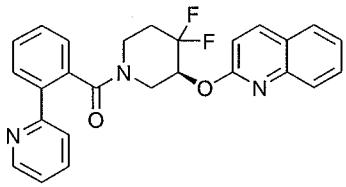
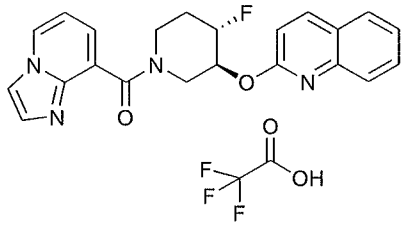
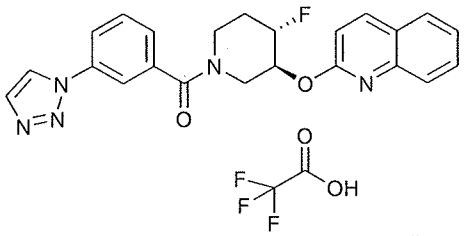
105		2-{[(3S)-1-{[3-bromo-5-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl]oxy}quinoline	514
106		2-{[(3S)-4,4-difluoro-1-{[4-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	437
107		2-{[(3S)-4,4-difluoro-1-{[4-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	437
108		2-({(3S)-1-[(3-chloroimidazo[1,2-a]pyridin-8-yl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline	443
109		2-{[(3S)-4,4-difluoro-1-{[3-(1,3-thiazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	452

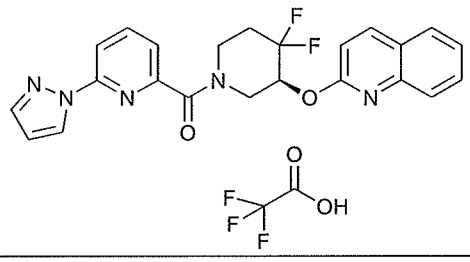
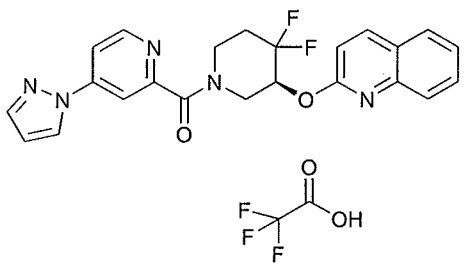
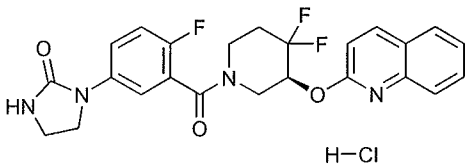
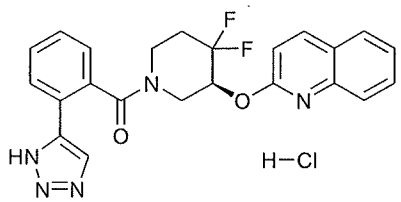
110		2-{[(3S)-4,4-difluoro-1-{[3-(1H-pyrazol-3-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	435
111		2-{[(3S)-4,4-difluoro-1-{[3-(2-methyl-1,3-thiazol-4-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	466
112		2-{[(3S)-4,4-difluoro-1-{[4-(1H-imidazol-1-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline	436
113		2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,4-triazol-5-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	436
114		2-({(3S)-4,4-difluoro-1-[(2-pyridin-3-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline	446

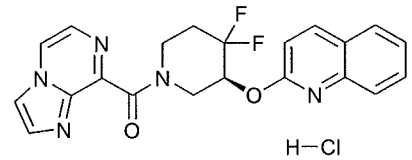
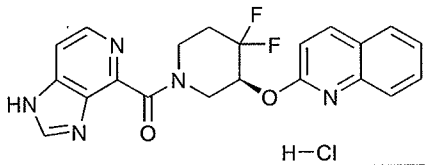
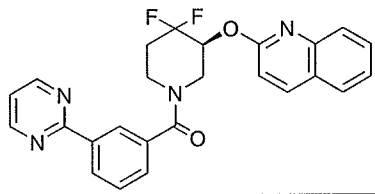
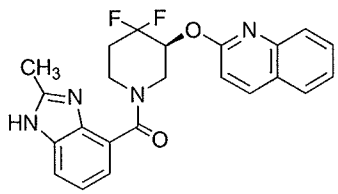
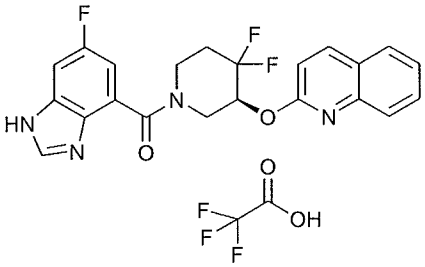
115	 H–Cl	2-{[(3S)-1-(1H-benzimidazol-4-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline hydrochloride	409
116		2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-indazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline	423
117		1-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}phenyl)-imidazolidin-2-one	453
118		2-{[(3S)-4,4-difluoro-1-{[2-(1H-pyrazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	435
119		2-({(3S)-4,4-difluoro-1-[(3-phenylpyridin-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline	446

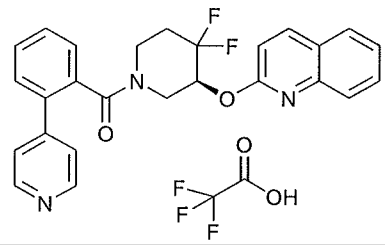
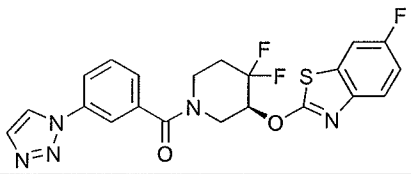
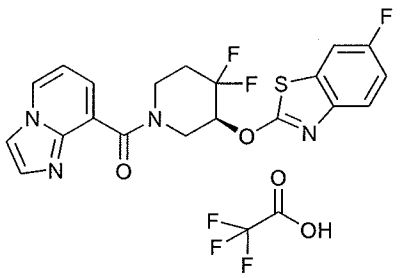
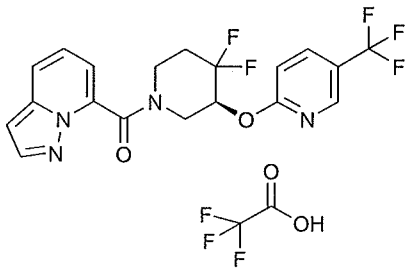
120		2-{[(3S)-4,4-difluoro-1-{[3-(1H-pyrazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	435
121		2-{[(3S)-4,4-difluoro-1-{[3-(1H-pyrazol-4-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	435
122		2-({(3S)-1-[(2,5-dimethoxyphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline	429
123		2-{[(3S)-4,4-difluoro-1-{[3-(1H-imidazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	435
124		2-({(3S)-4,4-difluoro-1-[(3-phenylpyridin-2-yl)carbonyl]piperidin-3-yl}oxy)quinoline	446

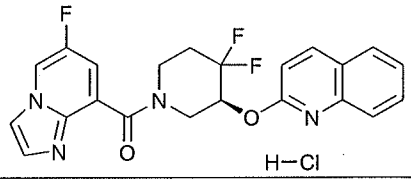
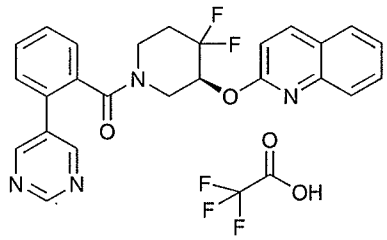
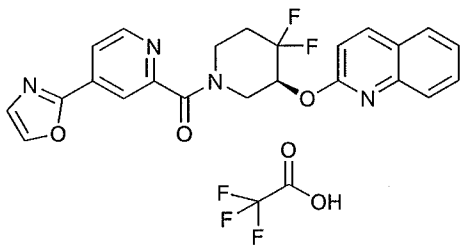
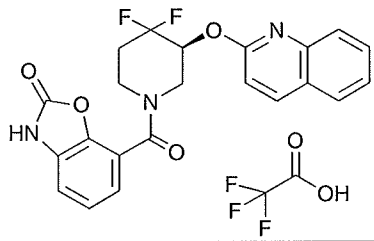
125		2-{[(3S)-1-(1H-benzimidazol-5-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline	409
126		2-{[(3S)-4,4-difluoro-1-(1H-indazol-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline	409
127		2-{[(3S)-4,4-difluoro-1-{[3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	454
128		2-{[(3S)-4,4-difluoro-1-{[2-(5-methyl-2H-tetrazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	451
129		2-{[(3S)-1-{[2-chloro-5-(4H-1,2,4-triazol-4-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl]oxy}quinoline trifluoroacetate	470

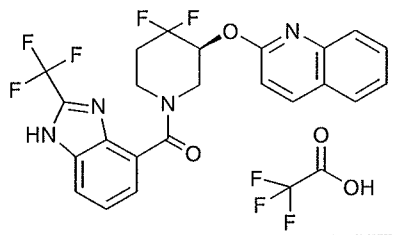
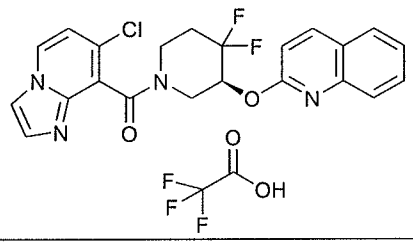
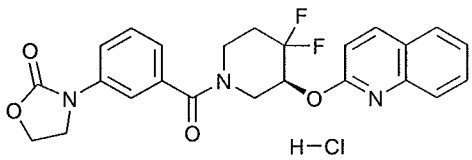
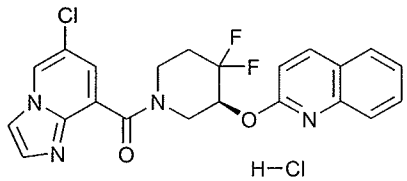
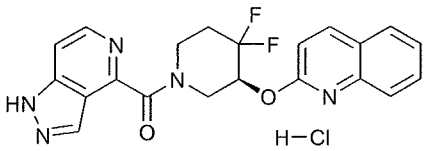
130		2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-4-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	436
131		2-{[(3S)-1-(1,3-benzoxazol-4-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline	410
132		2-({(3S)-4,4-difluoro-1-[(2-pyridin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline	446
133		2-{[(3S,4S)-4-fluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	391
134		2-{[(3S,4S)-4-fluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	418

