MODULATORS OF MUSCARINIC RECEPTORS

CLAIM OF PRIORITY

[001] This application claims the benefit of U.S. provisional application no. 60/602,731, filed on August 19, 2004, which is hereby incorporated by reference.

TECHNICAL FIELD OF THE INVENTION

[002] The present invention relates to modulators of muscarinic receptors. The present invention also provides compositions comprising such modulators, and methods therewith for treating muscarinic receptor mediated diseases.

BACKGROUND OF THE INVENTION

[003] The neurotransmitter acetylcholine binds to two types of cholinergic receptors: the ionotropic family of nicotinic receptors and the metabotropic family of muscarinic receptors. Muscarinic receptors belong to the large superfamily of plasma membrane-bound G protein coupled receptors (GPCRs). To date, five subtypes of muscarinic receptors (M_1-M_5) have been cloned and sequenced from a variety of species, and show a remarkably high degree of homology across species and receptor subtype. These M_1-M_5 muscarinic receptors are predominantly expressed within the parasympathetic nervous system which exerts excitatory and inhibitory control over the central and peripheral tissues and participate in a number of physiologic functions, including heart rate, arousal, cognition, sensory processing, and motor control.

[004] Muscarinic agonists such as muscarine and pilocarpine, and antagonists, such as atropine have been known for over a century, but little progress has been made in the discovery of receptor subtype-selective compounds, thereby making it difficult to assign specific functions to the individual receptors. See, e.g., DeLapp, N. *et al.*, "Therapeutic Opportunities for Muscarinic Receptors in the Central Nervous System," *J. Med. Chem.*, **43(23)**, pp. 4333-4353 (2000); Hulme, E. C. *et al.*, "Muscarinic Receptor Subtypes," *Ann. Rev. Pharmacol. Toxicol.*, **30**, pp. 633-673 (1990); Caulfield, M. P. *et al.*, "Muscarinic Receptors–Characterization, Coupling, and Function," *Pharmacol. Ther.*, 58, pp. 319-379 (1993); Caulfield, M. P. *et al.*, International Union of Pharmacology. XVII. Classification of Muscarinic Acetylcholine Receptors," *Pharmacol. Rev.*, 50, pp. 279-290 (1998), the disclosures of which are incorporated herein by reference.

[005] The Muscarinic family of receptors is the target of a large number of pharmacological agents used for various diseases, including leading drugs for COPD, asthma, urinary incontinence, glaucoma, Alzheimer's (AchE inhibitors). Despite the large therapeutic value of this family, cholinergic drugs are limited by the lack of selectivity of these agents, with significant activation of the parasympathetic autonomous system and elevated incidence of adverse effects. The molecular cloning of the muscarinic receptors and the identification of the physiological role of specific

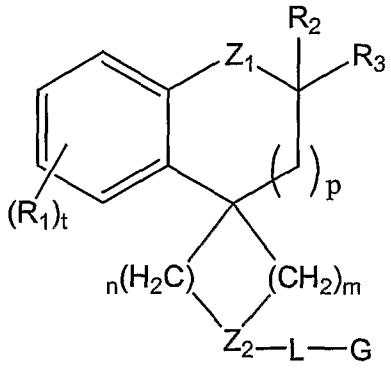
isoforms using knock-out mice, has recently delineated novel opportunities for selective muscarinic ligands, and has helped to define the selectivity profile that is required for enhanced efficacy and reduced side effects.

[006] There is a need for modulators of muscarinic receptors M_1-M_5. There is also a need for methods for treating muscarinic receptor-mediated diseases.

[007] There is also a need for modulators of muscarinic receptors that are selective as to subtypes M_1-M_5.

SUMMARY OF THE INVENTION

[008] The present invention provides methods of modulating activity of a muscarinic receptor using compounds of formula (I):



(I)

and pharmaceutically acceptable salts thereof.

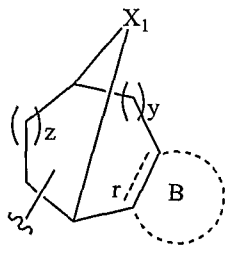
[009] Each of R_1, R_2, R_3 is independently Q_1 or Q_2, or R_2 and R_3 together form oxo.

[010] Z_1 is $-C(Q_1)_2-$, $-C(H)(Q_1)-$, $-C(H)(Q_5)-$, $-C(O)-$, $-CH_2-$, $-N(Q_1)-$, $-N(Q_2)-$, or O.

[011] Z_2 is N.

[012] L is a bond, an aliphatic group, C_3-C_6 cycloaliphatic, -O-, $-S(O)_z-$, $-S(O)_z-(C_1$-$C_4)$alkyl-, $-C(O)N(Q_2)-$, or $-S(O)_z N(Q_2)-$, in which the aliphatic group is optionally substituted with 1-3 of oxo, Q_1, or Q_2.

[013] G is a monocycloaliphatic group, a monocycloheteroaliphatic group, adamantyl, or a bicyclic or a tricyclic group of the formula (III)



(III)

in which the monocycloaliphatic group, the monocycloheteroalipahtic group, the adamantyl, and the bicyclic or tricyclic group are connected to L via any ring atom including those in X_1 and ring

B, and the monocycloaliphatic, the monocycloheteroaliphatic, the bicyclic, and the tricyclic groups are optionally substituted with 1-3 of oxo, =N-OQ_4, fluorine, Q_2, -C(O)-X_2-aliphatic in which X_2 is absent, -O-, -NH-, -NQ_2-, or -$S(O)_z$- and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3; bond r is a single or double bond and when ring B is present, bond r is fused with B; ring B, when present, is a 5-6 membered cycloaliphatic or heterocyclic ring; and ring B is optionally substituted with 1-3 of oxo, Q_1, or Q_2.

[014] X_1 is -$(CH_2)_i$-, -O-, -S-, -N(Q_2)-, -N(C(O)-X_2-aliphatic)- in which X_2 is absent, -O-, -NH-, -NQ_2-, or -$S(O)_z$- and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3;

[015] Each Q_1 is independently halo, -CN, -NO_2, -OQ_2, -$S(O)_zQ_2$, -$S(O)_zN(Q_2)_2$, -$N(Q_2)_2$, -C(O)OQ_2, -C(O)-Q_2, -C(O)$N(Q_2)_2$, -C(O)$N(Q_2)(OQ_2)$, -$N(Q_2)$C(O)-Q_2, -$N(Q_2)$C(O)$N(Q_2)_2$, -$N(Q_2)$C(O)O-Q_2, -$N(Q_2)S(O)_z$-Q_2 or aliphatic optionally including 1-3 substituents independently selected from Q_2 or Q_3.

[016] Each Q_2 is independently H, aliphatic, cycloaliphatic, aryl, arylalkyl, heterocyclic, or heteroaryl ring, each optionally substituted with 1-3 substituents independently selected from Q_3.

[017] Each Q_3 is halo, , oxo, CN, NO_2, CF_3, OCF_3, OH, -$S(O)_zQ_4$, -$N(Q_4)_2$, -$COOQ_4$, -$C(O)Q_4$, -OQ_4, or C_1-C_4 alkyl optionally substituted with 1-3 halo, oxo, -CN, -NO_2, -CF_3, -OCF_3, -OH, -SH, -$S(O)_zH$, -NH_2, or -COOH.

[018] Each Q_4 is aliphatic, cycloaliphatic, aryl, aralkyl, heterocycloaliphatic, heteroaralky, or heteroaryl, each optionally including 1-3 substituents selected from halo, oxo, CN, NO_2, CF_3, OCF_3, OH, SH, -$S(O)_zH$, -NH_2, or COOH.

[019] Each Q_5 is a heterocyclic ring optionally substituted with 1-3 substituents selected from halo, C_1-C_4 alkyl, oxo, CN, NO_2, CF_3, OCF_3, OH, SH, -$S(O)_zH$, -NH_2, COOH; and each i is independently 1, 2, or 3; each m and n is independently 1, 2, 3, or 4 provided that m + n is at least 4; each p is 0 or 1; each y is independently 0 or 1; t is 1 to 4; and each z is independently 0, 1, or 2.

[020] Additional aspects of the present invention provide compounds of formula (II), pharmaceutical compositions that are useful modulators of muscarinic receptors, and methods of treating muscarinic receptor mediated diseases using compounds of formulae (I and II).

[021] Advantageously, the compounds of the invention are generally selective for M_1 and M_4 muscarinic receptors. Unexpectedly, the compounds of the invention exhibit increased activity and/or efficacy for M_1 and/or M_4 muscarinic receptors relative to other muscarinic receptors.

DETAILED DESCRIPTION OF THE INVENTION

[022] As used herein, the following definitions shall apply unless otherwise indicated.

I. DEFINITIONS

[023] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausolito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[024] The term "muscarinic receptor," without a prefix specifying the receptor subtype, refers to one or more of the five receptor subtypes M_1-M_5.

[025] The term "modulating" as used herein means increasing or decreasing, e.g. activity, by a measurable amount. Compounds that modulate muscarinic activity by increasing the activity of the muscarinic receptors are called agonists. Compounds that modulate muscarinic activity by decreasing the activity of the muscarinic receptors are called antagonists. An agonist interacts with a muscarinic receptor to increase the ability of the receptor to transduce an intracellular signal in response to endogenous ligand binding. An antagonist interacts with a muscarinic receptor and competes with the endogenous ligand(s) or substrate(s) for binding site(s) on the receptor to decrease the ability of the receptor to transduce an intracellular signal in response to endogenous ligand binding.

[026] The phrase "treating or reducing the severity of a muscarinic receptor mediated disease" refers both to treatments for diseases that are directly caused by muscarinic activities and alleviation of symptoms of diseases not directly caused by muscarinic activities. Examples of diseases whose symptoms may be affected by muscarinic activity include, but are not limited to, CNS derived pathologies including cognitive disorders, Attention Deficit Hyperactivity Disorder (ADHD), obesity, Alzheimer's disease, various dementias such as vascular dementia, psychosis including schizophrenia, mania, bipolar disorders, pain conditions including acute and chronic syndromes, Huntington's Chorea, Friederich's ataxia, Gilles de la Tourette's Syndrome, Downs Syndrome, Pick disease, clinical depression, Parkinson's disease, peripheral disorders such as `reduction of intra ocular pressure in Glaucoma and treatment of dry eyes and dry mouth including Sjögren's Syndrome, bradhycardia, gastric acid secretion, asthma, GI disturbances and wound healing.

[027] As used herein the term "aliphatic' encompasses the terms alkyl, alkenyl, alkynyl.

[028] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-8 (e.g., 1-6 or 1-4) carbon atoms. An alkyl group can be straight or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl,

isobutyl, sec-butyl, tert-butyl, n-pentyl, n-heptyl, or 2-ethylhexyl. An alkyl group can be optionally substituted with one or more substituents such as halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, alkoxycarbonyl, alkylcarbonyloxy, nitro, cyano, amino, acyl, sulfonyl, sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carbamoyl, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, or hydroxyl. Without limitation, some examples of substituted alkyls include alkylcarbonylalkyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, carbonylalkyl, carboxyalkyl, hydroxyalkyl, oxoalkyl, aralkyl, alkoxyaralkyl, (alkylsulfonylamino)alkyl, (sulfonylamino)alkyl, carbonylaminoalkyl, aminocarbonylalkyl, cycloaliphaticalkyl, cyanoalkyl, aminoalkyl, oxoalkyl, alkoxycarbonylalkyl, (alkoxycarbonylheterocycloalkyl)alkyl, (cycloalkyl)alklyl, (cycloalkenyl)alkyl, (heterocycloalkyl)alkyl, or haloalkyl.

[029] As used herein, an "alkenyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to, allyl, isoprenyl, 2-butenyl, and 2-hexenyl. An alkenyl group may be optionally substituted with one or more substituents such as halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, alkoxycarbonyl, alkylcarbonyloxy, nitro, cyano, amino, acyl, sulfonyl, sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carbamoyl, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, or hydroxyl.

[030] As used herein, an "alkynyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and at least one triple bond. Like an alkyl group, an alkynyl group can be straight or branched. An alkynyl group may be optionally substituted with one or more substituents such as halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aroyl, heteroaroyl, alkoxycarbonyl, alkylcarbonyloxy, nitro, cyano, amino, acyl, sulfonyl, sulfinyl, sulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carbamoyl, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, or hydroxyl.

[031] As used herein, an "amino" group refers to $-NR^XR^Y$ wherein each of R^X and R^Y is independently hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, aralkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, heteroaryl, or carbonyl each of which are defined herein and are optionally substituted. Examples of amino groups include alkylcarbonylamino, alkylsulfonylamino, alkoxycarbonylamino, (azacycloalkylcarbonyl)amino, heteroaralkylcarbonylamino, heteroarylcarbonylamino, carbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkyl)alkylcarbonylamino, heteroarylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, (cycloalkyl)alkylcarbonylamino, cycloalkylcarbonylamino. When the term

"amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by -NR^{X}-. R^{X} has the same meaning as defined above. A nonexhaustive list of possible R^{X} and R^{Y} includes sulfonylamino, alkylamino, carbonylamino, carboxy, oxo, hydroxyl, sulfo, mercapto, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, aminocarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocycloalkylcarbonyl, heterocycloalkylalkylcarbonyl, heteroarylcarbonyl, or heteroaralkylcarbonyl.

[032] As used herein, a "carbonyl" group, when used alone or as part of another structure refers to -(CO)R^{X}, where R^{X} is defined above. When the term "carbonyl" is not the terminal group (e.g., arylaminoalkylcarbonyl) it is represented by -C(O)R^{X}. Without limitation, carbonyl groups can include optionally substituted aminocarbonyl, alkoxyalkoxycarbonyl, alkylaminocarbonyl, arylcarbonyl (e.g., haloarylcarbonyl), heterocycloalkylcarbonyl, heterocycloalkenylcarbonyl, arylaminocarbonyl (e.g., haloarylaminocarbonyl), cyanoalkylarylcarbonyl, heterocycloalkoxycarbonyl, alkynyloxycarbonyl, cycloalkoxycarbonyl, heterobicycloarylcarbonyl, alkylheteroarylaminocarbonyl, alkoxyarylcarbonyl (e.g., haloalkoxyarylcarbonyl), (alkylheterocyclo)alkenylcarbonyl, heteroarylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl (e.g., haloalkoxycarbonyl), alkylarylcarbonyl, cycloalkylcarbonyl, alkylheteroarylcarbonyl, arylsulfonylcarbonyl, aminocarbonyl, sulfonylcarbonyl, alkylcarbonyl, alkylsulfonylcarbonyl, alkylcarbonyl, arylaminocarbonyl, or the like. A nonexhaustive list of possible R^{X} and R^{Y} includes sulfonylaminocarbonyl, alkylcarbonyl, carbonylamino, carboxy, oxo, hydroxyl, sulfo, mercapto, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, aminocarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocycloalkylcarbonyl, heterocycloalkylalkylcarbonyl, heteroarylcarbonyl, or heteroaralkylcarbonyl.