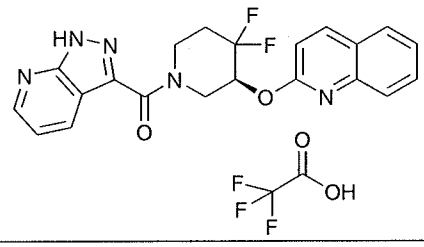
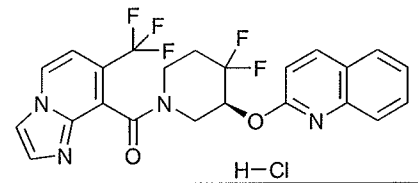
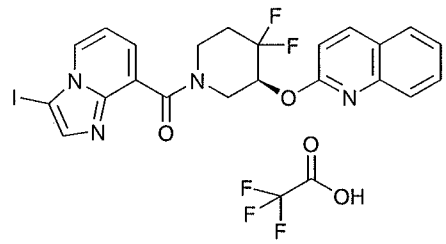
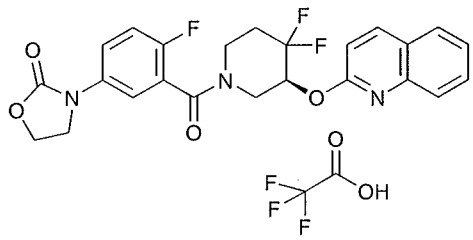
135		2-{[(3S)-4,4-difluoro-1-{[6-(1H-pyrazol-1-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	436
136		2-{[(3S)-4,4-difluoro-1-{[4-(1H-pyrazol-1-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	436
137		1-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-fluorophenyl)imidazolidin-2-one hydrochloride	471
138		2-{[(3S)-4,4-difluoro-1-{[2-(1H-1,2,3-triazol-5-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline hydrochloride	436

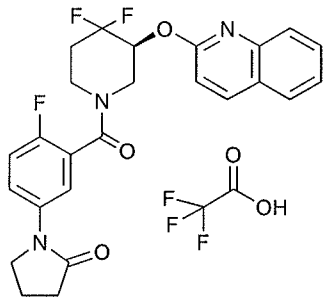
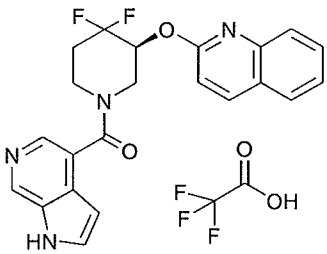
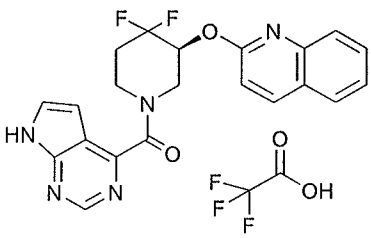
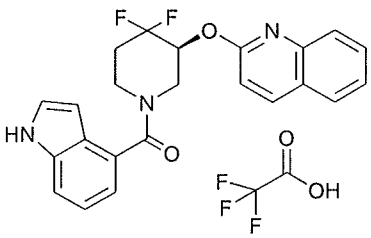
139	 H—Cl	2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyrazin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline hydrochloride	410
140	 H—Cl	2-{[(3S)-4,4-difluoro-1-(1H-imidazo[4,5-c]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline hydrochloride	410
141		2-({(3S)-4,4-difluoro-1-[(3-pyrimidin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline	447
142		2-({(3S)-4,4-difluoro-1-[(2-methyl-1H-benzimidazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline	423
143		2-({(3S)-4,4-difluoro-1-[(6-fluoro-1H-benzimidazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	427

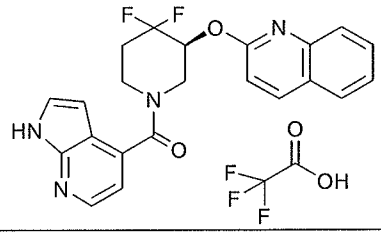
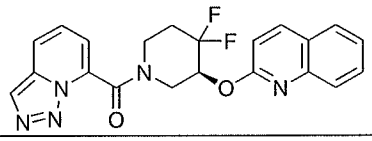
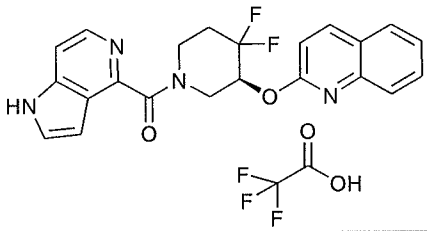
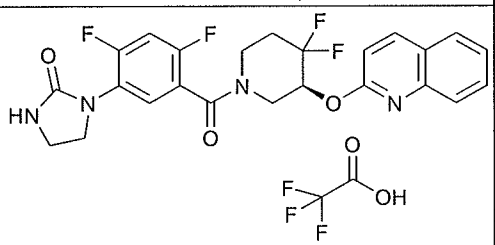
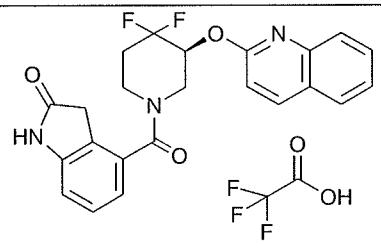
144		2-({(3S)-4,4-difluoro-1-[(2-pyridin-4-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	446
145		2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-6-fluoro-1,3-benzothiazole	460
146		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-6-fluoro-1,3-benzothiazole trifluoroacetate	433
147		7-{[(3S)-4,4-difluoro-3-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl]carbonyl}pyrazolo[1,5-a]pyridine trifluoroacetate	427

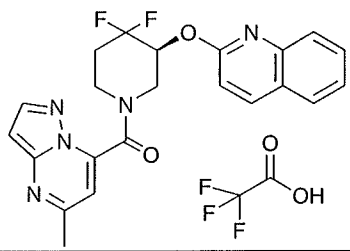
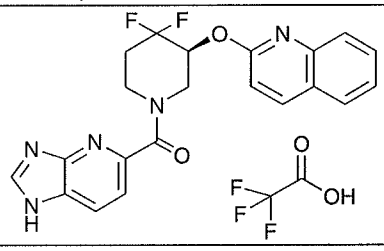
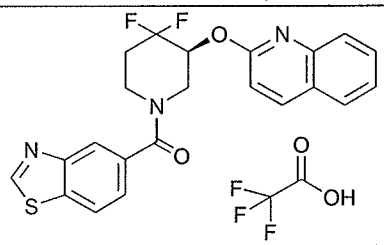
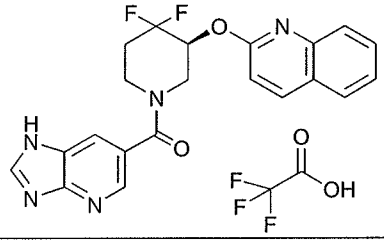
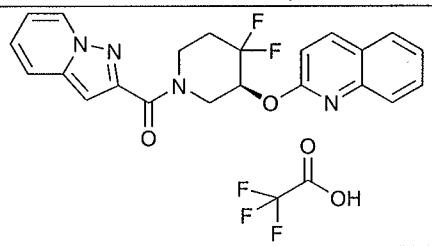
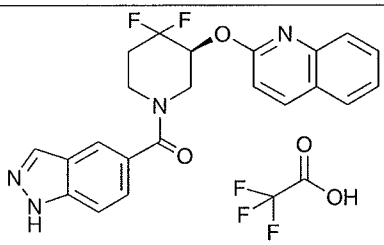
148	 H–Cl	2-({(3S)-4,4-difluoro-1-[(6-fluoroimidazo[1,2-a]pyridin-8-yl)carbonyl]piperidin-3-yl}oxy)quinoline hydrochloride	427
149		2-({(3S)-4,4-difluoro-1-[(2-pyrimidin-5-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	447
150		2-{[(3S)-4,4-difluoro-1-{[4-(1,3-oxazol-2-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	437
151		7-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-benzoxazol-2(3H)-one trifluoroacetate	426

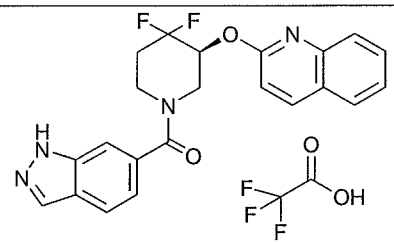
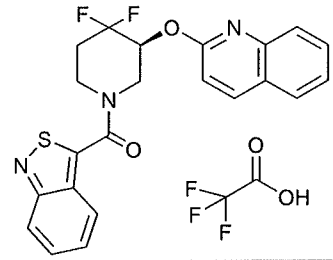
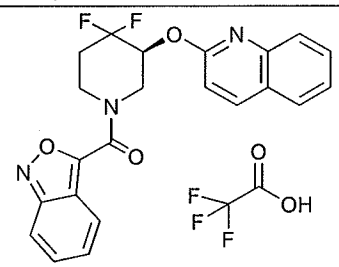
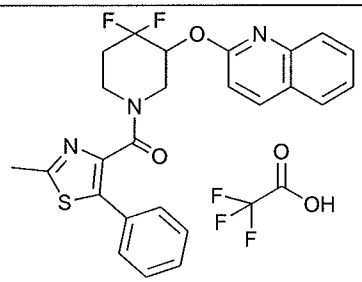
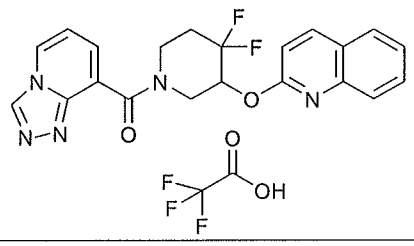
152		2-{[(3S)-4,4-difluoro-1-{[2-(trifluoromethyl)-1H-benzimidazol-4-yl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	477
153		2-({(3S)-1-[(7-chloroimidazo[1,2-a]pyridin-8-yl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline trifluoroacetate	443
154		3-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}phenyl)-1,3-oxazolidin-2-one hydrochloride	454
155		2-({(3S)-1-[(6-chloroimidazo[1,2-a]pyridin-8-yl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline hydrochloride	443
156		2-{[(3S)-4,4-difluoro-1-(1H-pyrazolo[4,3-c]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline hydrochloride	410

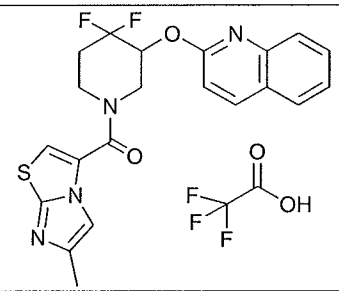
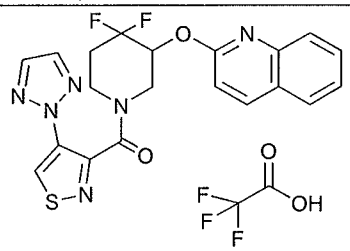
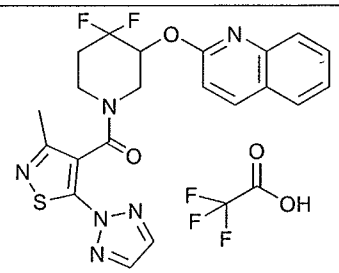
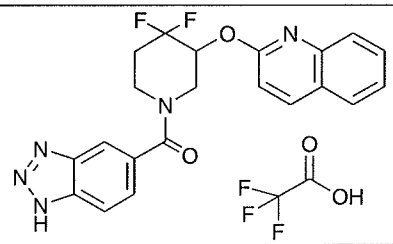
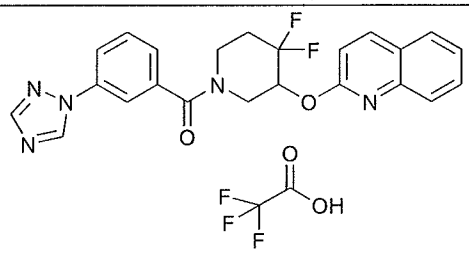
157		2-{[(3S)-4,4-difluoro-1-(1H-pyrazolo[3,4-b]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
158		2-{[(3S)-4,4-difluoro-1-{[7-(trifluoromethyl)imidazo[1,2-a]pyridin-8-yl]carbonyl}piperidin-3-yl]oxy}quinoline hydrochloride	477
159		2-({(3S)-4,4-difluoro-1-[(3-iodoimidazo[1,2-a]pyridin-8-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	535
160		3-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-fluorophenyl)-1,3-oxazolidin-2-one trifluoroacetate	472

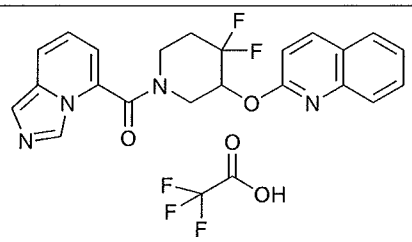
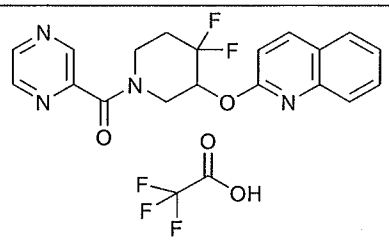
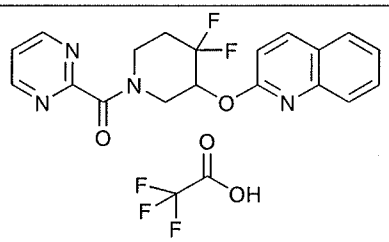
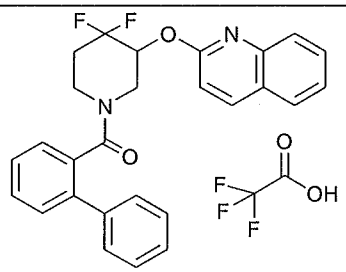
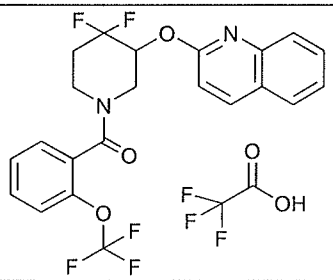
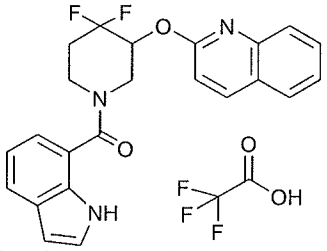
161		1-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-fluorophenyl)pyrrolidin-2-one trifluoroacetate	470
162		2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[2,3-c]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
163		2-{[(3S)-4,4-difluoro-1-(7H-pyrrolo[2,3-d]pyrimidin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
164		2-{[(3S)-4,4-difluoro-1-(1H-indol-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	408

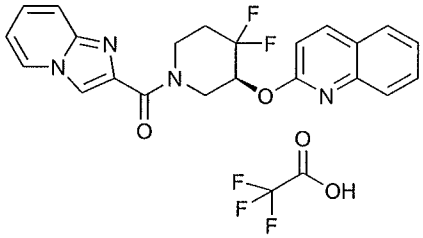
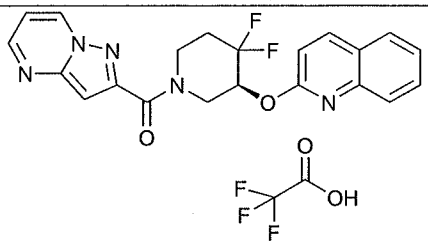
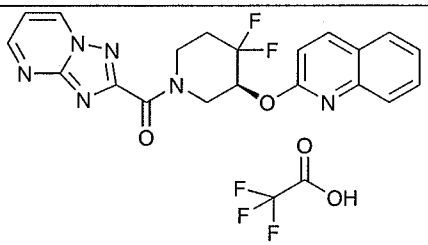
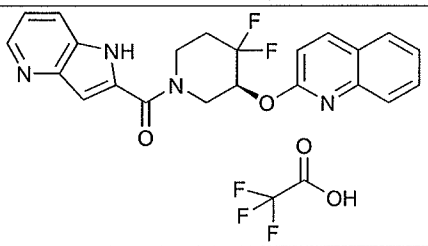
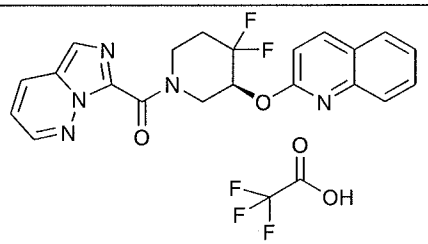
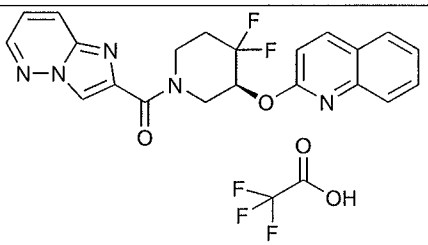
165		2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[2,3-b]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline	409
166		2-{[(3S)-4,4-difluoro-1-([1,2,3]triazolo[1,5-a]pyridin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline	410
167		2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[3,2-c]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
168		1-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4,6-difluorophenyl)imidazolidin-2-one trifluoroacetate	489
169		4-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-dihydro-2H-indol-2-one	424

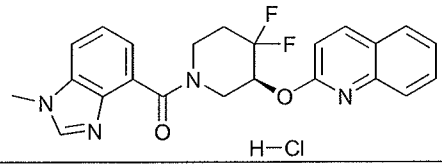
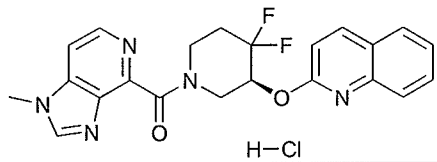
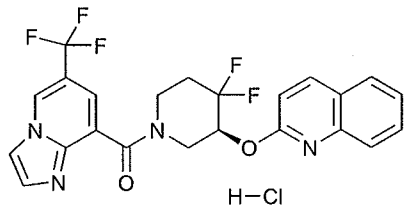
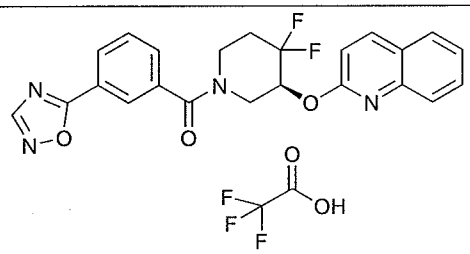
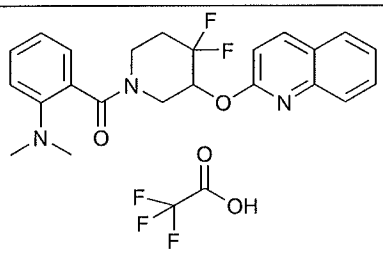
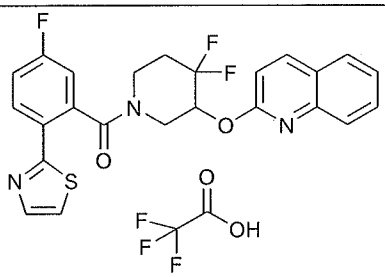
170		2-({(3S)-4,4-difluoro-1-[(5-methylpyrazolo[1,5-a]pyrimidin-7-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	424
171		2-{[(3S)-4,4-difluoro-1-(1H-imidazo[4,5-c]pyridin-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
172		2-{[(3S)-1-(1,3-benzothiazol-5-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline	426
173		2-{[(3S)-4,4-difluoro-1-(1H-imidazo[4,5-b]pyridin-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline	410
174		2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyridin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
175		2-{[(3S)-4,4-difluoro-1-(1H-indazol-5-ylcarbonyl)piperidin-3-yl]oxy}quinoline	409

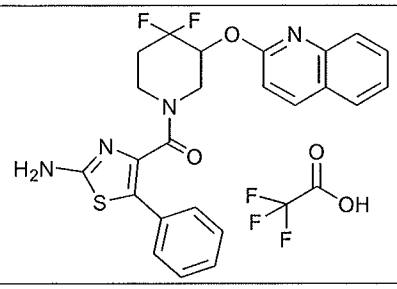
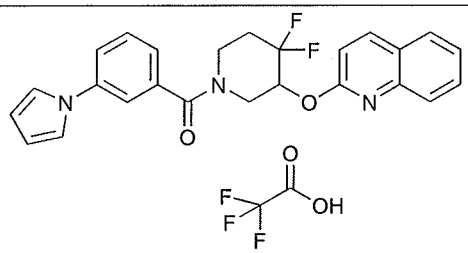
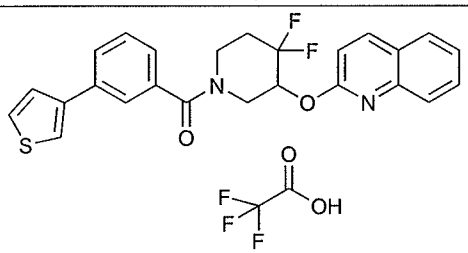
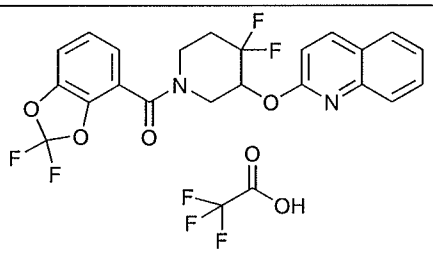
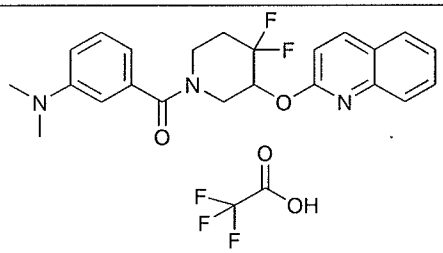
176		2-{[(3S)-4,4-difluoro-1-(1H-indazol-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
177		2-{[(3S)-1-(2,1-benzisothiazol-3-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline trifluoroacetate	426
178		2-{[(3S)-1-(2,1-benzisoxazol-3-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline trifluoroacetate	410
179		2-({4,4-difluoro-1-[(2-methyl-5-phenyl-1,3-thiazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	466
180		2-{[4,4-difluoro-1-([1,2,4]triazolo[4,3-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410