[033] As used herein, an "aryl" group used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl" refers to monocyclic (e.g., phenyl); bicyclic (e.g., indenyl, naphthalenyl, tetrahydronaphthyl, tetrahydroindenyl); tricyclic (e.g., fluorenyl, tetrahydrofluorenyl, anthracenyl, or tetrahydroanthracenyl); or a benzofused group having 3 rings. For example, a benzofused group includes phenyl fused with two or more C_{4-8} carbocyclic moieties. An aryl is optionally substituted with one or more substituents including aliphatic (e.g., alkyl, alkenyl, or alkynyl); cycloalkyl; (cycloalkyl)alkyl; heterocycloalkyl; (heterocycloalkyl)alkyl; aryl; heteroaryl; alkoxy; cycloalkyloxy; heterocycloalkyloxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; aroyl; heteroaroyl; amino; aminoalkyl; nitro; carboxy; carbonyl (e.g., alkoxycarbonyl, alkylcarbonyl, aminocarbonyl, (alkylamino)alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, ; or sulfonylcarbonyl); aryalkylcarbonyloxy; sulfonyl (e.g., alkylsulfonyl

or aminosulfonyl); sulfinyl (e.g., alkylsulfinyl); sulfanyl (e.g., alkylsulfanyl); cyano; halo; hydroxyl; acyl; mercapto; sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl. Alternatively, an aryl may be unsubstituted.

[034] Examples of substituted aryls include haloaryl, alkoxycarbonylaryl, alkylaminoalkylaminocarbonylaryl, *p,m*-dihaloaryl, *p*-amino-*p*-alkoxycarbonylaryl, *m*-amino-*m*-cyanoaryl, aminoaryl, alkylcarbonylaminoaryl, cyanoalkylaryl, alkoxyaryl, aminosulfonylaryl, alkylsulfonylaryl, aminoaryl, *p*-halo-*m*-aminoaryl, cyanoaryl, hydroxyalkylaryl, alkoxyalkylaryl, hydroxyaryl, carboxyalkylaryl, dialkylaminoalkylaryl, *m*-heterocycloaliphatic-*o*-alkylaryl, heteroarylaminocarbonylaryl, nitroalkylaryl, alkylsulfonylaminoalkylaryl, heterocycloaliphaticcarbonylaryl, alkylsulfonylalkylaryl, cyanoalkylaryl, heterocycloaliphaticcarbonylaryl, alkylcarbonylaminoaryl, hydroxyalkylaryl, alkylcarbonylaryl, aminocarbonylaryl, alkylsulfonylaminoaryl, dialkylaminoaryl, alkylaryl, and trihaloalkylaryl.

[035] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with an aryl group. Both "alkyl" and "aryl" are defined herein. An example of an aralkyl group is benzyl. A "heteroaralkyl" group refers to an alkyl group that is substituted with a heteroaryl. Both "alkyl" and "heteroaryl" are defined herein.

[036] As used herein, a "bicyclic ring system" includes 8-12 (e.g., 9, 10, or 11) membered structures that form two rings, wherein the two rings have at least one atom in common (e.g., 2 atoms in common). Bicyclic ring structures include bicycloaliphatics (e.g., bicycloalkyl or bicycloalkenyl), bicycloheteroaliphatics (e.g., bicycloheteroalkyl or bicycloheteroalkenyl), bicyclic aryls, and bicyclic heteroaryls.

[037] The term "cycloaliphatic" means a saturated or partially unsaturated monocyclic, bicyclic, or tricyclic hydrocarbon ring that has a single point of attachment to the rest of the molecule. Cycloaliphatic rings are 3-8 membered monocyclic rings (e.g., 3-6 membered rings). Cycloaliphatic rings also include 8-12 membered bicyclic hydrocarbon rings, (e.g., 10 membered bicyclic hydrocarbon rings). A cycloaliphatic group encompasses a "cycloalkyl" group and a "cycloalkenyl" group.

[038] As used herein, a "cycloalkyl" group refers to a saturated carbocyclic mono-, bi-, or tri-, or multicyclic (fused or bridged) ring of 3-10 (e.g., 5-10) carbon atoms. Without limitation, examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or the like. Without limitation, examples of bicyclic cycloalkyl groups include octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2.]decyl, bicyclo[2.2.2]octyl, bicycle[2.2.1]heptanyl, bicycle[3.1.1]heptanyl, or the like. Without limitation, multicyclic groups include adamantyl,

cubyl, norbornyl, or the like. Cycloalkyl rings can be optionally substituted at any chemically viable ring position.

[039] A "cycloalkenyl" group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bonds. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, cyclooctenyl, hexahydro-indenyl, octahydro-naphthyl, cyclohexenyl, cyclopentenyl, bicyclo[2.2.2]octenyl, and bicyclo[3.3.1]nonenyl. Cycloalkenyl ring structures can be optionally substituted at any chemically viable position on the ring or rings.

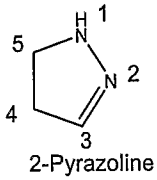
[040] A cycloalkyl or cycloalkenyl group can be optionally substituted with one or more substituents such as aliphatic (e.g., alkyl, alkenyl, or alkynyl), cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, amino, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkyl)alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkyl)alkylcarbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxyl, acyl, mercapto, sulfonyl (e.g., alkylsulfonyl or arylsulfonyl), sulfinyl (e.g., alkylsulfinyl), sulfanyl (e.g., alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carbamoyl, or the like.

[041] Without limitation, examples of substituted cycloaliphatics include alkylcycloalkyl (e.g., propylcyclohexyl), alkylbicyclo[3.1.1]heptyl, alkylcycloalkenyl, or the like.

[042] As used herein, the term "heterocycloaliphatic" and "heterocyclic" encompasses a heterocycloalkyl group and a heterocycloalkenyl group.

[043] As used herein, a "heterocycloalkyl" group refers to a 3-10 membered mono or bicyclic (fused or bridged) (e.g., 5 to 10 membered mono or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof). Examples of a heterocycloalkyl group include optionally substituted piperidyl, piperazyl, tetrahydropyranyl, tetrahydrofuryl, 1,4-dioxolanyl, 1,4-dithianyl, 1,3-dioxolanyl, oxazolidyl, isoxazolidyl, morpholinyl, thiomorpholyl, octahydro-benzofuryl, octahydro-chromenyl, octahydro-thiochromenyl, octahydro-indolyl, octahydro-pyrindinyl, decahydro-quinolinyl, octahydro-benzo[*b*]thiopheneyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octanyl, 2,6-dioxa-tricyclo[3.3.1.$0^{3,7}$]nonyl, tropane. A monocyclic heterocycloalkyl group may be fused with a phenyl moiety such as tetrahydroisoquinoline. Heterocycloalkyl ring structures can be optionally substituted at any chemically viable position on the ring or rings.

[044] A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicylic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom (e.g., N, O, or S). Examples of heterocycloalkenyls include 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, or 2-pyrazolyl. Monocyclic heteroaliphatics are numbered according to standard chemical nomenclature. For instance:



2-Pyrazoline

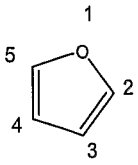
[045] A heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl (such as a benzimidazolidinyl), (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy (two alkoxy groups on the same atom or adjacent atoms may form a ring together with the atom(s) to which they are bound), cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, amino, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkyl)alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkyl)alkylcarbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxyl, acyl, mercapto, sulfonyl (such as alkylsulfonyl or arylsulfonyl), sulfinyl (such as alkylsulfinyl), sulfanyl (such as alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[046] Without limitation, examples of substituted heterocycloaliphatics include alkoxycarbonylheterocycloalkyl (e.g., ethoxycarbonyltropane), alkoxycarbonylheterocycloalkyl (e.g., ethoxycarbonylpiperidyl), or the like.

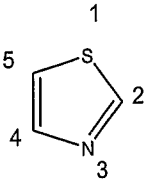
[047] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring structure having 4 to 15 ring atoms wherein one or more of the ring atoms is a heteroatom (e.g., N, O, S, or combinations thereof) and wherein one or more rings of the bicyclic or tricyclic ring structure is aromatic. A heteroaryl group includes a benzofused ring system having 2 to 3 rings. For example, a benzofused group includes benzo fused with one or two C_{4-8} heterocyclic moieties (e.g., indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinolinyl, or isoquinolinyl). Some examples of heteroaryl are azetidinyl, pyridyl, 1H-indazolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, benzofuryl, isoquinolinyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, benzo[1,3]dioxole, benzo[*b*]furyl, benzo[*b*]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, puryl, cinnolyl,

quinolyl, quinazolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, isoquinolyl, 4H-quinolizyl, benzo-1,2,5-thiadiazolyl, or 1,8-naphthyridyl.

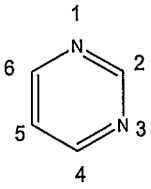
[048] Without limitation, monocyclic heteroaryls include furyl, thiophenyl, 2H-pyrrolyl, pyrrolyl, oxazolyl, thazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4-H-pranyl, pyridyl, pyridazyl, pyrimidyl, pyrazolyl, pyrazyl, or 1,3,5-triazyl. Monocyclic heteroaryls are numbered according to standard chemical nomenclature. For instance:



Furan

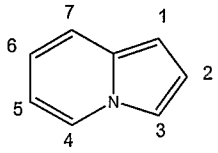


Thiazole

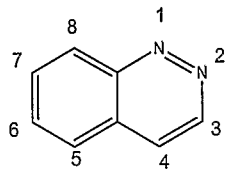


Pyrimidine

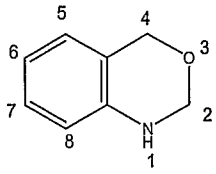
[049] Without limitation, bicyclic heteroaryls include indolizyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thiophenyl, quinolinyl, isoquinolinyl, indolizyl, isoindolyl, indazolyl, benzimidazyl, benzthiazolyl, purinyl, 4H-quinolizyl, quinolyl, isoquinolyl, cinnolyl, phthalazyl, quinazolyl, quinoxalyl, 1,8-naphthyridyl, or pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature. For instance:



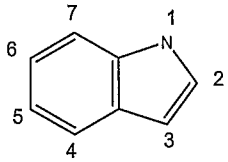
Indolizine



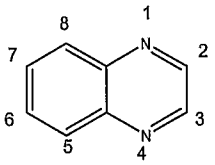
Cinnoline



3,1-Benzoxazine



Indolizine



Quinoxaline

[050] A heteroaryl is optionally substituted with one or more substituents such as aliphatic including alkyls (e.g., alkoxyalkyl, carboxyalkyl, hydroxyalkyl, oxoalkyl, aralkyl, (alkylsulfonylamino)alkyl, (sulfonylamino)alkyl, cyanoalkyl, aminoalkyl, oxoalkyl, alkoxycarbonylalkyl, (cycloalkyl)alkyl heterocycloalkyl, (heterocycloalkyl)alkyl aralkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl; cycloaliphatic including cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl); heterocycloaliphatic including heterocylcoalkyl (e.g., thiomorpholyl, piperazinyl, 1,3,5-trithianyl, morpholinyl, pyrrolyl, 1,3-dioxolanyl, pyrazolidyl, or piperidinyl); aryl, heteroaryl (e.g., quinolyl, indolyl, 3H-indolyl, isoindolyl, benzo[*b*]-4H-pyranyl, cinnolyl, quinoxylyl, benzimidazyl, benzo-1,2,5-thiadiazolyl, benzo-1,2,5-oxadiazolyl, or benzthiophenyl); alkoxy; cycloalkyloxy; heterocycloalkyloxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; aroyl; heteroaroyl; amino (e.g., carbonylamino, alkylcarbonylamino, alkylsulfonylamino, arylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, (heterocycloalkyl)carbonylamino, (cycloalkyl)alkylcarbonylamino, sulfanylamino, and (heterocycloalkyl)alkylcarbonylamino); nitro;

carboxy; carbonyl (e.g., alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, arylaminocarbonyl, thiazoleaminocarbonyl, thiomorpholinecarbonyl, aminoalkylaminocarbonyl); alkylcarbonyloxy; cyano; halo; hydroxyl; acyl; mercapto; sulfonyl (e.g., aminosulfonyl, alkylsulfonyl, morpholinesulfonyl, or arylsulfonyl); sulfinyl (e.g., alkylsulfinyl); sulfanyl (e.g., alkylsulfanyl); sulfoxy; urea; thiourea; sulfamoyl; sulfamide; oxo; or carbamoyl.

[051] Examples of substituted heteroaryls include haloheteroaryl, alkoxycarbonylheteroaryl, alkylaminoalkylaminocarbonylheteroaryl, dihaloheteroaryl, cyanoheteroaryl, aminoheteroaryl, alkylcarbonylaminoheteroaryl, cyanoalkylheteroaryl, alkoxyheteroaryl, aminosulfonylheteroaryl, alkylsulfonylheteroaryl, aminoheteroaryl, aminoheteroaryl, hydroxyalkylheteroaryl, alkoxyalkylheteroaryl, hydroxyheteroaryl, carboxyalkylheteroaryl, dialkylaminoalkylheteroaryl, heterocycloaliphaticheteroaryl, heteroarylaminocarbonylheteroaryl, nitroalkylheteroaryl, alkylsulfonylaminoalkylheteroaryl, heterocycloaliphaticcarbonylheteroaryl, alkylsulfonylalkylheteroaryl, cyanoalkylheteroaryl, heterocycloaliphaticcarbonylheteroaryl, alkylcarbonylaminoheteroaryl, hydroxyalkylheteroaryl, alkylcarbonylheteroaryl, aminocarbonylheteroaryl, alkylsulfonylaminoheteroaryl, dialkylaminoheteroaryl, alkylheteroaryl, and trihaloalkylheteroaryl.

[052] A "heteroaralkyl" group, as used herein, refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with a heteroaryl group. Both "alkyl" and "heteroaryl" have been defined above.

[053] As used herein, "cyclic moiety" includes cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, each of which has been defined previously.

[054] As used herein, an "acyl" group refers to a formyl group or alkyl-C(=O)- (also referred to as "alkylcarbonyl") where "alkyl" has been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[055] As used herein, a "carbamoyl" group refers to a group having the structure -O-CO-NR^xR^y or -NR^x-CO-O-R^z wherein R^x and R^y have been defined above and R^z can be alkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroaralkyl.

[056] As used herein, a "carboxy" and a "sulfo" group refer to –COOH or -$COOR^X$ and -SO_3H or -SO_3R^X, respectively.

[057] As used herein, an "alkoxy" group refers to an alkyl-O- group where "alkyl" has been defined previously. Moreover an alkoxy group includes structures comprising two alkoxy groups on the same atom or adjacent atoms that form a ring together with the atom(s) to which they are bound.

[058] As used herein, a "sulfoxy" group refers to -O-SO-R^X or –SO-O-R^X, where R^X has been defined above.

[059] As used herein, a "mercapto" group refers to –SH.

[060] As used herein, a "sulfonyl" group refers to $-S(O)_2-R^X$, wherein R^X has been defined above. Examples of sulfonyls include optionally substituted alkylsulfonyl, arylsulfonyl (e.g., haloarylsulfonyl), heteroarylsulfonyl (e.g., alkylheteroarylsulfonyl), or the like.

[061] As used herein a "sulfinyl" group refers to $-S(O)-R^X$, wherein R^X has been defined above. Examples of sulfinyls include alkylsulfinyl.

[062] As used herein a "sulfanyl" group refers to $-S-R^X$, wherein R^X has been defined above. Examples of sulfanyls include alkylsulfanyl.