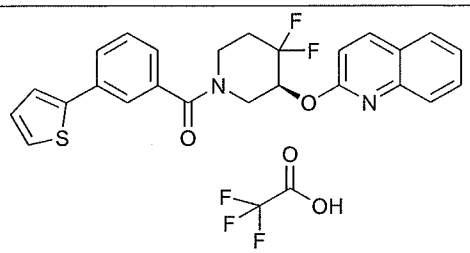
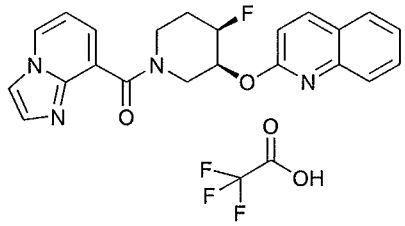
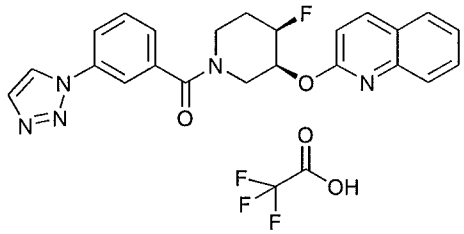
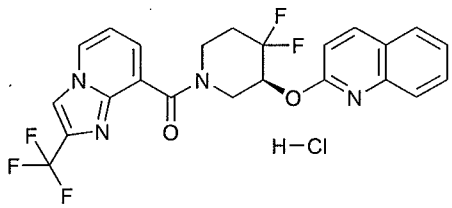
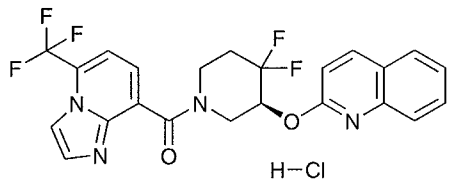
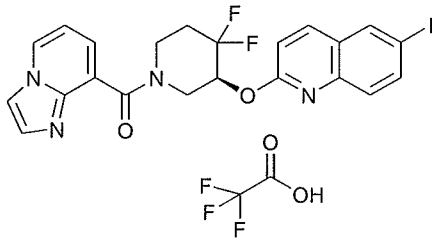
181		2-({4,4-difluoro-1-[(6-methylimidazo[2,1-b][1,3]thiazol-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	429
182		2-[(4,4-difluoro-1-{[4-(2H-1,2,3-triazol-2-yl)isothiazol-3-yl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	443
183		2-[(4,4-difluoro-1-{[3-methyl-5-(2H-1,2,3-triazol-2-yl)isothiazol-4-yl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	457
184		2-{[1-(1H-benzotriazol-5-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline trifluoroacetate	410
185		2-[(4,4-difluoro-1-{[3-(1H-1,2,4-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	436

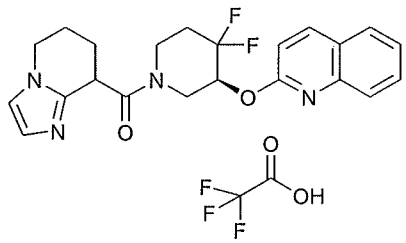
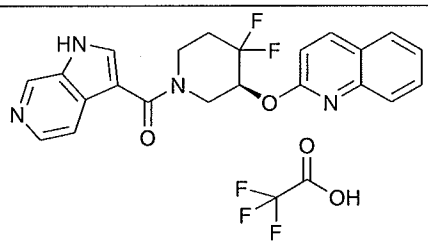
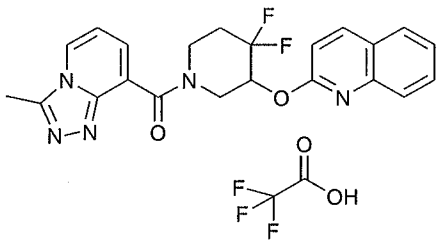
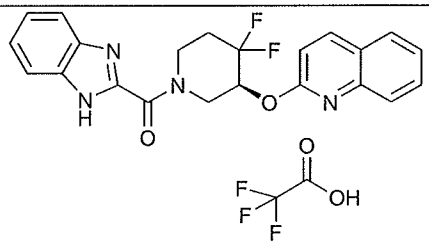
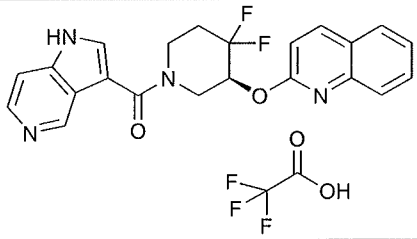
186		2-{[4,4-difluoro-1-(imidazo[1,5-a]pyridin-5-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
187		2-{[4,4-difluoro-1-(pyrazin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	371
188		2-{[4,4-difluoro-1-(pyrimidin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	371
189		2-{[1-(biphenyl-2-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline trifluoroacetate	445
190		2-[(4,4-difluoro-1-{[2-(trifluoromethoxy)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	453
191		2-{[4,4-difluoro-1-(1H-indol-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	408

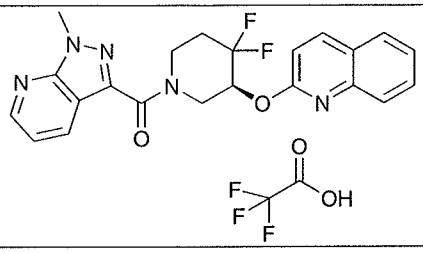
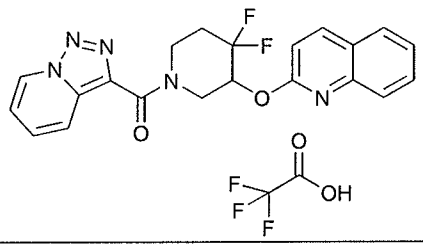
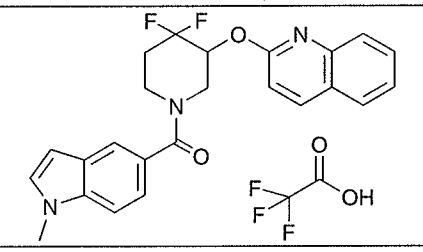
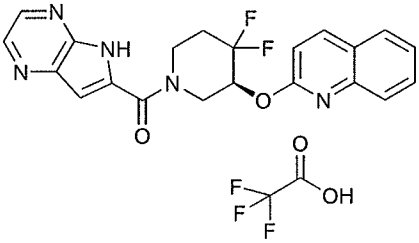
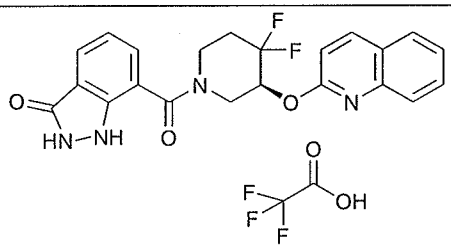
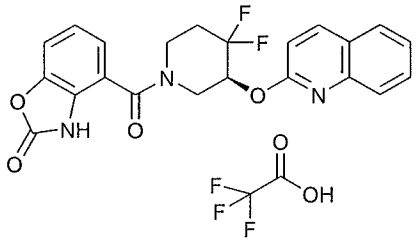
192		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
193		2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyrimidin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
194		2-{[(3S)-4,4-difluoro-1-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline	411
195		2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[3,2-b]pyridin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
196		2-{[(3S)-4,4-difluoro-1-(imidazo[1,5-b]pyridazin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
197		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-b]pyridazin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410

198	 H–Cl	2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-benzimidazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline hydrochloride	423
199	 H–Cl	2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline hydrochloride	424
200	 H–Cl	2-{[(3S)-4,4-difluoro-1-{[6-(trifluoromethyl)imidazo[1,2-a]pyridin-8-yl]carbonyl}piperidin-3-yl]oxy}quinoline hydrochloride	477
201		2-{[(3S)-4,4-difluoro-1-{[3-(1,2,4-oxadiazol-5-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	437
202		2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-N,N-dimethylaniline trifluoroacetate	412
203		2-[(4,4-difluoro-1-{[5-fluoro-2-(1,3-thiazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	470

204		4-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-5-phenyl-1,3-thiazol-2-amine trifluoroacetate	467
205		2-[(4,4-difluoro-1-{[3-(1H-pyrrol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline trifluoroacetate	434
206		2-({4,4-difluoro-1-[(3-thiophen-3-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	451
207		2-({1-[(2,2-difluoro-1,3-benzodioxol-4-yl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline trifluoroacetate	449
208		3-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-N,N-dimethylaniline trifluoroacetate	412

209		2-({(3S)-4,4-difluoro-1-[(3-thiophen-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	451
210		2-{[(3S,4R)-4-fluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	391
211		2-{[(3S,4R)-4-fluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline trifluoroacetate	418
212		2-{[(3S)-4,4-difluoro-1-{[2-(trifluoromethyl)imidazo[1,2-a]pyridin-8-yl]carbonyl}piperidin-3-yl]oxy}quinoline hydrochloride	477
213		2-{[(3S)-4,4-difluoro-1-{[5-(trifluoromethyl)imidazo[1,2-a]pyridin-8-yl]carbonyl}piperidin-3-yl]oxy}quinoline hydrochloride	477
214		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-6-iodoquinoline trifluoroacetate	535

215		2-{[(3S)-4,4-difluoro-1-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	413
216		2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[2,3-c]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409
217		2-({4,4-difluoro-1-[(3-methyl[1,2,4]triazolo[4,3-a]pyridin-8-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	424
218		2-{[(3S)-1-(1H-benzimidazol-2-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline trifluoroacetate	409
219		2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[3,2-c]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	409

220		2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline	424
221		2-{[4,4-difluoro-1-([1,2,3]triazolo[1,5-a]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
222		2-({4,4-difluoro-1-[(1-methyl-1H-indol-5-yl)carbonyl]piperidin-3-yl}oxy)quinoline trifluoroacetate	422
223		2-{[(3S)-4,4-difluoro-1-(5H-pyrrolo[2,3-b]pyrazin-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	410
224		7-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,2-dihydro-3H-indazol-3-one trifluoroacetate	425
225		4-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-benzoxazol-2(3H)-one trifluoroacetate	426