[063] As used herein, a "halogen" or "halo" group refers to fluorine, chlorine, bromine or iodine.

[064] As used herein, a "haloaliphatic" group refers to an aliphatic group substituted with 1-3 halogen. For instance, the term haloalkyl includes the group $-CF_3$.

[065] As used herein, a "sulfamoyl" group refers to the structure $-S(O)_2-NR^xR^y$ or $-NR^x-S(O)_2-R^z$ wherein R^x, R^y, and R^z have been defined above.

[066] As used herein, a "sulfamide" group refers to the structure $-NR^X-S(O)_2-NR^YR^Z$ wherein R^X, R^Y, and R^Z have been defined above.

[067] As used herein, a "carbonylamino" group used alone or in connection with another group refers to an amido group such as $Rx-C(O)-NR^X-$. For instance an alkylcarbonylamino includes $alkyl-C(O)-NR^X-$, wherein R^x has been defined above.

[068] As used herein, a "aminocarbonyl" group used alone or in connection with another group refers to an amido group such as $N(Rx)_2-C(O)-$.

[069] As used herein, an "alkoxycarbonyl" used alone or in connection with another group refers to a carbonyl group such as alkyl-O-C(O)-.

[070] As used herein, an "alkoxyalkyl" refers to an alkyl group such as alkyl-O-alkyl-, wherein alkyl has been defined above.

[071] As used herein, an "aminocarbonyl" refers to an amido group such as $-NR^X-C(O)-$, wherein R^x has been defined above.

[072] As used herein, an "aminosulfonyl" refers to the structure $-N(R^X)_2-S(O)_2-$, wherein R^x has been defined above.

[073] As used herein, an "oxo" refers to =O.

[074] As used herein, an "aminoalkyl" refers to the structure $N(R^X)_2$-alkyl-.

[075] As used herein, a "cyanoalkyl" refers to the structure (CN)-alkyl-.

[076] As used herein, an "alkylsulfonyl' group refers to the structure $alkyl-S(O)_2-$.

[077] As used herein, a "sulfonylamino" group refers to the structure $Rx-S(O)_2-N(R^X)_2-$, wherein R^x has been defined above.

[078] As used herein, a "urea" group refers to the structure $-NR^X-CO-NR^YR^Z$ and a "thiourea" group refers to the structure $-NR^X-CS-NR^YR^Z$. R^X, R^Y, and R^Z have been defined above.

[079] In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, may be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[080] The phrase "stable or chemically feasible," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[081] As used herein, an effective amount is defined as the amount required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight, and condition of the patient. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich et al., *Cancer Chemother. Rep.*, 50: 219 (1966). Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, New York, 537 (1970). As used herein, "patient" refers to a mammal, including a human.

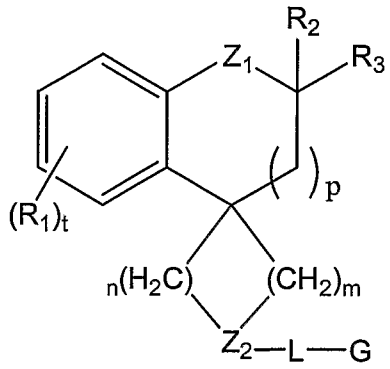
[082] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in

the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

II. COMPOUNDS

[083] The present invention provides methods of modulating muscarinic receptor activity using compounds of formulae (I and II), described above, that are useful in modulating activity of a muscarinic receptor.

[084] Methods of modulating muscarinic receptors according to one aspect of the present invention involve compounds of formula (I):



(I)

or pharmaceutically acceptable salts thereof.

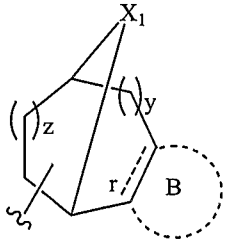
[085] Each of R_1, R_2, R_3 is independently Q_1 or Q_2, or R_2 and R_3 together form oxo.

[086] Z_1 is $-C(Q_1)_2-$, $-C(H)(Q_1)-$, $-C(H)(Q_5)-$, $-C(O)-$, $-CH_2-$, $-N(Q_1)-$, $-N(Q_2)-$, or O.

[087] Z_2 is N.

[088] L is a bond, an aliphatic group, C_3-C_6 cycloaliphatic, -O-, $-S(O)_z-$, $-S(O)_z-(C_1-C_4)$alkyl-, $-C(O)N(Q_2)-$, or $-S(O)_z N(Q_2)-$, in which the aliphatic group is optionally substituted with 1-3 of oxo, Q_1, or Q_2.

[089] G is a monocycloaliphatic group, a monocycloheteroaliphatic group, adamantyl, or a bicyclic or a tricyclic group of the formula (III)



(III)

in which the monocycloaliphatic group, the monocycloheteroalipahtic group, the adamantyl, and the bicyclic or tricyclic group are connected to L via any ring atom including those in X_1 and ring

B, and the monocycloaliphatic, the monocycloheteroaliphatic, the bicyclic, and the tricyclic groups are optionally substituted with 1-3 of oxo, =N-OQ_4, fluorine, Q_2, -C(O)-X_2-aliphatic in which X_2 is absent, -O-, -NH-, -NQ_2-, or -$S(O)_z$- and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3; bond r is a single or double bond and when ring B is present, bond r is fused with B; ring B, when present, is a 5-6 membered cycloaliphatic or heterocyclic ring; and ring B is optionally substituted with 1-3 of oxo, Q_1, or Q_2.

[090] X_1 is -$(CH_2)_i$-, -O-, -S-, -N(Q_2)-, -N(C(O)-X_2-aliphatic)- in which X_2 is absent, -O-, -NH-, -NQ_2-, or -$S(O)_z$- and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

[091] Each Q_1 is independently halo, -CN, -NO_2, -OQ_2, -$S(O)_zQ_2$, -$S(O)_zN(Q_2)_2$, -$N(Q_2)_2$, -$C(O)OQ_2$, -C(O)-Q_2, -$C(O)N(Q_2)_2$, -$C(O)N(Q_2)(OQ_2)$, -$N(Q_2)C(O)$-Q_2, -$N(Q_2)C(O)N(Q_2)_2$, -$N(Q_2)C(O)O$-Q_2, -$N(Q_2)S(O)_z$-Q_2 or aliphatic optionally including 1-3 substituents independently selected from Q_2 or Q_3.

[092] Each Q_2 is independently H, aliphatic, cycloaliphatic, aryl, arylalkyl, heterocyclic, or heteroaryl ring, each optionally including 1-3 substituents independently selected from Q_3.

[093] Each Q_3 is halo, oxo, CN, NO_2, CF_3, OCF_3, OH, -$S(O)_zQ_4$, -$N(Q_4)_2$, -$COOQ_4$, -$C(O)Q_4$, -OQ_4, or C_1-C_4 alkyl optionally substituted with 1-3 of halo, oxo, -CN, -NO_2, -CF_3, -OCF_3, -OH, -SH, -$S(O)_zH$, -NH_2, or -COOH.

[094] Each Q_4 is aliphatic, cycloaliphatic, aryl, aralkyl, heterocyclic, heteroaralyl, or heteroaryl ring, each optionally substituted with 1-3 substituents selected from halo, oxo, CN, NO_2, CF_3, -OCF_3, -OH, -SH, -$S(O)_zH$, -NH_2, -COOH.

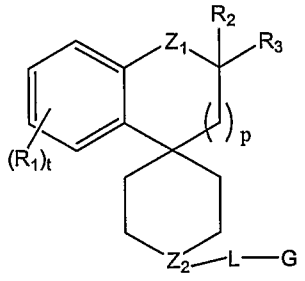
[095] Each Q_5 is a heterocyclic ring optionally substituted with 1-3 substituents selected from halo, C_1-C_4 alkyl, oxo, CN, NO_2, CF_3, OCF_3, OH, SH, -$S(O)_zH$, -NH_2, COOH; and each i is independently 1, 2, or 3.

[096] Each m and n is independently 1, 2, 3, or 4 provided that m + n is at least 4.

[097] Each p is 0 or 1.

[098] Each y is independently 0 or 1; each t is 1 to 4; and each z is independently 0, 1, or 2.

[099] Another aspect of the invention provides compounds of formula (II) including:



(II)

or pharmaceutically acceptable salts thereof.

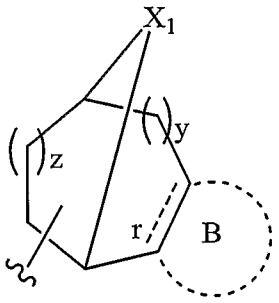
[0100] Each of R_1, R_2, R_3 is independently Q_1 or Q_2, or R_2 and R_3 together form oxo.

[0101] Z_1 is $-C(Q_1)_2-$, $-C(H)(Q_1)-$, $-C(H)(Q_5)-$, $-C(O)-$, $-CH_2-$, $-N(Q_1)-$, $-N(Q_2)-$, or O.

[0102] Z_2 is N.

[0103] L is a bond, an aliphatic group, C_3-C_6 cycloaliphatic, -O-, $-S(O)_z-$, $-S(O)_z-(C_1-C_4)$alkyl-, $-C(O)N(Q_2)-$, or $-S(O)_z\,N(Q_2)-$, in which the aliphatic group is optionally substituted with 1-3 of oxo, Q_1, or Q_2.

[0104] G is a monocycloaliphatic group, a monocycloheteroaliphatic group, adamantyl, or a bicyclic or a tricyclic group of formula (III)



(III)

in which the monocycloaliphatic group, the monocycloheteroaliphatic group, the adamantyl, and the bicyclic or tricyclic group are connected to L via any ring atom including those in X_1 and ring B, and the monocycloaliphatic, the monocycloheteroaliphatic, the bicyclic, and the tricyclic groups are optionally substituted with 1-3 of oxo, $=N-OQ_4$, fluorine, Q_2, $-C(O)-X_2-$aliphatic in which X_2 is absent, –O-, -NH-, $-NQ_2-$, or $-S(O)_z-$ and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3; bond r is a single or double bond and when ring B is present, bond r is fused with B; ring B, when present, is a 5-6 membered cycloaliphatic or heterocyclic ring, and is optionally substituted with 1-3 of oxo, Q_1, or Q_2.

[0105] X_1 is $-(CH_2)_i-$, -O-, -S-, $-N(Q_2)-$, $-N(C(O)-X_2-$aliphatic$)-$ in which X_2 is absent, -O-, -NH-, $-NQ_2-$, or $-S(O)_z-$ and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

[0106] Each Q_1 is independently halo, -CN, $-NO_2$, $-OQ_2$, $-S(O)_zQ_2$, $-S(O)_zN(Q_2)_2$, $-N(Q_2)_2$, $-C(O)OQ_2$, $-C(O)-Q_2$, $-C(O)N(Q_2)_2$, $-C(O)N(Q_2)(OQ_2)$, $-N(Q_2)C(O)-Q_2$, $-N(Q_2)C(O)N(Q_2)_2$, $-N(Q_2)C(O)O-Q_2$, $-N(Q_2)S(O)_z-Q_2$ or aliphatic optionally including 1-3 substituents independently selected from Q_2 or Q_3.

[0107] Each Q_2 is independently H, aliphatic, cycloaliphatic, aryl, arylalkyl, heterocyclic, or heteroaryl ring, each optionally substituted with 1-3 substituents independently selected from Q_3.

[0108] Each Q_3 is halo, oxo, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, -OH, $-S(O)_zQ_4$, $-N(Q_4)_2$, $-COOQ_4$, $-C(O)Q_4$, $-OQ_4$, or C_1-C_4 alkyl optionally substituted with 1-3 halo, oxo, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, -OH, -SH, $-S(O)_zH$, $-NH_2$, or -COOH.

[0109] Each Q_4 is aliphatic, cycloaliphatic, aryl, aralkyl, heterocycloaliphatic, heteroaralky, or heteroaryl, each optionally including 1-3 substituents selected from halo, oxo, CN, NO_2, CF_3, OCF_3, OH, SH, $-S(O)_zH$, $-NH_2$, or COOH.

[0110] Each Q_5 is a heterocyclic ring optionally substituted with 1-3 substituents selected from halo, oxo, C_1-C_4alkyl, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, -OH, -SH, $-S(O)_zH$, $-NH_2$, and -COOH.

[0111] Each i is independently 1, 2, or 3.

[0112] Each p is 0 or 1.

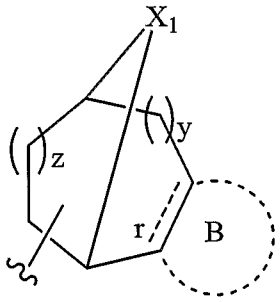
[0113] Each y is independently 0 or 1.

[0114] Each z is independently 0, 1, or 2.

III. SPECIFIC EMBODIMENTS

a. Substituent G

[0115] G is a monocycloaliphatic group, a monocycloheteroaliphatic group, adamantyl, or a bicyclic or a tricyclic group of formula (III)



(III)

in which the monocycloaliphatic group, the monocycloheteroaliphatic group, the adamantyl, and the bicyclic or tricyclic group are connected to L via any ring atom including those in X_1 and ring B, and the monocycloaliphatic, the monocycloheteroaliphatic, the bicyclic, and the tricyclic groups are optionally substituted with 1-3 of oxo, $=N-OQ_4$, fluorine, Q_2, $-C(O)-X_2$-aliphatic in which X_2 is absent, –O-, -NH-, $-NQ_2$-, or $-S(O)_z$- and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3; bond r is a single or double bond and when ring B is present, bond r is fused with B; ring B, when present, is a 5-6 membered cycloaliphatic or heterocyclic ring, and is optionally substituted with 1-3 of oxo, Q_1, or Q_2.

[0116] In certain embodiments, G is an optionally substituted monocycloaliphatic group.

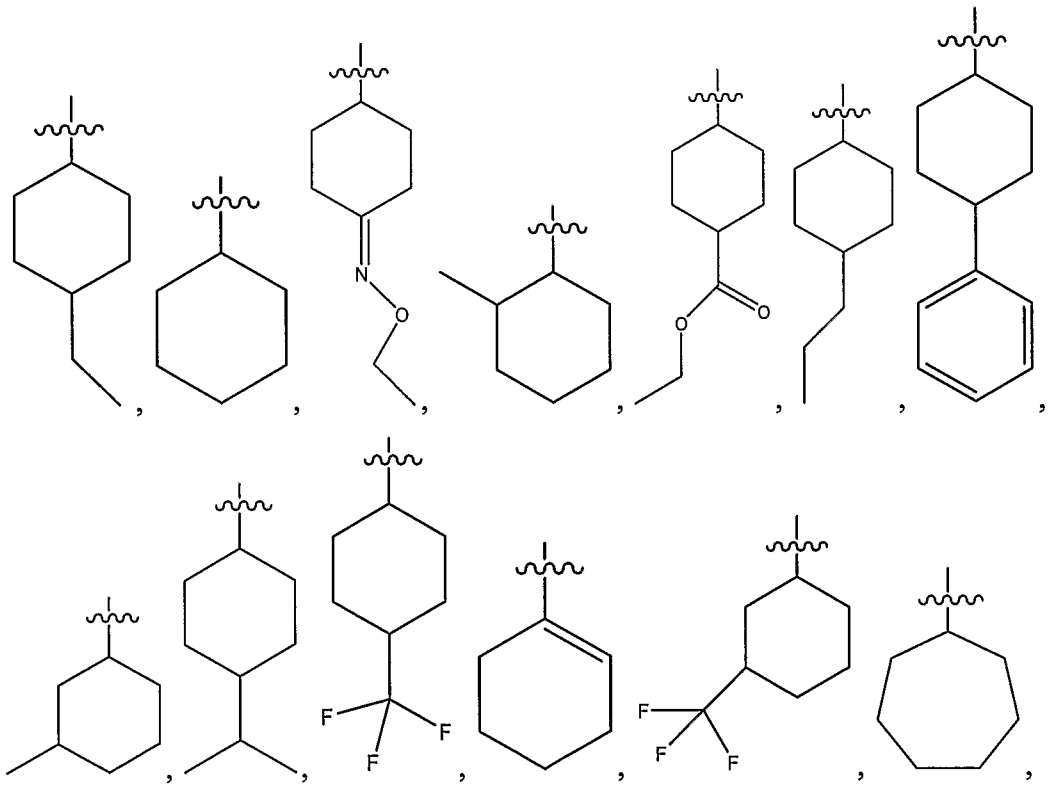
[0117] In several embodiments, G is an optionally substituted cycloaliphatic. In examples of this embodiment, G is an optionally substituted monocycloaliphatic. Specific examples of G include, but are not limited to, 5 to 8 membered monocycloalkyls or a 5 to 8 membered monocycloalkenyls. In other examples, G can be an optionally substituted cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, or cyclooctyl.

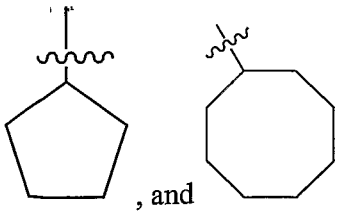
[0118] In several embodiments, G is optionally substituted with Q_2, or -C(O)-X_2-aliphatic, where X_2 is absent, -O-, -NH-, or -NQ_2-, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3. In examples of these embodiments, G can be substituted with carbonyl, sulfonyl, alkoxy, combinations thereof, or the like.

[0119] In several embodiments, G is optionally substituted with 1 to 3 of carbonyl, sulfonyl, or combinations thereof. Examples of G include, but are not limited to, alkoxycarbonyl, aliphaticcarbonyl (e.g., alkylcarbonyl, alkenylcarbonyl, or alkynylcarbonyl), aliphatic, alkoxyalkoxycarbonyl, cycloalkoxycarbonyl, heterocycloalkoxycarbonyl, aminoaliphatic, aliphaticamino, arylcarbonyl, or heteroarylcarbonyl, each of which is optionally substituted.

[0120] In several embodiments, G is substituted with alkyl, aryl, haloalkyl, alkoxycarbonyl, or alkoxyamino.

[0121] In several embodiments, G is selected from



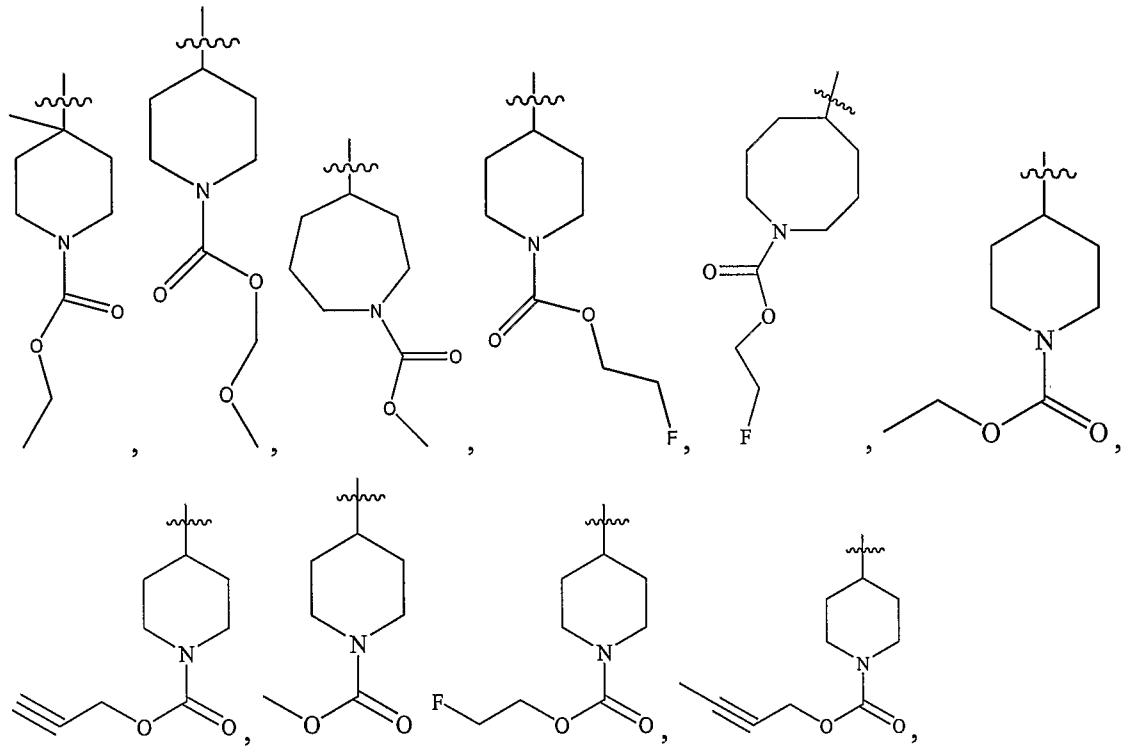


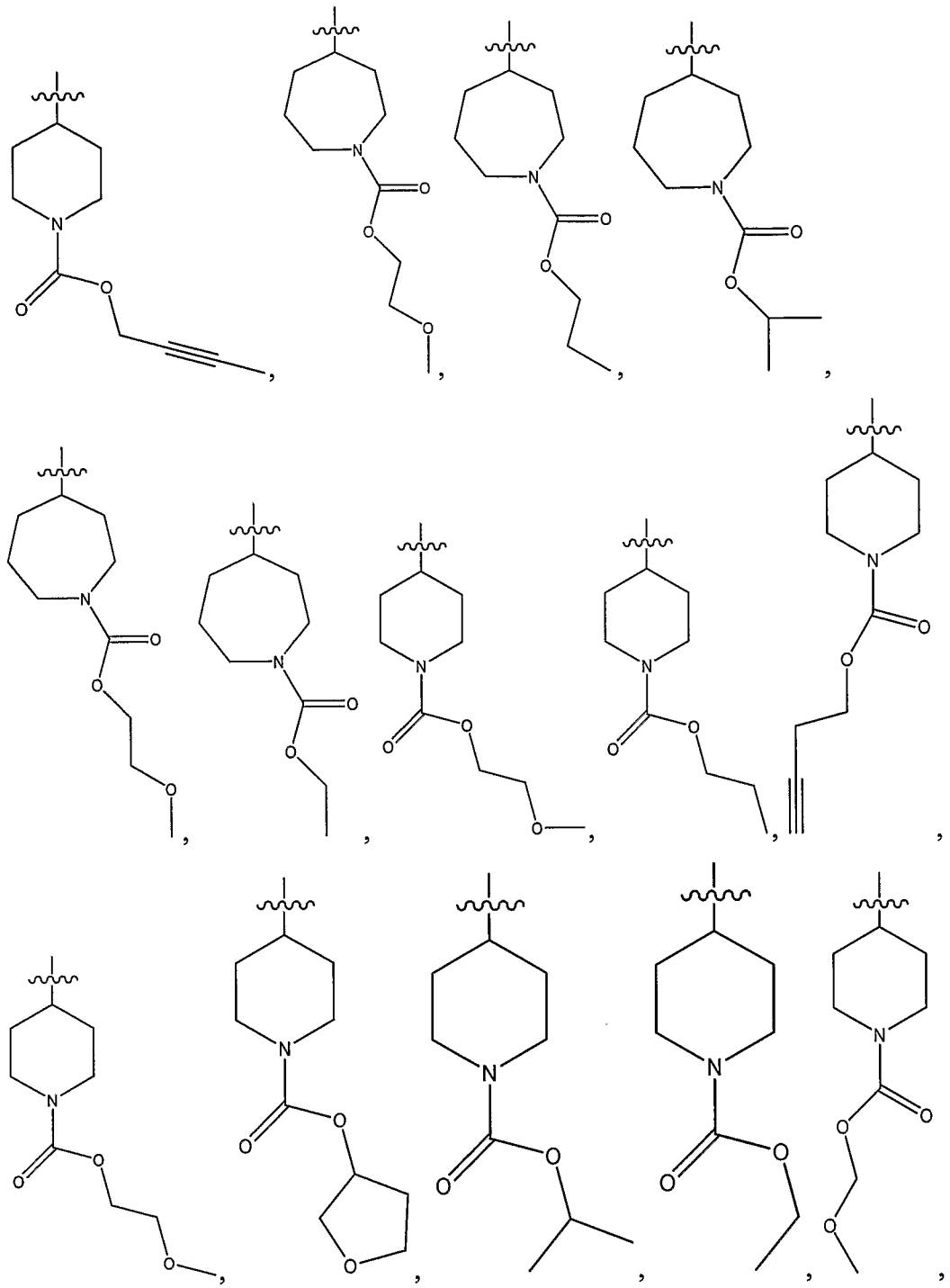
[0122] In several embodiments, G is an optionally substituted monoheterocycloaliphatic group. Examples of G include, but are not limited to, optionally substituted 5 to 7 membered monoheterocycloaliphatic groups.

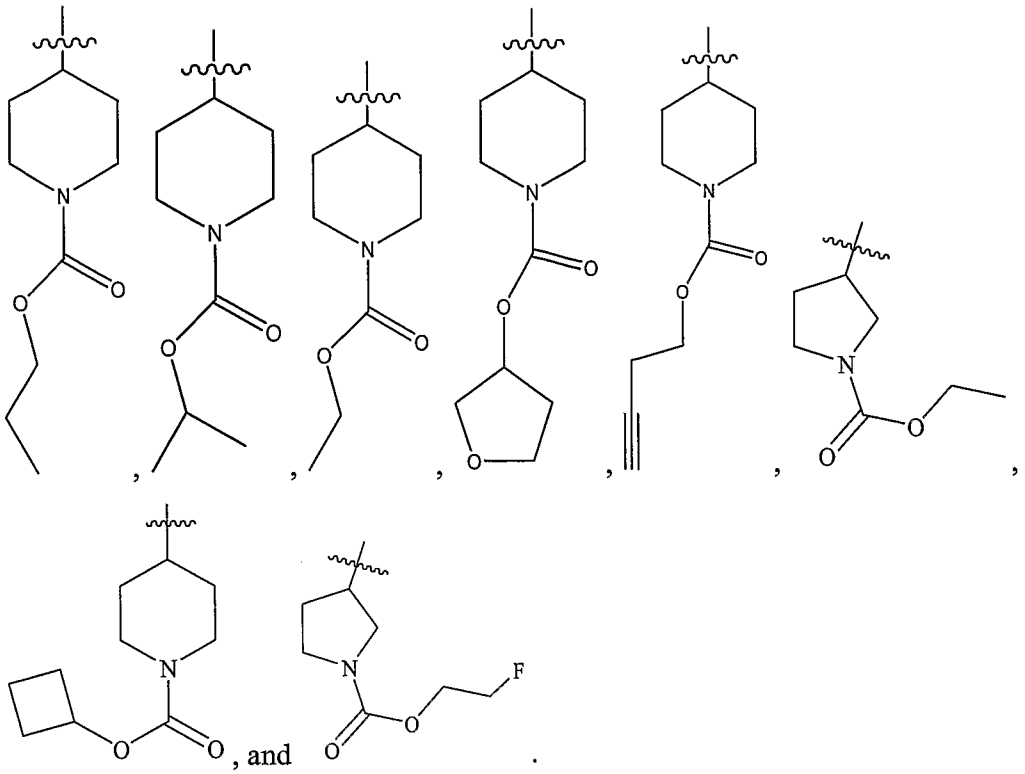
[0123] In several embodiments, G includes at least 1 nitrogen atom. G can be substituted with 1 to 3 substituents independently selected from Q_2, and -C(O)-X_2-aliphatic, where X_2 is absent, -O-, -NH-, or -NQ_2-, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

[0124] In several embodiments, G is optionally substituted with 1 to 2 substituents independently selected from alkoxycarbonyl, alkynyloxycarbonyl, alkoxyalkoxycarbonyl, haloalkoxycarbonyl, heterocycloalkoxycarbonyl, and cycloalkoxycarbonyl.

[0125] In other embodiments, G is one selected from

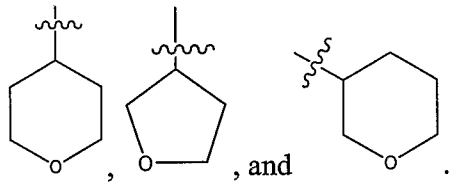






[0126] In several embodiments, G includes at least one O atom. In several examples, G is optionally substituted with 1 to 3 substituents independently selected from independently selected from alkoxycarbonyl, alkynyloxycarbonyl, alkoxyalkoxycarbonyl, haloalkoxycarbonyl, heterocycloalkoxycarbonyl, and cycloalkoxycarbonyl. In other examples, G is unsubstituted.

[0127] In several embodiments, G is one selected from

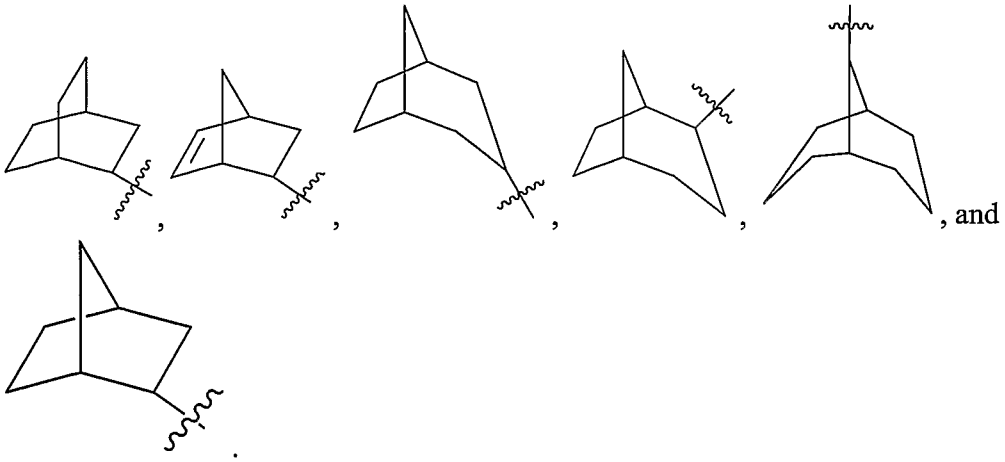


[0128] In other embodiments, G is an optionally substituted bicyclic group of formula (III). In one group of examples, ring B is absent from the bicyclic group of formula (III).

[0129] In several embodiments, X_1 is $-(CH)_{2i}-$.