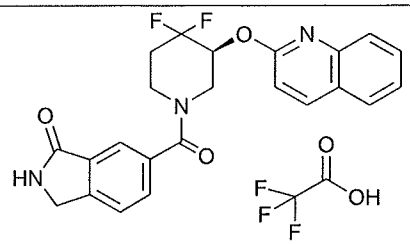
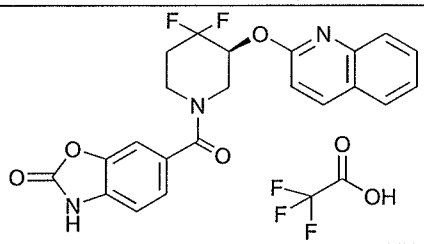
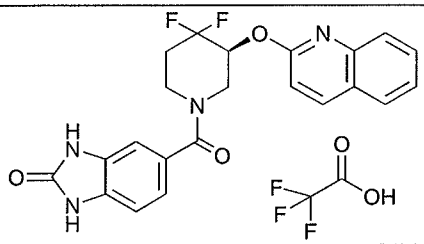
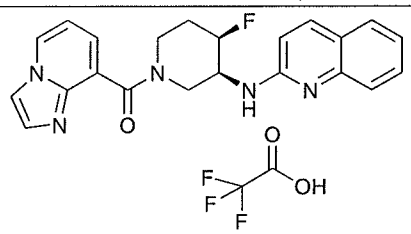
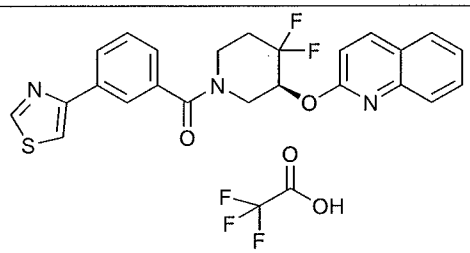
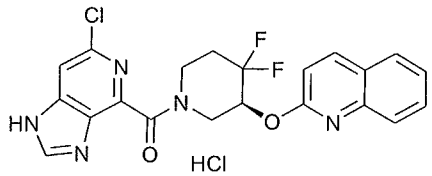
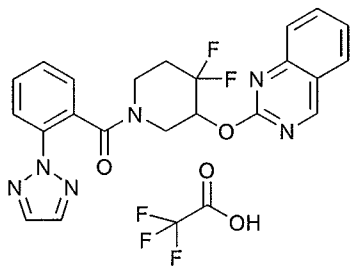
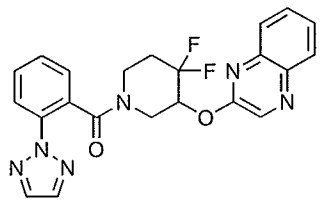
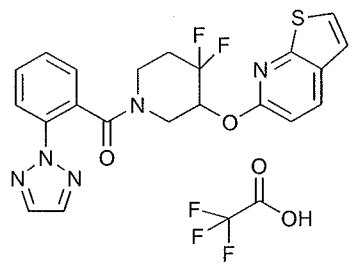
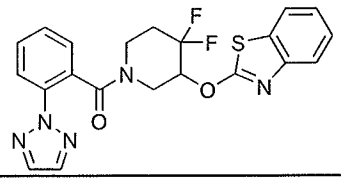
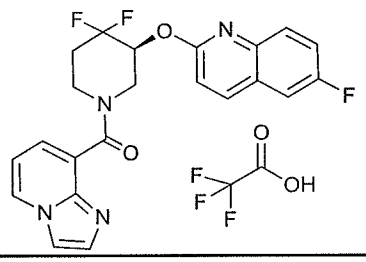
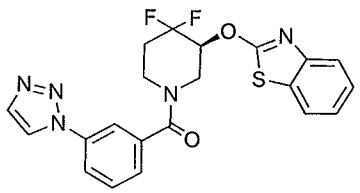
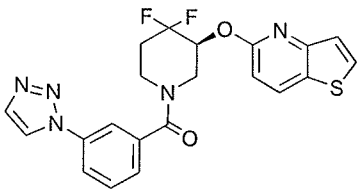
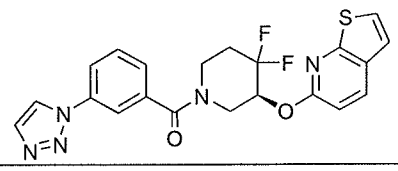
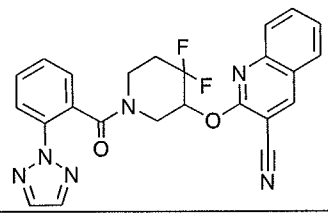
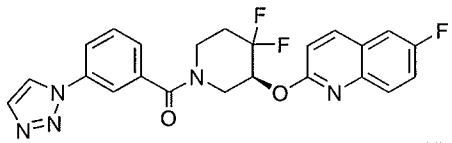
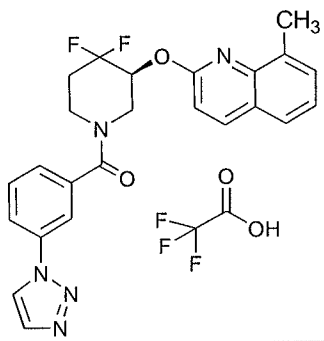
226		6-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-2,3-dihydro-1H-isoindol-1-one trifluoroacetate	424
227		6-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-benzoxazol-2(3H)-one trifluoroacetate	426
228		5-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-dihydro-2H-benzimidazol-2-one trifluoroacetate	425
229		(3*S*,4*R*)-4-fluoro-3-(quinolin-2-ylamino)piperidin-1-yl](imidazo[1,2-*a*]pyridin-8-yl)methanone	390
230		[(3*S*)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl][3-(1,3-thiazol-4-yl)phenyl]methanone trifluoroacetate	452
231		(6-chloro-1*H*-imidazo[4,5-*c*]pyridin-4-yl)[(3*S*)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]methanone hydrochloride	444

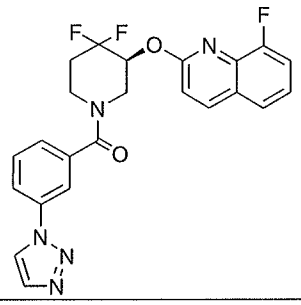
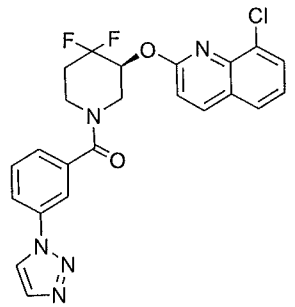
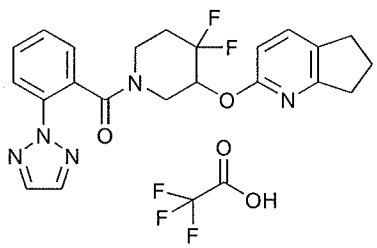
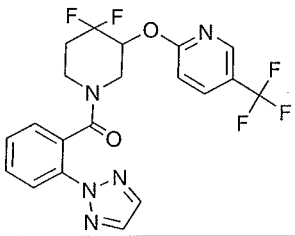
TABLE 2

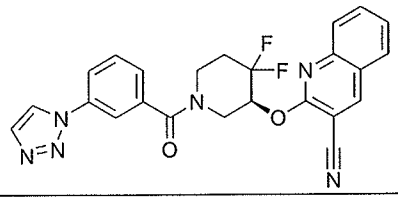
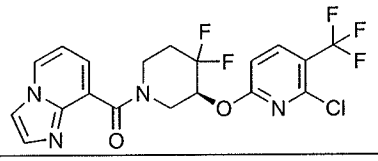
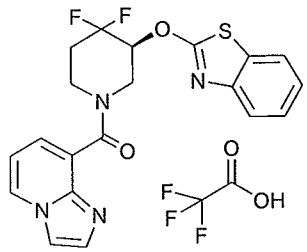
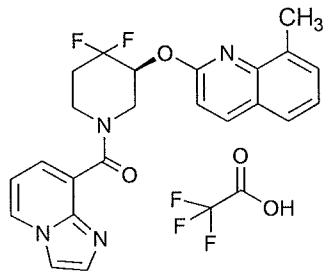
The following compounds were prepared using the foregoing methodology and general procedure described in Example 2, but substituting the appropriate acid for 3-(1*H*-1,2,3-triazol-1-yl)benzoic acid (Step 2) and the appropriate alkylating agent for 2-chlorobenzothiazole (Step 3), as described in the foregoing Reaction Schemes and Examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis from commercially available reagents using conventional reactions without undue experimentation.

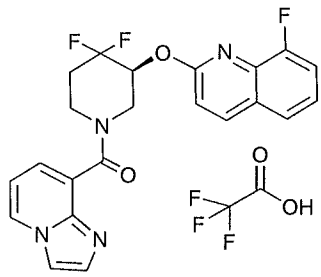
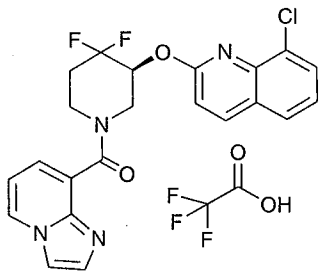
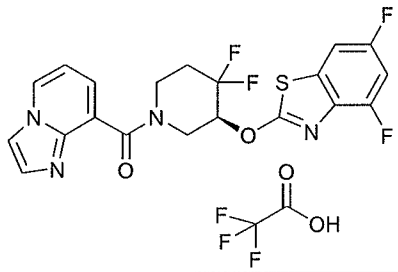
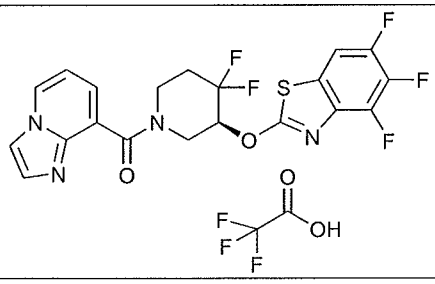
Example	Structure	Name	MS (M+1)
232		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinazoline trifluoroacetate	437
233		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoxaline	437
234		6-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]thieno[2,3-b]pyridine trifluoroacetate	442