[0130] In several alternative embodiments, the bicyclic group of formula (III) includes 7 to 9 ring atoms. In specific examples, G is an optionally substituted bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[3.3.1]nonyl, bicyclo[2.2.2]octyl, or bicyclo[2.2.1]heptanyl. In yet another group of the examples, G can be substituted with 1 to 3 substituents independently selected from Q_2, and $-C(O)-X_2$-aliphatic, where X_2 is absent, -O-, -NH-, or $-NQ_2-$, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

[0131] In several embodiments, G is one selected from



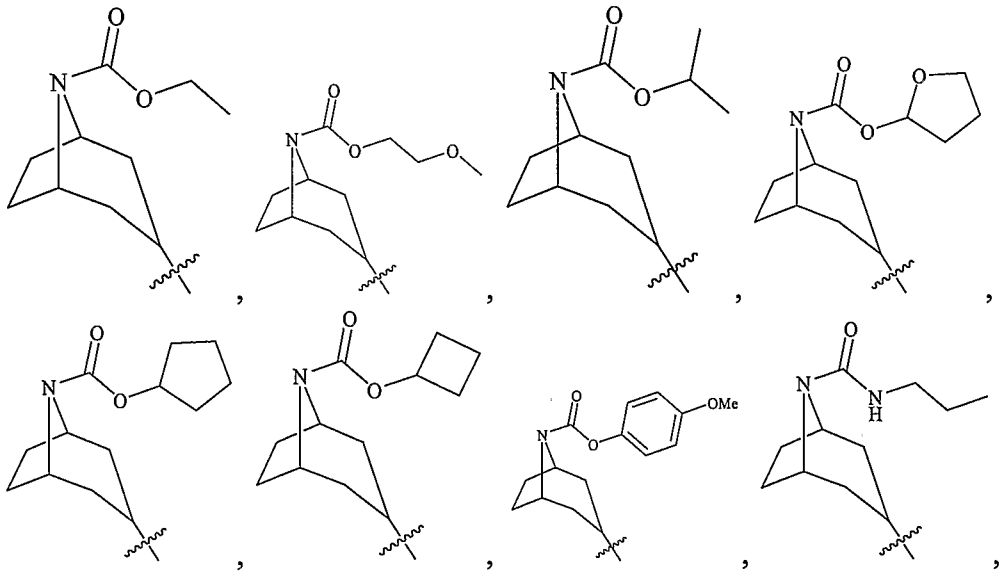
[0132] In other embodiments, G is optionally substituted adamantly.

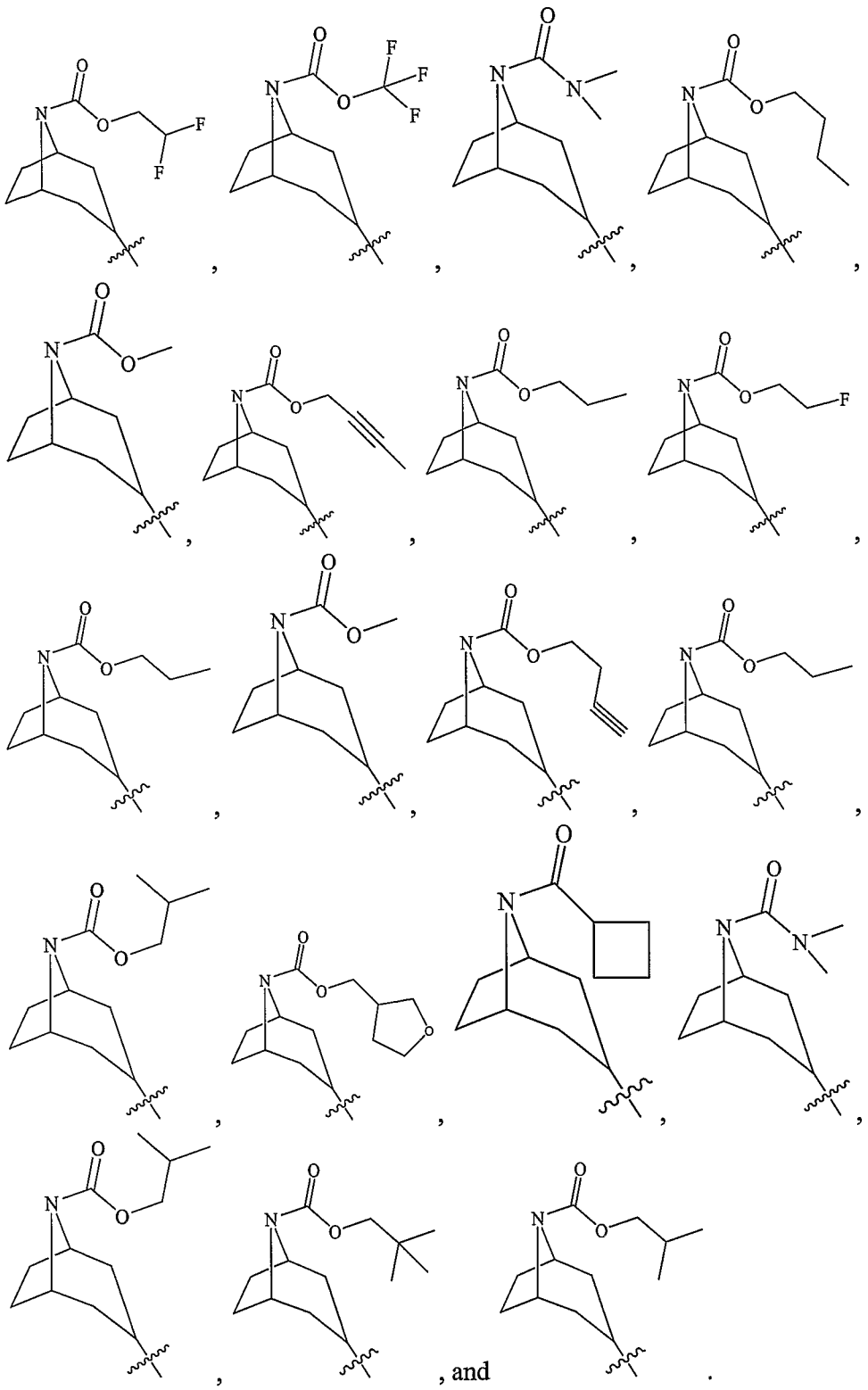
[0133] In several embodiments, X_1 is $-N(Q_2)-$ or $-N(C(O)-X_2\text{-aliphatic})$, where X_2 is absent, -O-, -NH-, or $-NQ_2-$, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3. In one group of examples, G is an optionally substituted tropane.

[0134] In other examples, G is substituted with Q_2, and $-C(O)-X_2$-aliphatic, where X_2 is absent, -O-, -NH-, or $-NQ_2-$, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

[0135] In several embodiments, G is substituted with alkoxycarbonyl, alkoxyalkoxycarbonyl, heterocycloalkoxycarbonyl, cycloalkoxycarbonyl, alkoxyaryloxycarbonyl, alkylaminocarbonyl, haloalkoxycarbonyl, alkynyloxycarbonyl, or heterocycloalkylalkoxycarbonyl.

[0136] In several embodiments, G is one selected from





, and .

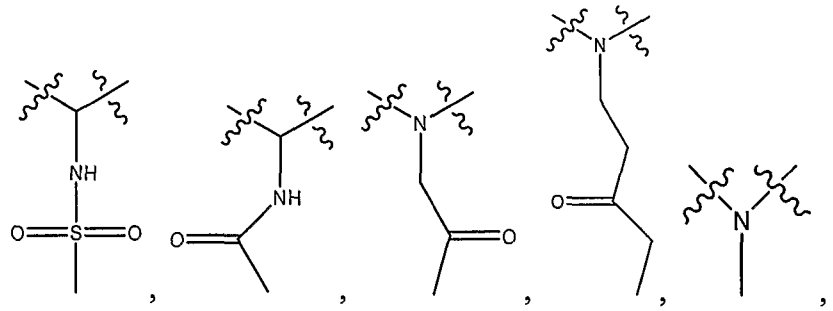
b. Substituent Z_1

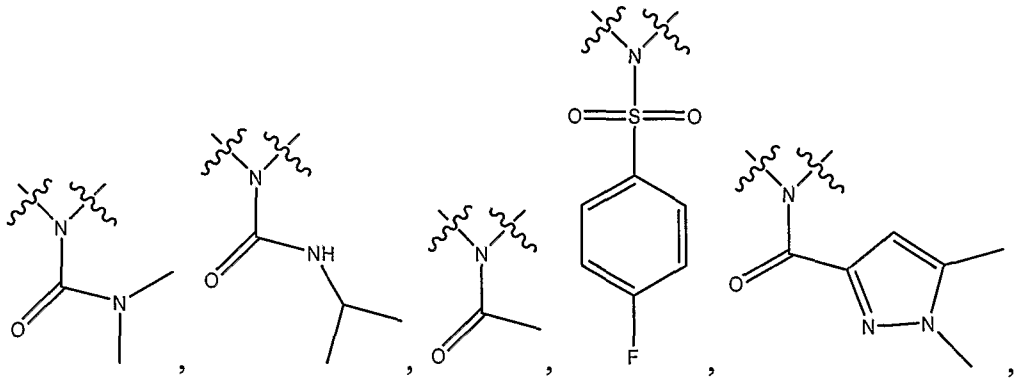
[0137] Z_1 is $-C(Q_1)_2-$, $-C(H)(Q_1)-$, $-C(H)(Q_5)-$, $-C(O)-$, $-CH_2-$, $-N(Q_1)-$, $-N(Q_2)-$, or O.

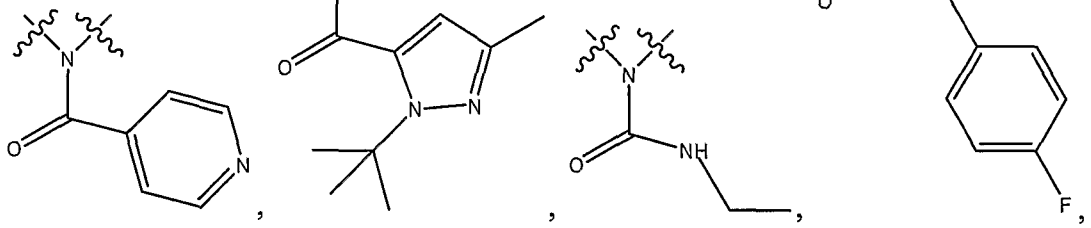
[0138] In several embodiments, Z_1 is optionally substituted carbon or nitrogen atom. In one group of examples, Z_1 is substituted with amino, alkylcarbonylamino, alkylsulfonylamino,

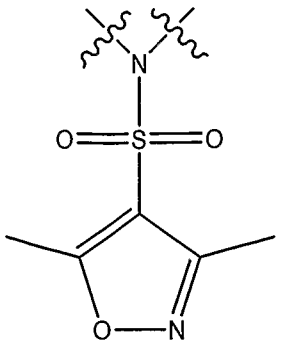
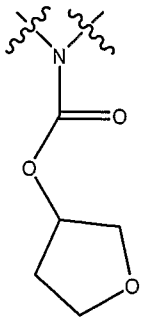
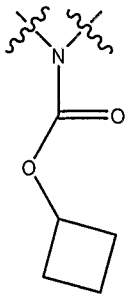
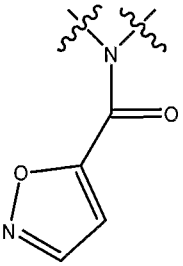
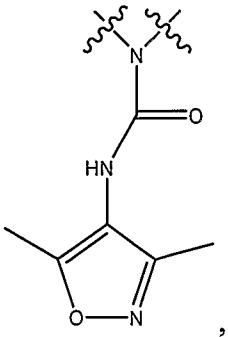
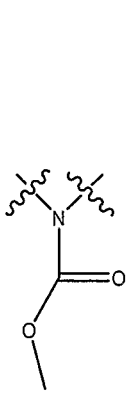
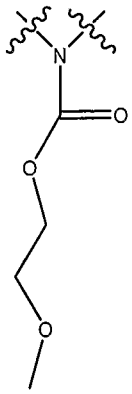
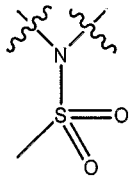
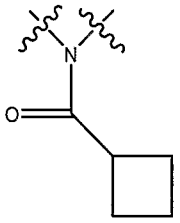
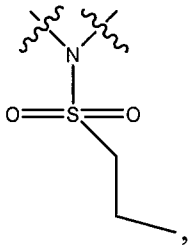
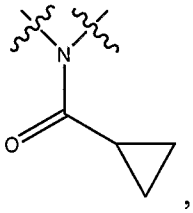
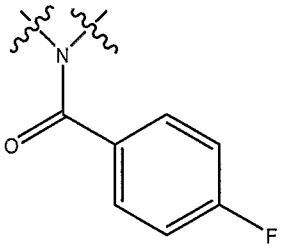
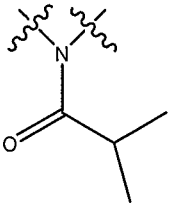
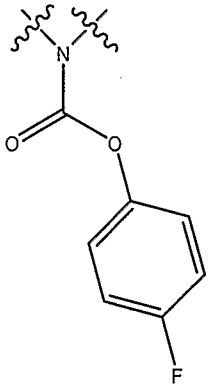
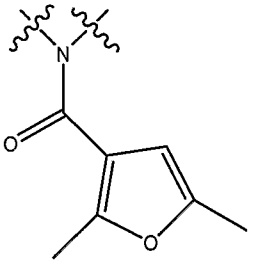
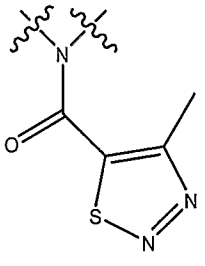
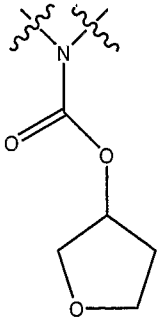
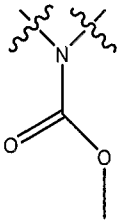
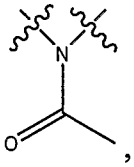
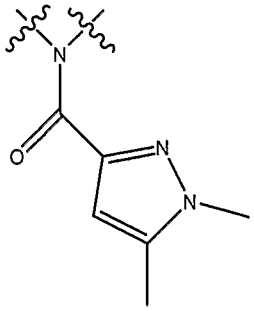
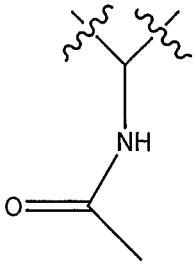
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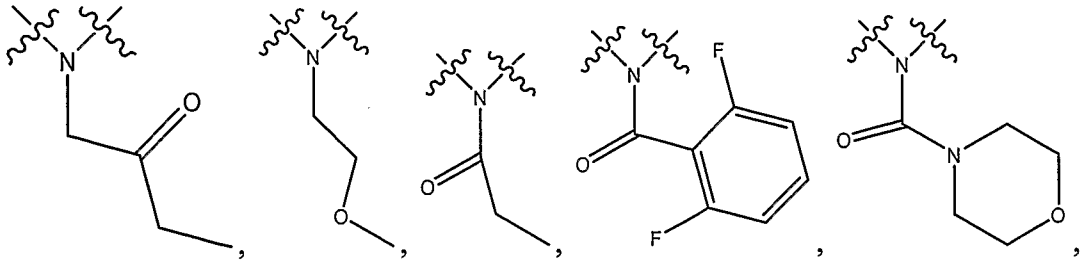
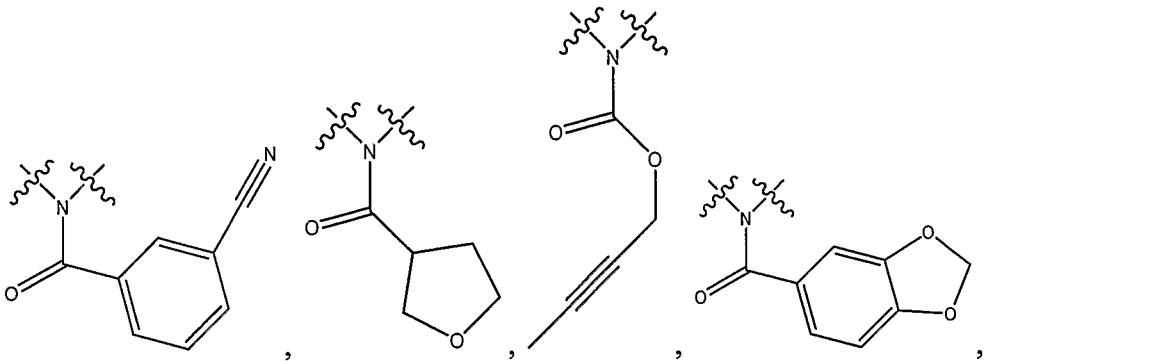
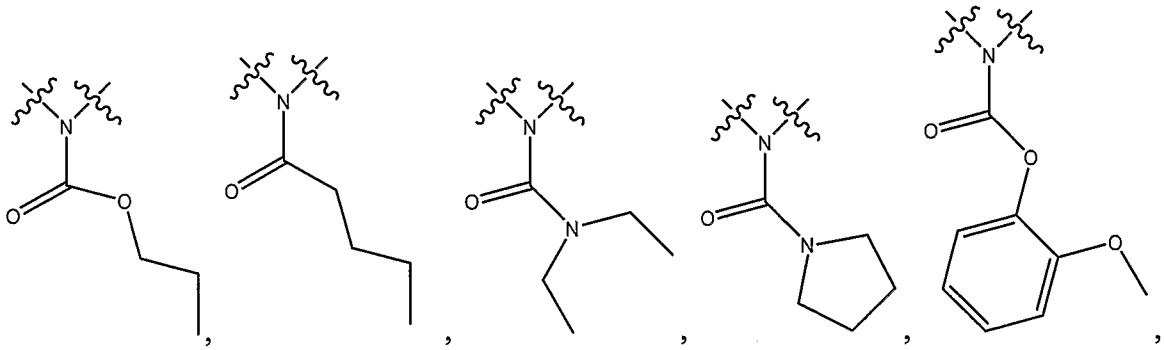
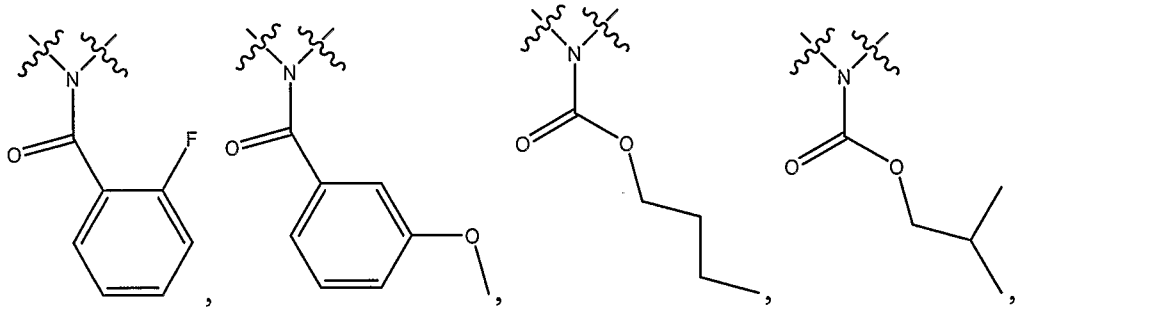
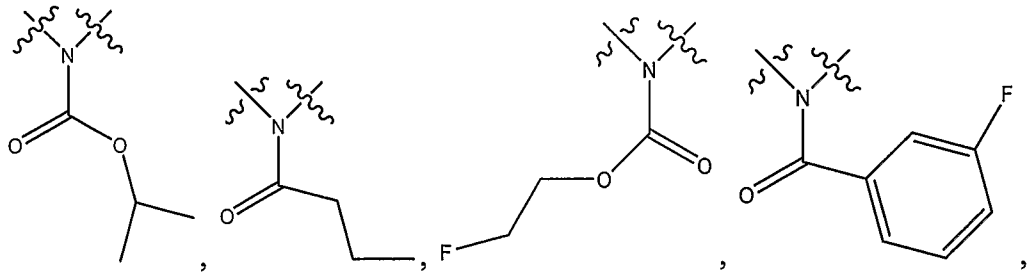
[0139] *In several embodiments,* Z_1 *is one selected from*

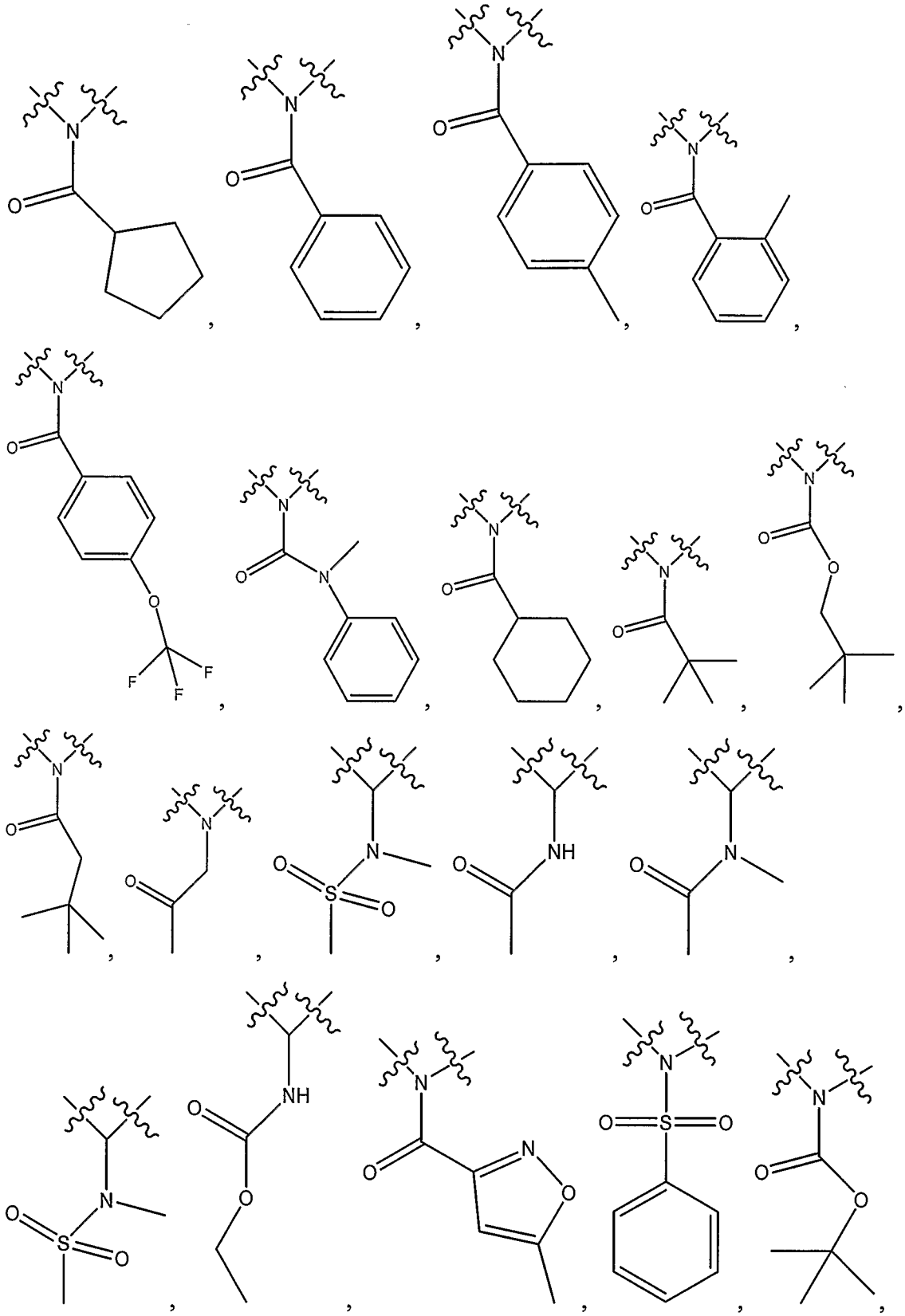
$-CH_2-$, -C(O)-, -NH-, -O-, 

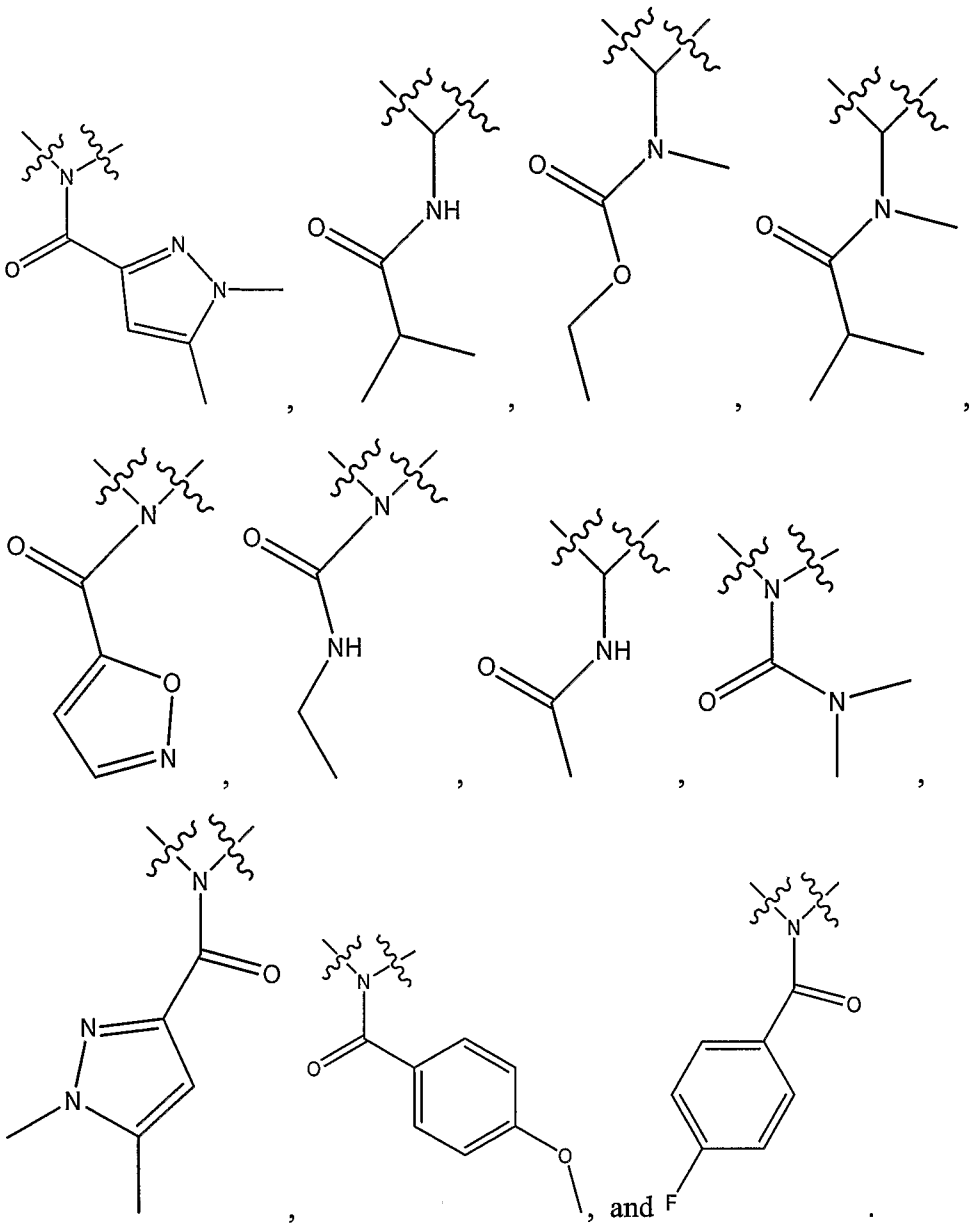





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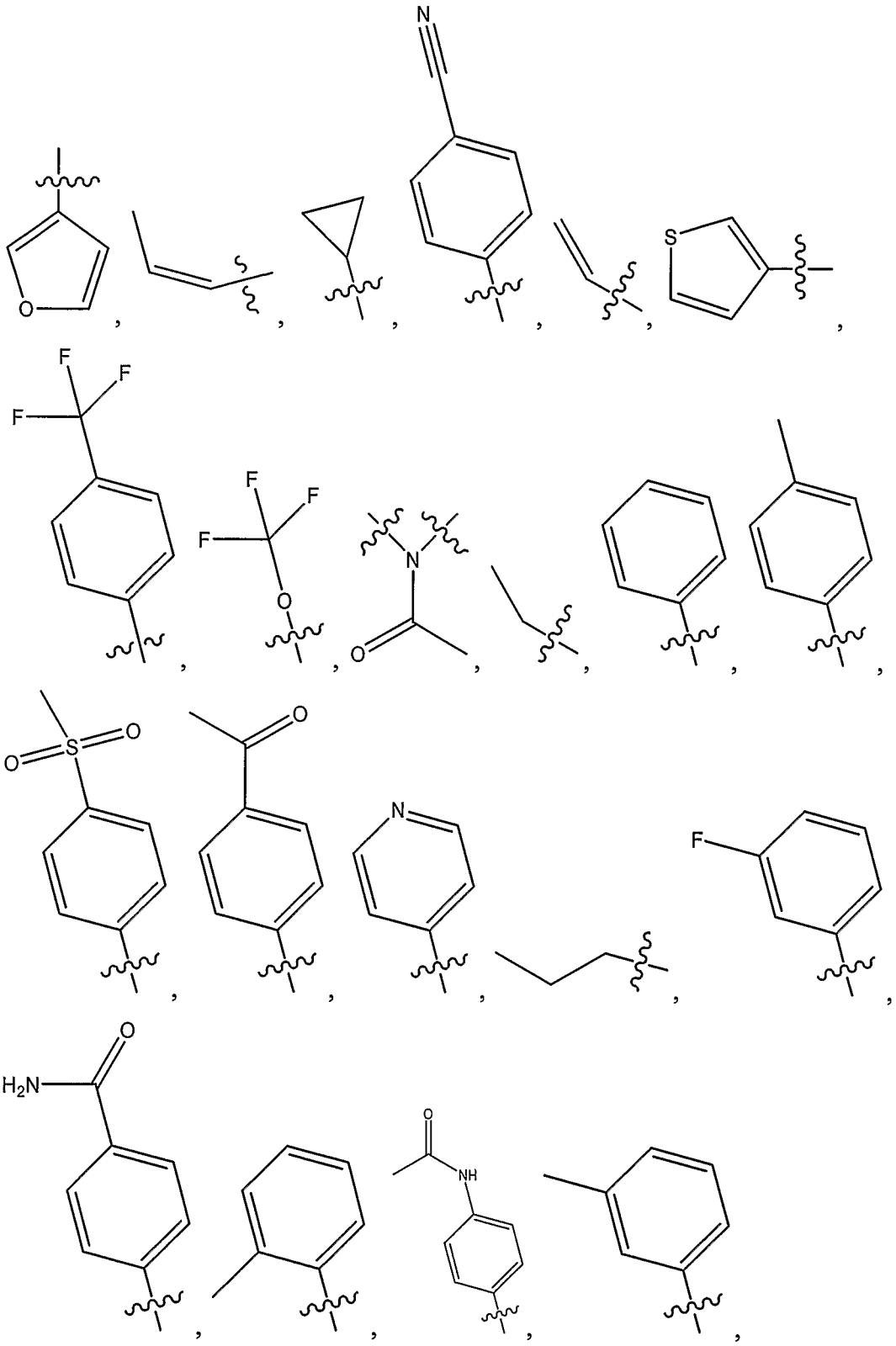