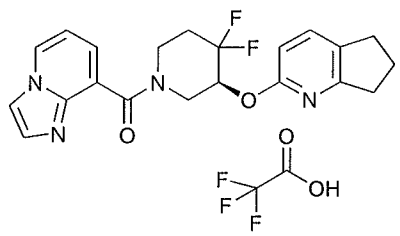
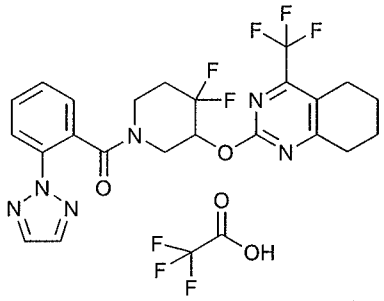
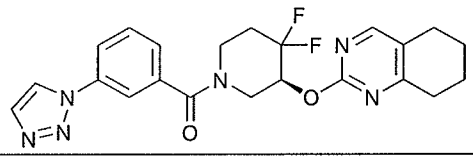
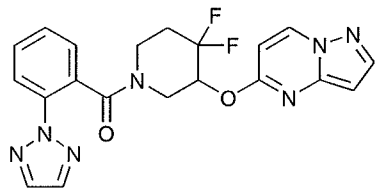
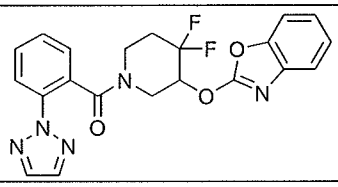
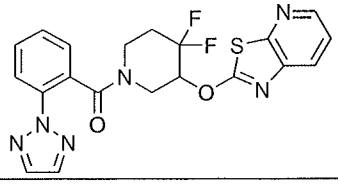
235		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-1,3-benzothiazole	442
236		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-6-fluoroquinoline trifluoroacetate	427
236		2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-1,3-benzothiazole	442
237		5-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}thieno[3,2-b]pyridine	442

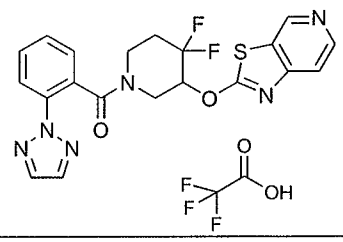
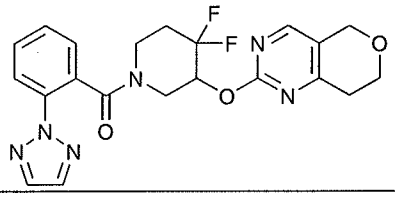
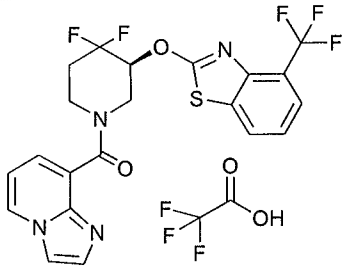
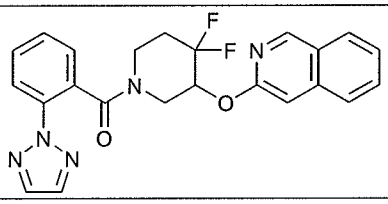
238		6-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}thieno[2,3-b]pyridine	442
239		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline-3-carbonitrile	461
240		2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-6-fluoroquinoline	454
241		2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-8-methylquinoline trifluoroacetate	450

242		2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-8-fluoroquinoline	454
243		8-chloro-2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline	470
244		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-6,7-dihydro-5H-cyclopenta[b]pyridine trifluoroacetate	426
245		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-5-(trifluoromethyl)pyridine	454

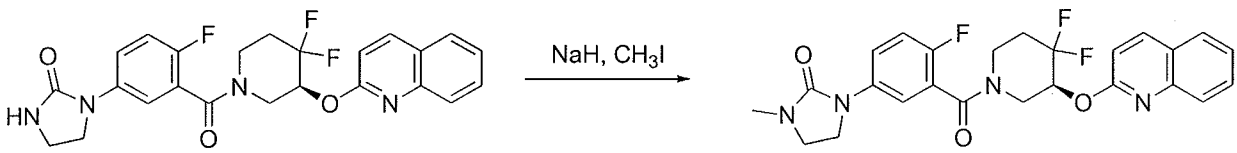
246		2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline-3-carbonitrile	461
247		8-{[(3S)-3-{[6-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4,4-difluoropiperidin-1-yl]carbonyl}imidazo[1,2-a]pyridine	461
248		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-1,3-benzothiazole trifluoroacetate	415
249		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-8-methylquinoline trifluoroacetate	423

250		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-8-fluoroquinoline trifluoroacetate	427
251		8-chloro-2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline trifluoroacetate	443
252		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-4,6-difluoro-1,3-benzothiazole trifluoroacetate	451
253		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-4,5,6-trifluoro-1,3-benzothiazole trifluoroacetate	469

254		8-{[(3S)-3-(6,7-dihydro-5H-cyclopenta[b]pyridin-2-yloxy)-4,4-difluoropiperidin-1-yl]carbonyl}imidazo[1,2-a]pyridine trifluoroacetate	399
255		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-4-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline trifluoroacetate	509
256		2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-5,6,7,8-tetrahydroquinazoline	441
257		5-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]pyrazolo[1,5-a]pyrimidine	426
258		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-1,3-benzoxazole	426
259		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy][1,3]thiazolo[5,4-b]pyridine	443

260		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy][1,3]thiazolo[5,4-c]pyridine trifluoroacetate	443
261		2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine	443
262		2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-4-(trifluoromethyl)-1,3-benzothiazole trifluoroacetate	483
263		3-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]isoquinoline	436

EXAMPLE 264

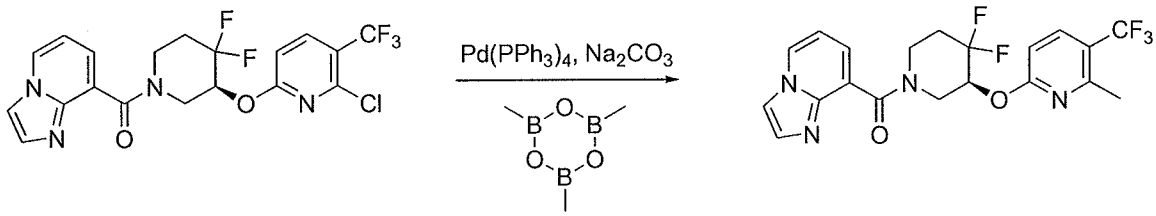


1-(3-{[(3S)-4,4-Difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-fluorophenyl)-3-methylimidazolidin-2-one

Sodium hydride (54.73 mg, 0.118 mmol) was added to a solution of 1-(3-{[(3*S*)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-fluorophenyl)imidazolidin-2-one

(20.0 mg, 0.039 mmol) in DMSO (1 mL) and the solution was stirred at ambient temperature for 0.5 h. Iodomethane (0.0037 mL, 0.059 mmol) was added and the solution was stirred for 16 h . The reaction mixture was purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compound as the trifluoroacetate salt. MS: m/z = 485 (M + 1); HRMS: m/z = 485.1781 (M+1); calculated m/z = 485.1795 (M+1) for $C_{25}H_{24}F_3N_4O_3$.

EXAMPLE 265



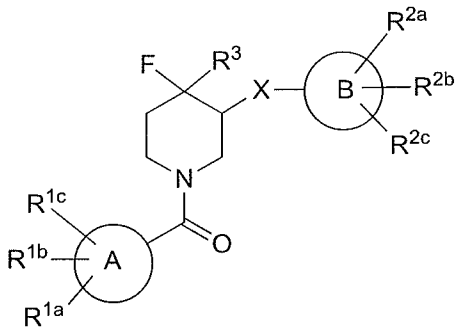
[(3*S*)-4,4-Difluoro-3-{[6-methyl-5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl](imidazo[1,2-a]pyridin-8-yl)methanone

A degassed solution of [(3*S*)-3-{[6-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4,4-difluoropiperidin-1-yl](imidazo[1,2-a]pyridin-8-yl)methanone (Example XX, 20.0 mg, 0.043 mmol), trimethylboroxine (0.049 mL, 0.174 mmol, 50 wt% solution), tetrakis(triphenylphosphine)palladium (5.02 mg, 4.34 μmol), and sodium carbonate (0.043 mL, 0.087 mmol) in dioxane (1 mL) was heated for 4 d at 100 °C. After 1 d, additional trimethylboroxine (0.049 mL, 0.174 mmol) and tetrakis(triphenylphosphine)palladium (5.02 mg, 4.34 μmol) were added. The reaction mixture was filtered and purified directly by HPLC using a reversed phase C18 column and eluting with a gradient of H_2O:CH_3CN:CF_3CO_2H – 90:10:0.1 to 5:95:0.1. The desired fractions were concentrated to yield the title compound as the trifluoroacetate salt. MS: m/z = 441 (M + 1); HRMS: m/z = 441.1352 (M+1); calculated m/z = 441.1344 (M+1) for $C_{20}H_{18}F_5N_4O_2$.

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.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

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

B is selected from the group consisting of phenyl, napthyl and heteroaryl;

X is $-NR^4-$, -O- or $-CH_2-$,

wherein R^4 is selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

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

(4) $-CF_3$;

R^{1a}, R^{1b} and R^{1c} may be absent if the valency of A does not permit such substitution and are 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 or more substituents selected from R^{13},

(5) $-(C=O)_m-O_n-C_{3-6}$cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(6) -$(C=O)_m$-C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(7) -$(C=O)_m$-C_{2-4}alkynyl, where the alkynyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(8) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(9) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{13},

(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^{14},

(c) C_{3-6}alkenyl, which is unsubstituted or substituted with R^{14},

(d) C_{3-6}alkynyl, which is unsubstituted or substituted with R^{14},

(e) C_{3-6}cycloalkyl which is unsubstituted or substituted with R^{14},

(f) phenyl, which is unsubstituted or substituted with R^{14}, and

(g) heterocycle, which is unsubstituted or substituted with R^{14},

(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^{2a}, R^{2b} and R^{2c} may be absent if the valency of B does not permit such substitution and are independently selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) -$(C=O)_m$-O_n-C_{1-6}alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(5) -$(C=O)_m$-O_n-C_{3-6}cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{13},

(6) -$(C=O)_m$-C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(7) -$(C=O)_m$-C_{2-4}alkynyl, where the alkynyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(8) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{13},
(9) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{13},
(10) -$(C=O)_m$-$NR^{10}R^{11}$,
(11) -$S(O)_2$-$NR^{10}R^{11}$,
(12) -$S(O)_q$-R^{12},
(13) -CO_2H,
(14) -CN, and
(15) -NO_2;

R^3 is selected from the group consisting of:
(1) hydrogen,
(2) halogen, and
(3) C_{1-6}alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{14},

R^{13} is selected from the group consisting of:
(1) halogen,
(2) hydroxyl,
(3) -$(C=O)_m$-O_n-C_{1-6}alkyl, where the alkyl is unsubstituted or substituted with one or more substituents selected from R^{14},
(4) -O_n-(C_{1-3})perfluoroalkyl,
(5) -$(C=O)_m$-O_n-C_{3-6}cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents selected from R^{14},
(6) -$(C=O)_m$-C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents selected from R^{14},
(7) -$(C=O)_m$-C_{2-4}alkynyl, where the alkynyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(8) -$(C=O)_m$-O_n-phenyl or -$(C=O)_m$-O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents selected from R^{14},

(9) -$(C=O)_m$-O_n-heterocycle, where the heterocycle is unsubstituted or substituted with one or more substituents selected from R^{14},

(10) -$(C=O)_m$-$NR^{10}R^{11}$,

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

(12) -$S(O)_q$-R^{12},

(13) -CO_2H,

(14) -CN, and

(15) oxo;

R^{14} 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-C_{1-6}alkyl,

(8) phenyl,

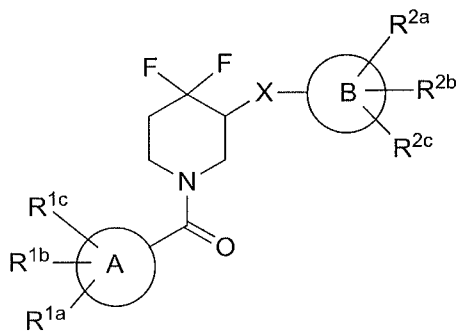
(9) heterocycle,

(10) -CO_2H, and

(11) -CN;

or a pharmaceutically acceptable salt thereof.