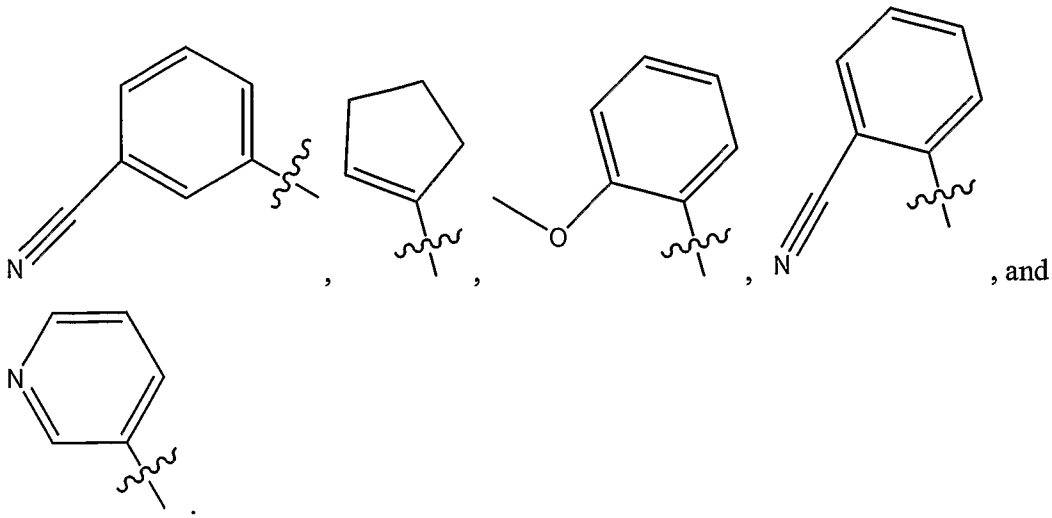
c. Substituents R_1, R_2, and R_3

[0140] Each of R_1, R_2, R_3 is independently Q_1 or Q_2, or R_2 and R_3 together form oxo.

[0141] In several embodiments, R_1 is hydrogen, halo, or optionally substituted alkyl, heteroaryl, alkoxy, alkenyl, cycloalkyl, cyanoalkylaryl, alkylaryl, alkylsulfonylaryl, alkylcarbonylaryl, aryl, aminocarbonylaryl, alkylcarbonylaminoaryl, cycloalkenyl, or alkoxyaryl. R_1 groups can be optionally substituted with 1 to 3 substituents selected from amino, carbonyl, alkoxycarbonyl, aminocarbonyl, aryl, aliphatic, alkoxy, and sulfonyl.

[0142] In other embodiments, R_1 is one selected from hydrogen, halo, methyl, $-OCH_3$,





[0143] In several embodiments, R_2 and R_3 are independently hydrogen, alkyl, arylalkyl, or R_2 and R_3 together form an oxo or amino.

[0144] In still other embodiments, R_2 and R_3 are independently hydrogen, alkyl, or R_2 and R_3 together form an oxo.

d. L Groups

[0145] L is a bond, an aliphatic group, C_3-C_6 cycloaliphatic, -O-, -$S(O)_z$-, -$S(O)_z$-(C_1-C_4)alkyl-, -$C(O)N(Q_2)$-, or -$S(O)_z N(Q_2)$-, in which the aliphatic group is optionally substituted with 1-3 of oxo, Q_1, or Q_2. In some embodiments, L is a bond or an aliphatic group in which the aliphatic group is optionally substituted with 1-3 of oxo, Q_1, or Q_2. In other embodiments, L is a bond. In still further embodiments, L is an aliphatic group optionally substituted with 1-3 of oxo, Q_1, or Q_2. L is CH_2.

e. Combinations of Embodiments

[0146] Other embodiments include any combination of the aforementioned substituents G, Z_1, L, R_1, R_2, and R_3.

f. Excluded Compounds

[0147] In several embodiments, when Z_1 is -CH_2- or -$N(CH_3)$-, L is a bond, and G is an optionally substituted monocycloaliphatic, an optionally substituted monocycloheteroalipahtic group, or a norbornanyl group, then the R_1 substituent on the indane or indole is other than H.

[0148] In several embodiments, when L is -C(O)-CH_2- and Z_1 is -$N(Q_1)$-, and Q_1 on Z_1 is -$S(O)_2$-optionally substituted phenyl, then the R_1 substituent on the indole is other than H.

[0149] In several embodiments, when L is -$S(O)_2$-(C_1-C_4)alkyl-, Z_1 is -CH_2-, then the R_1 substituent on the indane or tetrahydronaphthyl is other than H.

[0150] In several embodiments, when L is $-S(O)_2-(C_1-C_4)$alkyl-, R_2 and R_3 form =O, Z_1 is $-N(Q_1)-$, and Q_1 is aliphatic or $-S(O)_2$-aliphatic, then the R_1 substituent on the indole is other than H.

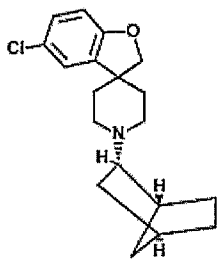
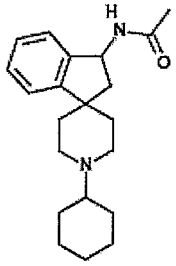
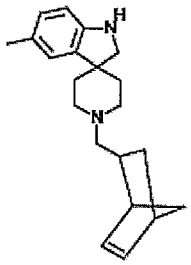
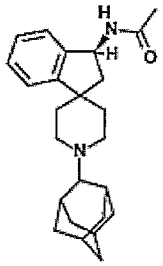
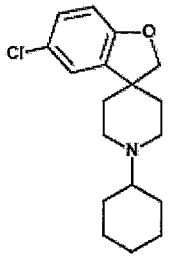
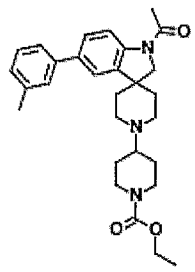
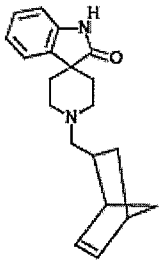
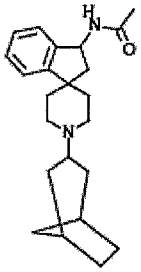
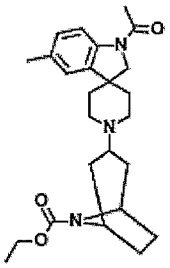
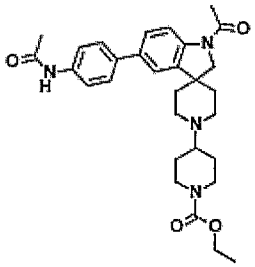
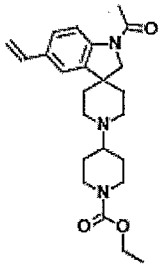
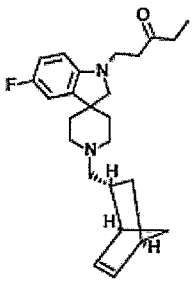
[0151] In several embodiments, when L is aliphatic, and R_2 and R_3 form =O, and Z_1 is $-N(Q_1)-$, Q_1 is aliphatic, G is a substituted monocycloheteroaliphatic group, then the R_1 substituent on the indole is other than H.

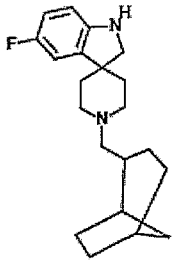
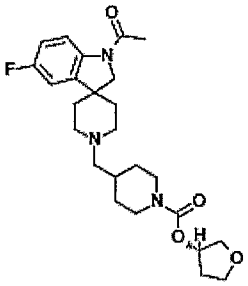
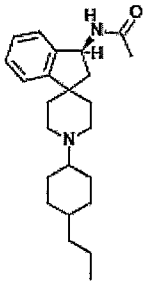
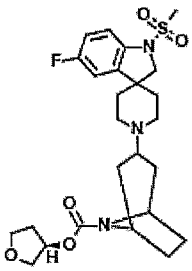
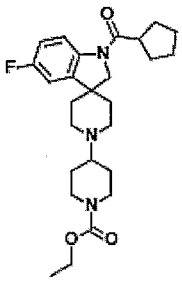
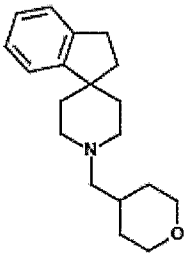
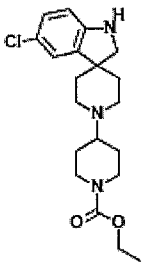
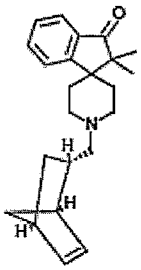
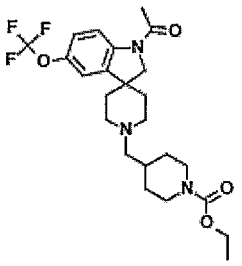
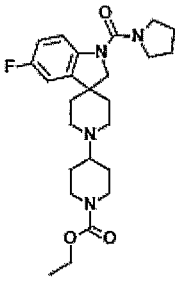
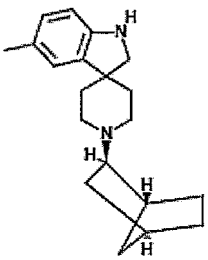
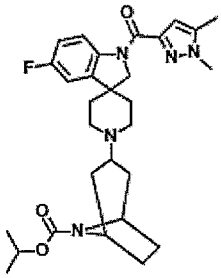
[0152] In certain embodiments, L is not $-S(O)_2-(C_1-C_4)$alkyl-.

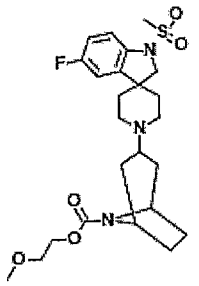
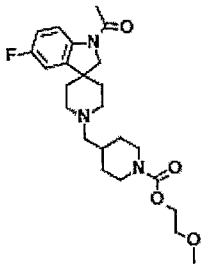
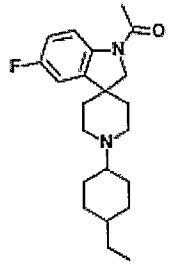
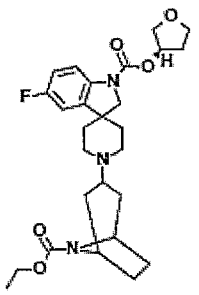
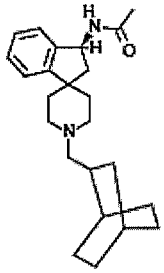
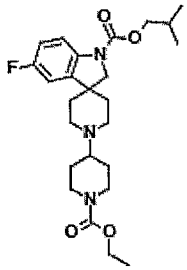
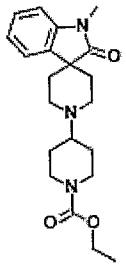
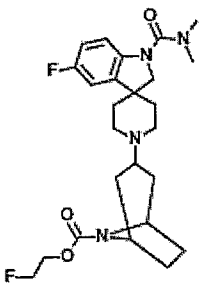
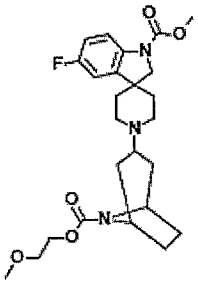
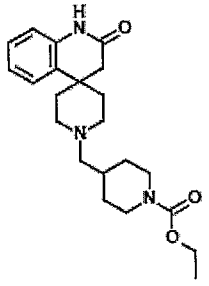
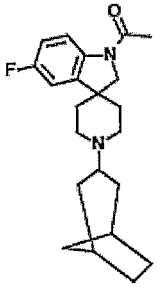
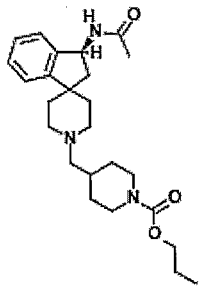
g. Specific Embodiments

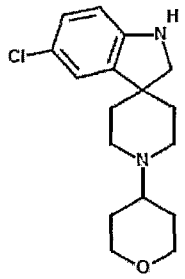
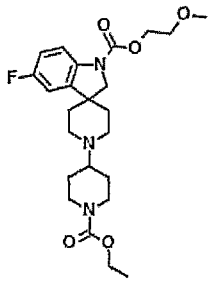
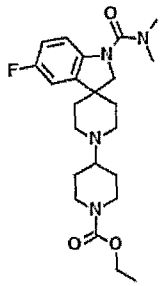
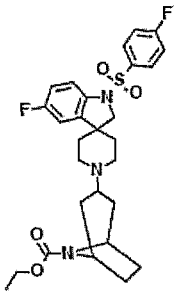
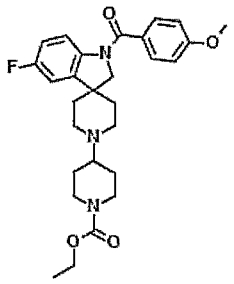
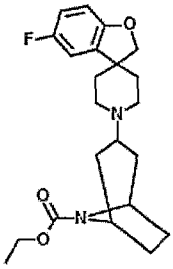
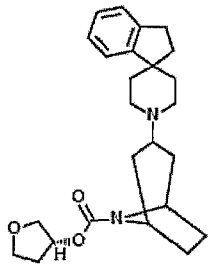
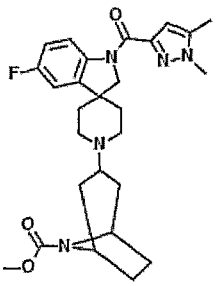
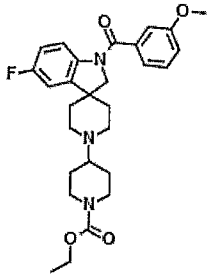
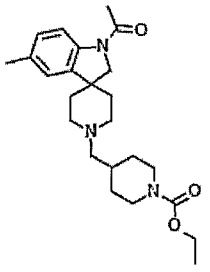
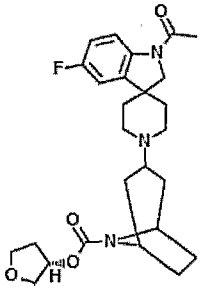
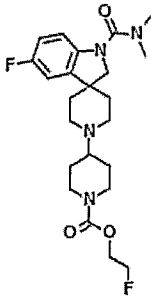
[0153] Specific compounds of formulae (I or II) are shown below. Compounds 1-120 and 122-430 share the core structure of formula II.