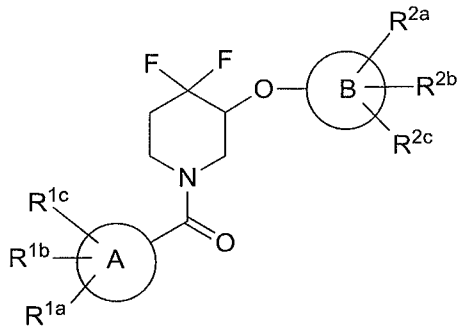
2. The compound of Claim 1 of the formula Ia:



Ia

or a pharmaceutically acceptable salt thereof.

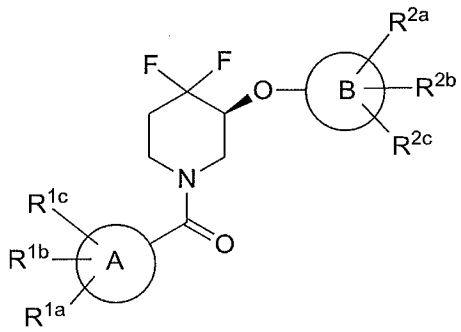
3. The compound of Claim 1 of the formula Ib:



Ib

or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 1 of the formula Ib':



Ib'

or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 1 or a pharmaceutically acceptable salt thereof wherein A is selected from the group consisting of: phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyrazolyl, thiazolyl, isothiazolyl, thiophneyl, benzimidazolyl, azabenzimidazolyl, benzimidazolonyl, indazolyl, dihydroindazolonyl, azaindazolyl, indolyl, indolonyl, dihydroisoindolonyl, azaindolyl, benzofuranyl, dihyrobenzofuranyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl,

imidazopyridinyl, tetrahydroimidazopyridinyl, imidazopyrazinyl, imidazopyridazinyl, imidazothiazolyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrrolopyrimidinyl, pyrrolopyrazinyl, triazolopyridinyl, triazolopyrimidinyl, and tetrazolopyridinyl.

6. The compound of Claim 1 or a pharmaceutically acceptable salt thereof wherein B is selected from the group consisting of:

(1) phenyl,
(2) quinoline,
(3) isoquinoline,
(4) benzoxazole,
(5) thienopyridine,
(6) pyridine,
(7) quinazoline,
(8) pyrimidine,
(9) benzothiazole, and
(10) quinoxaline.

7. The compound of Claim 1 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 or napthyl,
(5) -O-C_{1-6}alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl,
(6) heteroaryl, wherein heteroaryl is selected from triazolyl, oxazolyl, imidazolyl, pyrazolyl, thiazolyl, oxadiazolyl, tetrazolyl, imidazolidinonyl, oxazolidinonyl, pyrrolidinonyl, pyridyl, and pyrimidinyl, which is unsubstituted or substituted with halogen, hydroxyl or C_{1-6}alkyl,
(7) phenyl, which is unsubstituted or substituted with halogen, hydroxyl or C_{1-6}alkyl,
(8) C_{3-6}cycloalkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl, and
(9) -CN.

8. The compound of Claim 1 or a pharmaceutically acceptable salt thereof wherein R^{2a}, R^{2b} and R^{2c} 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, and
(6) -CN.

9. The compound of Claim 1 or a pharmaceutically acceptable salt thereof wherein R^3 is fluoro.

10. A compound which is selected from the group consisting of:
(3S)-(4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl)(2,6-difluoro-3-methoxyphenyl)methanone;
(S)-(3-(1H-1,2,3-triazol-1-yl)phenyl)(3-(benzo[d]thiazol-2-yloxy)-4,4-difluoropiperidin-1-yl)methanone;
2-[(4,4-difluoro-1-{[5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(3S)-(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-({4,4-difluoro-1-[(5-fluoro-2-pyrimidin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({4,4-difluoro-1-[(4-fluoro-2-pyrimidin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-[(4,4-difluoro-1-{[2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(1-{[5-bromo-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl)oxy]quinoline;
2-[(1-{[5-chloro-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[3-(1,3-thiazol-4-yl)pyridin-2-yl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(1,3-thiazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(1,3-thiazol-5-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(1,3-oxazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;

2-[(4,4-difluoro-1-{[2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-{[4,4-difluoro-1-(quinolin-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
3-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}phenol;
2-({4,4-difluoro-1-[(2-fluorophenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({4,4-difluoro-1-[(2-methylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-[(4,4-difluoro-1-{[2-(trifluoromethyl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-({4,4-difluoro-1-[(3-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({1-[(2-ethoxyphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
2-({4,4-difluoro-1-[(3-methylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}benzonitrile
2-({1-[(3-cyclopropylphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
2-[(4,4-difluoro-1-{[2-(methylsulfanyl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(1H-imidazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(1H-1,2,4-triazol-5-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(1H-imidazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(1H-pyrazol-4-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-({4,4-difluoro-1-[(2-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-[(4,4-difluoro-1-{[2-(1H-1,2,4-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(methylsulfanyl)-1H-benzimidazol-7-yl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-{[4,4-difluoro-1-(1H-indazol-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({4,4-difluoro-1-[(2-pyrazin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({4,4-difluoro-1-[(3-methyl-1H-indol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-[(4,4-difluoro-1-{[2-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-fluoro-6-(1,3-thiazol-4-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[5-fluoro-2-(1,3-thiazol-4-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-{[4,4-difluoro-1-(imidazo[1,2-a]pyrazin-5-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[4,4-difluoro-1-([1,2,4]triazolo[1,5-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
3-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-2-fluorophenol;
2-[(4,4-difluoro-1-{[4-(2H-1,2,3-triazol-2-yl)pyridin-3-yl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-piperidin-3-yl)oxy]quinoline;

[3-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(2H-1,2,3-triazol-2-yl)phenyl]methanol;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)thiophen-3-yl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[3-(2H-1,2,3-triazol-2-yl)thiophen-2-yl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[2-(4-methyl-1H-pyrazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-{[4,4-difluoro-1-(tetrazolo[1,5-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({4,4-difluoro-1-[(4-pyrrolidin-1-ylpyridin-2-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1H-pyrazol-1-yl)phenol;
2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1H-imidazol-4-yl)phenol;
2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1,3-thiazol-4-yl)phenol;
2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1H-pyrazol-3-yl)phenol;
2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1,3-oxazol-4-yl)phenol;
2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-(1,3-oxazol-2-yl)phenol;
2-[(1-{[2-chloro-5-(1H-pyrazol-1-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl)oxy]quinoline;
2-({4,4-difluoro-1-[(5-furan-2-yl-1-methyl-1H-pyrazol-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-[(4,4-difluoro-1-{[3-(1,3-oxazol-5-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-({1-[(2,6-dimethoxyphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
2-({1-[(5-chloro-2-methylphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
2-({1-[(2,5-difluorophenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
2-({4,4-difluoro-1-[(2-fluoro-6-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[1-(2,3-dihydro-1-benzofuran-7-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-({4,4-difluoro-1-[(2-fluoro-3-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({1-[(2,3-difluorophenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
2-({4,4-difluoro-1-[(2-methoxy-5-methylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-[(4,4-difluoro-1-{[3-(1H-imidazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-({4,4-difluoro-1-[(3-furan-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({4,4-difluoro-1-[(3-methoxy-5-methylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({4,4-difluoro-1-[(2-methyl-1-benzofuran-7-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[4,4-difluoro-1-(1H-imidazo[4,5-c]pyridin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyridin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;

2-({(3S)-4,4-difluoro-1-[(2-fluoro-5-methoxyphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[4,4-difluoro-1-(imidazo[2,1-b][1,3]thiazol-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(2-methyl-2H-indazol-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-1-(1,2-benzisoxazol-3-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(2-phenylpyridin-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({(3S)-4,4-difluoro-1-[(4-phenylpyridin-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyrimidin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[2,3-b]pyridin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[3,2-b]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-indol-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-indazol-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-indazol-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,5-a]pyridin-1-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,5-a]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(5H-pyrrolo[2,3-b]pyrazin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
4-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}phenyl)-1,3-thiazol-2-amine;
2-{[(3S)-4,4-difluoro-1-{[2-(1H-tetrazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[2-(2H-tetrazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[2-fluoro-5-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[2-fluoro-5-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}-piperidin-3-yl]oxy}quinoline;
2-{[(3S)-1-{[5-bromo-2-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[2-fluoro-5-(1H-pyrazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1,2,4-oxadiazol-3-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1,3-oxazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
(3S)-(4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl)(imidazo[1,2-a]pyridin-8-yl)methanone;
2-({(3S)-1-[(2,6-difluoro-3-methoxyphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;

2-{[(3S)-4,4-difluoro-1-{[3-fluoro-5-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}-piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-fluoro-5-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}-piperidin-3-yl]oxy}quinoline;
2-{[(3S)-1-{[3-bromo-5-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[4-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[4-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-({(3S)-1-[(3-chloroimidazo[1,2-a]pyridin-8-yl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1,3-thiazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-pyrazol-3-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(2-methyl-1,3-thiazol-4-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[4-(1H-imidazol-1-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,4-triazol-5-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(2-pyridin-3-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-1-(1H-benzimidazol-4-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-indazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
1-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}phenyl)-imidazolidin-2-one;
2-{[(3S)-4,4-difluoro-1-{[2-(1H-pyrazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(3-phenylpyridin-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-pyrazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-pyrazol-4-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-({(3S)-1-[(2,5-dimethoxyphenyl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-imidazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(3-phenylpyridin-2-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-1-(1H-benzimidazol-5-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-indazol-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline;

2-{[(3S)-4,4-difluoro-1-{[3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[2-(5-methyl-2H-tetrazol-2-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-1-{[2-chloro-5-(4H-1,2,4-triazol-4-yl)phenyl]carbonyl}-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-4-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-1-(1,3-benzoxazol-4-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(2-pyridin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S,4S)-4-fluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S,4S)-4-fluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[6-(1H-pyrazol-1-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[4-(1H-pyrazol-1-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
1-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-fluorophenyl)imidazolidin-2-one;
2-{[(3S)-4,4-difluoro-1-{[2-(1H-1,2,3-triazol-5-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyrazin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-imidazo[4,5-c]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(3-pyrimidin-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({(3S)-4,4-difluoro-1-[(2-methyl-1H-benzimidazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({(3S)-4,4-difluoro-1-[(6-fluoro-1H-benzimidazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({(3S)-4,4-difluoro-1-[(2-pyridin-4-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-6-fluoro-1,3-benzothiazole;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-6-fluoro-1,3-benzothiazole;
7-{[(3S)-4,4-difluoro-3-{[5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl]carbonyl}pyrazolo[1,5-a]pyridine;
2-({(3S)-4,4-difluoro-1-[(6-fluoroimidazo[1,2-a]pyridin-8-yl)carbonyl]piperidin-3-yl}oxy)quinoline;

2-({(3S)-4,4-difluoro-1-[(2-pyrimidin-5-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-{[4-(1,3-oxazol-2-yl)pyridin-2-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
7-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-benzoxazol-2(3H)-one;
2-{[(3S)-4,4-difluoro-1-{[2-(trifluoromethyl)-1H-benzimidazol-4-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-({(3S)-1-[(7-chloroimidazo[1,2-a]pyridin-8-yl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
3-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}phenyl)-1,3-oxazolidin-2-one;
2-({(3S)-1-[(6-chloroimidazo[1,2-a]pyridin-8-yl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-pyrazolo[4,3-c]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-pyrazolo[3,4-b]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[7-(trifluoromethyl)imidazo[1,2-a]pyridin-8-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(3-iodoimidazo[1,2-a]pyridin-8-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
3-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-fluorophenyl)-1,3-oxazolidin-2-one;
1-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-fluorophenyl)pyrrolidin-2-one;
2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[2,3-c]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(7H-pyrrolo[2,3-d]pyrimidin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-indol-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[2,3-b]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-([1,2,3]triazolo[1,5-a]pyridin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[3,2-c]pyridin-4-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
1-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4,6-difluorophenyl)imidazolidin-2-one;
4-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-dihydro-2H-indol-2-one;
2-({(3S)-4,4-difluoro-1-[(5-methylpyrazolo[1,5-a]pyrimidin-7-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-imidazo[4,5-c]pyridin-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-1-(1,3-benzothiazol-5-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;

2-{[(3S)-4,4-difluoro-1-(1H-imidazo[4,5-b]pyridin-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyridin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-indazol-5-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-indazol-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-1-(2,1-benzisothiazol-3-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-{[(3S)-1-(2,1-benzisoxazol-3-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-({4,4-difluoro-1-[(2-methyl-5-phenyl-1,3-thiazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[4,4-difluoro-1-([1,2,4]triazolo[4,3-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({4,4-difluoro-1-[(6-methylimidazo[2,1-b][1,3]thiazol-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-[(4,4-difluoro-1-{[4-(2H-1,2,3-triazol-2-yl)isothiazol-3-yl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-[(4,4-difluoro-1-{[3-methyl-5-(2H-1,2,3-triazol-2-yl)isothiazol-4-yl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-{[1-(1H-benzotriazol-5-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-[(4,4-difluoro-1-{[3-(1H-1,2,4-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-{[4,4-difluoro-1-(imidazo[1,5-a]pyridin-5-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[4,4-difluoro-1-(pyrazin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[4,4-difluoro-1-(pyrimidin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[1-(biphenyl-2-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-[(4,4-difluoro-1-{[2-(trifluoromethoxy)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-{[4,4-difluoro-1-(1H-indol-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(pyrazolo[1,5-a]pyrimidin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-([1,2,4]triazolo[1,5-a]pyrimidin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[3,2-b]pyridin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,5-b]pyridazin-7-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-b]pyridazin-2-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-benzimidazol-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-{[6-(trifluoromethyl)imidazo[1,2-a]pyridin-8-yl]carbonyl}piperidin-3-yl]oxy}quinoline;

2-{[(3S)-4,4-difluoro-1-{[3-(1,2,4-oxadiazol-5-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-N,N-dimethylaniline;
2-[(4,4-difluoro-1-{[5-fluoro-2-(1,3-thiazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
4-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-5-phenyl-1,3-thiazol-2-amine;
2-[(4,4-difluoro-1-{[3-(1H-pyrrol-1-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;
2-({4,4-difluoro-1-[(3-thiophen-3-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-({1-[(2,2-difluoro-1,3-benzodioxol-4-yl)carbonyl]-4,4-difluoropiperidin-3-yl}oxy)quinoline;
3-{[4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-N,N-dimethylaniline;
2-({(3S)-4,4-difluoro-1-[(3-thiophen-2-ylphenyl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S,4R)-4-fluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S,4R)-4-fluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[2-(trifluoromethyl)imidazo[1,2-a]pyridin-8-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-{[5-(trifluoromethyl)imidazo[1,2-a]pyridin-8-yl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-6-iodoquinoline;
2-{[(3S)-4,4-difluoro-1-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[2,3-c]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({4,4-difluoro-1-[(3-methyl[1,2,4]triazolo[4,3-a]pyridin-8-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-1-(1H-benzimidazol-2-ylcarbonyl)-4,4-difluoropiperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(1H-pyrrolo[3,2-c]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({(3S)-4,4-difluoro-1-[(1-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[4,4-difluoro-1-([1,2,3]triazolo[1,5-a]pyridin-3-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-({4,4-difluoro-1-[(1-methyl-1H-indol-5-yl)carbonyl]piperidin-3-yl}oxy)quinoline;
2-{[(3S)-4,4-difluoro-1-(5H-pyrrolo[2,3-b]pyrazin-6-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
7-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,2-dihydro-3H-indazol-3-one;
4-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-benzoxazol-2(3H)-one;
6-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-2,3-dihydro-1H-isoindol-1-one;

6-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-benzoxazol-2(3H)-one;
5-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-1,3-dihydro-2H-benzimidazol-2-one;
(3S,4R)-4-fluoro-3-(quinolin-2-ylamino)piperidin-1-yl](imidazo[1,2-a]pyridin-8-yl)methanone;
[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl][3-(1,3-thiazol-4-yl)phenyl]methanone;
(6-chloro-1H-imidazo[4,5-c]pyridin-4-yl)[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]methanone;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinazoline
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoxaline
6-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]thieno[2,3-b]pyridine;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-1,3-benzothiazole
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-6-fluoroquinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-1,3-benzothiazole;
5-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}thieno[3,2-b]pyridine;
6-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}thieno[2,3-b]pyridine;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]quinoline;-3-carbonitrile;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-6-fluoroquinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-8-methylquinoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-8-fluoroquinoline;
8-chloro-2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-6,7-dihydro-5H-cyclopenta[b]pyridine;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-5-(trifluoromethyl)pyridine;

2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}quinoline;-3-carbonitrile;
8-{[(3S)-3-{[6-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4,4-difluoropiperidin-1-yl]carbonyl}imidazo[1,2-a]pyridine;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-1,3-benzothiazole;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-8-methylquinoline;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-8-fluoroquinoline;
8-chloro-2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}quinoline;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-4,6-difluoro-1,3-benzothiazole;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-4,5,6-trifluoro-1,3-benzothiazole;
8-{[(3S)-3-(6,7-dihydro-5H-cyclopenta[b]pyridin-2-yloxy)-4,4-difluoropiperidin-1-yl]carbonyl}imidazo[1,2-a]pyridine;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-4-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline;
2-{[(3S)-4,4-difluoro-1-{[3-(1H-1,2,3-triazol-1-yl)phenyl]carbonyl}piperidin-3-yl]oxy}-5,6,7,8-tetrahydroquinazoline;
5-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]pyrazolo[1,5-a]pyrimidine;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-1,3-benzoxazole;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy][1,3]thiazolo[5,4-b]pyridine;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy][1,3]thiazolo[5,4-c]pyridine;
2-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine;
2-{[(3S)-4,4-difluoro-1-(imidazo[1,2-a]pyridin-8-ylcarbonyl)piperidin-3-yl]oxy}-4-(trifluoromethyl)-1,3-benzothiazole;
3-[(4,4-difluoro-1-{[2-(2H-1,2,3-triazol-2-yl)phenyl]carbonyl}piperidin-3-yl)oxy]isoquinoline;

1-(3-{[(3S)-4,4-difluoro-3-(quinolin-2-yloxy)piperidin-1-yl]carbonyl}-4-fluorophenyl)-3-methylimidazolidin-2-one; and
[(3S)-4,4-difluoro-3-{[6-methyl-5-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl](imidazo[1,2-a]pyridin-8-yl)methanone;
or a pharmaceutically acceptable salt thereof.

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

12. A compound of Claim 1 or a pharmaceutically acceptable salt thereof for use in medicine.

13. Use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a sleep disorder.

14. A method for enhancing the quality of sleep in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

15. A method for treating a disease or disorder selected from a sleep disorder, a mood disorder, an anxiety disorder, a feeding disorder, addiction, and pain in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

16. A method for treating insomnia in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

17. A method for treating or controlling obesity in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/11209

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/445; A61K 31/4523 (2014.01)
USPC - 514/317; 514/330
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)
IPC(8): A61K 31/445; A61K 31/4523 (2014.01)
USPC: 514/317; 514/330

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/315; 514/319; 514/320; 514/323

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar, Patentscope, PubWEST
piperidine, disubstituted, fluoropiperidine, difluoropiperidine, 4,4-difluoro, N-aroyl, cyclic amine, orexin receptor antagonist

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/0201632 A1 (BRESLIN et al.) 18 August 2011 (18.08.2011) para [0003], [0182], [0184] -[0187]; pg 24-25, Table 2	1-17
Y	JIANG et al. 'Disubstituted piperidines as potent orexin (hypocretin) receptor antagonists', Bioorganic & Medicinal Chemistry Letters, 15 June 2012, Vol.22(12), pp 3890-3894. [Downloaded from: http://www.sciencedirect.com/science/article/pii/S0960894X12005811] Entire Document, especially pg 3893, Table 3.	1-17
A,P	WO 2013/127913 A1 (STASI et al.) 06 September 2013 (06.09.2013) Entire Document	1-17

☐ Further documents are listed in the continuation of Box C. ☐

* 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
02 April 2014 (02.04.2014)	18 APR 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)