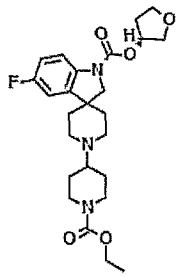
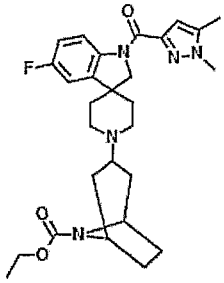
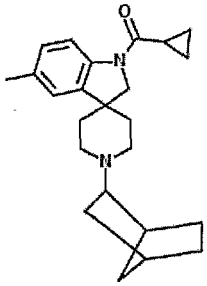
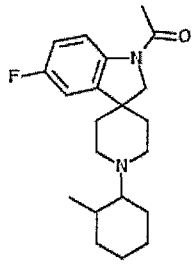
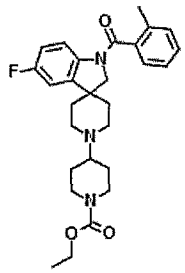
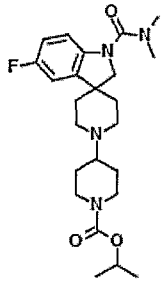
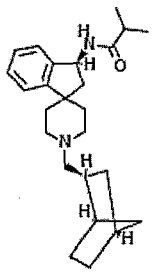
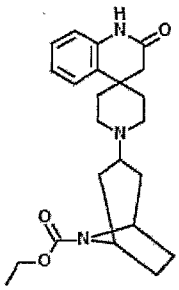
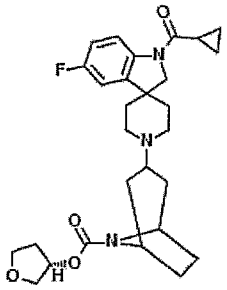
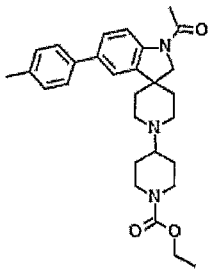
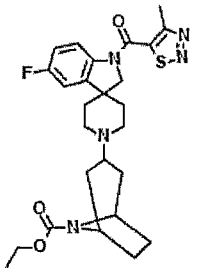
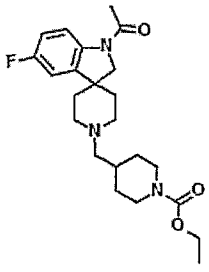
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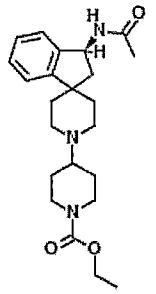
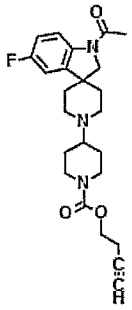
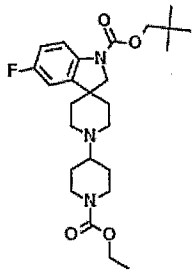
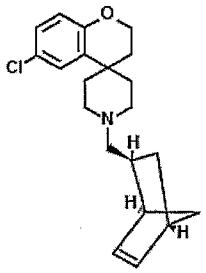
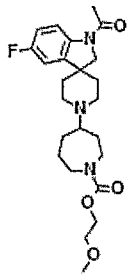
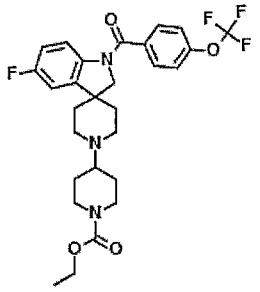
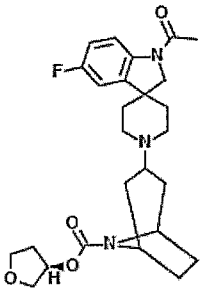
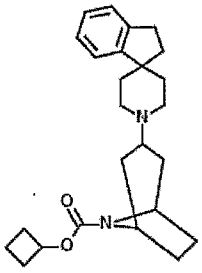
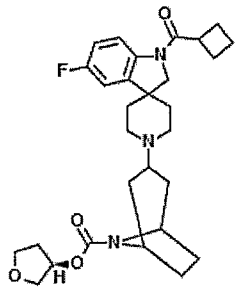
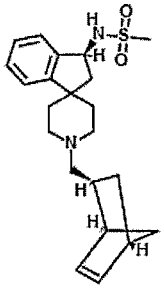
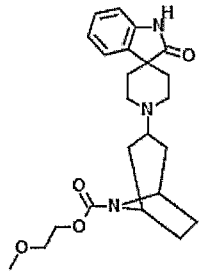
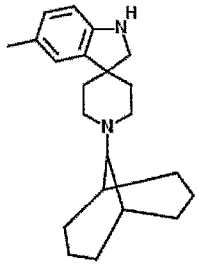
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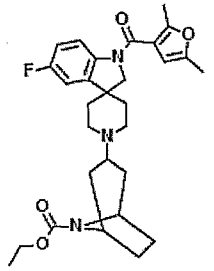
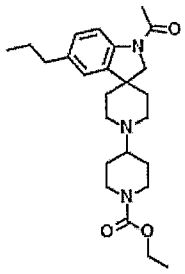
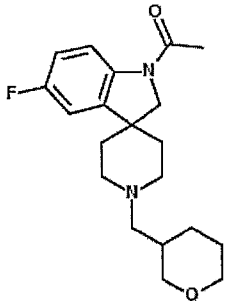
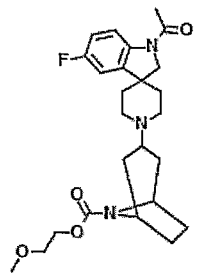
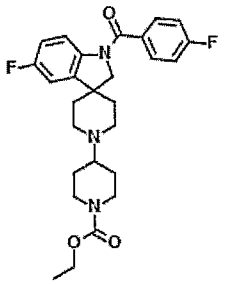
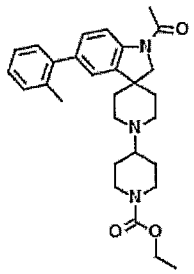
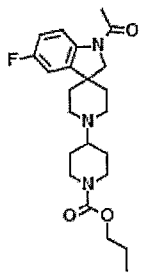
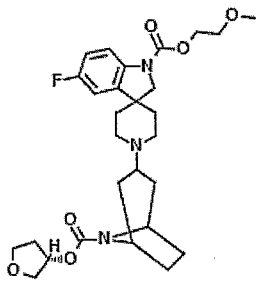
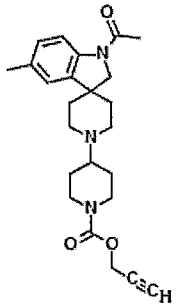
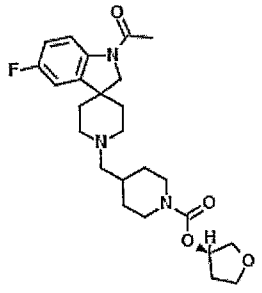
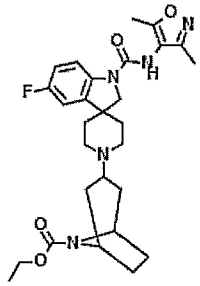
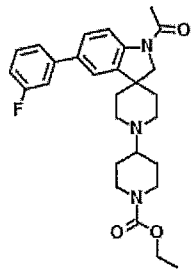
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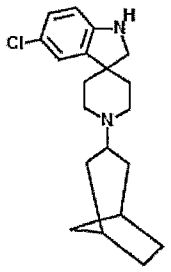
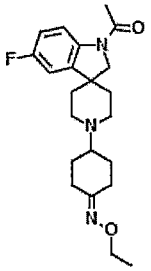
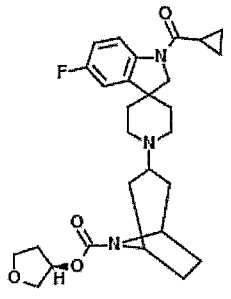
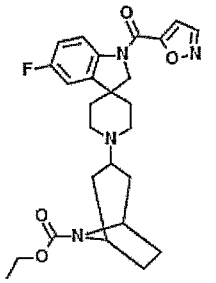
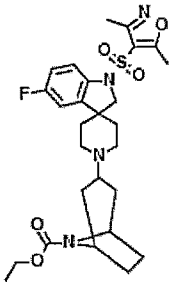
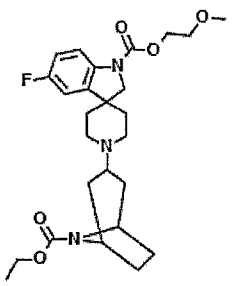
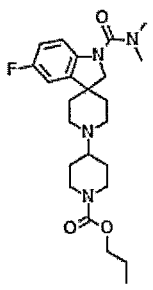
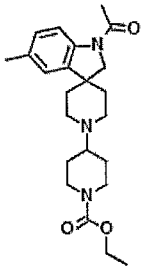
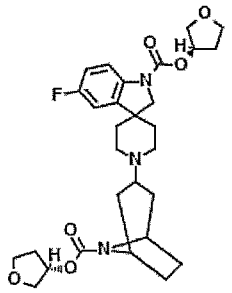
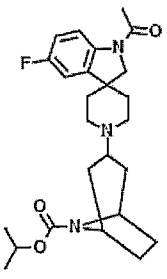
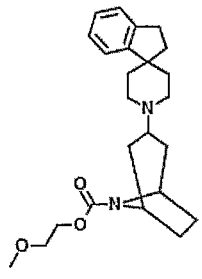
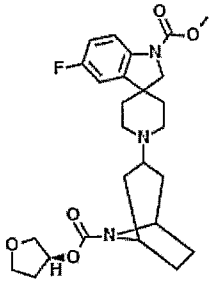
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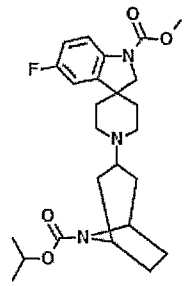
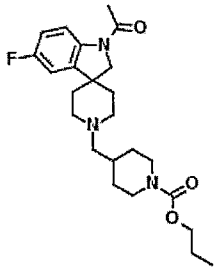
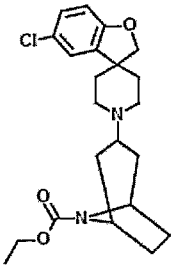
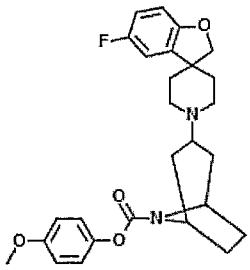
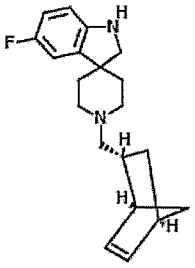
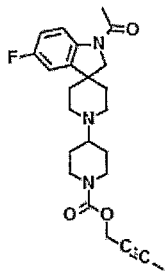
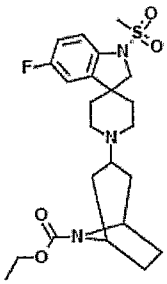
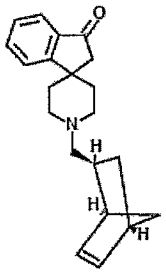
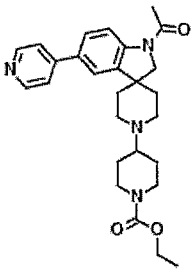
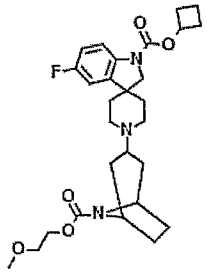
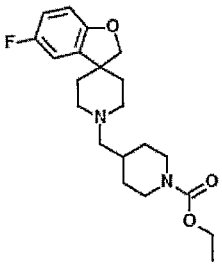
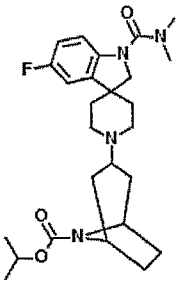
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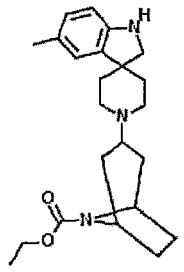
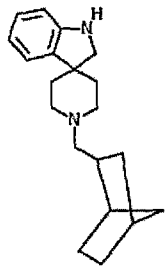
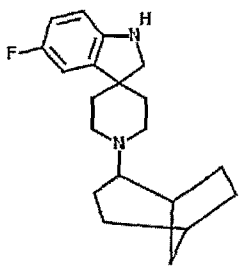
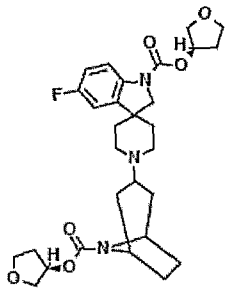
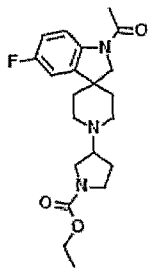
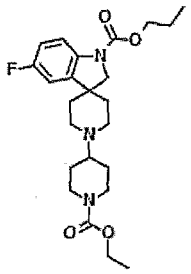
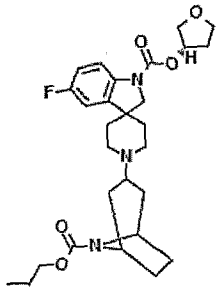
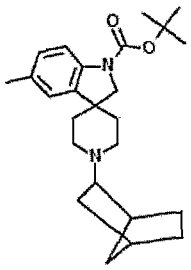
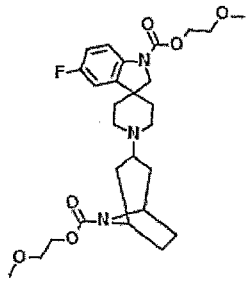
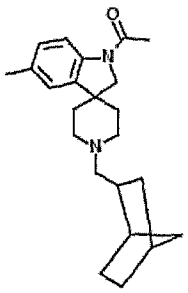
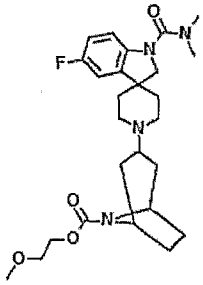
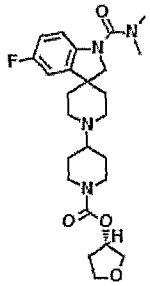
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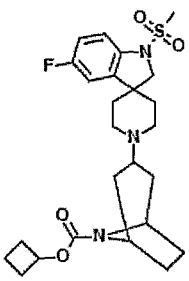
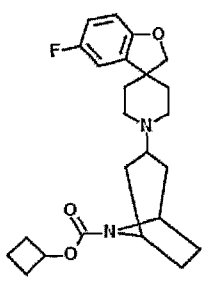
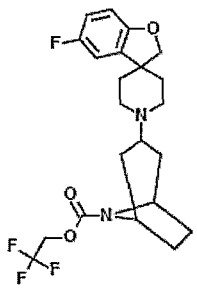
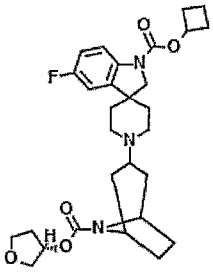
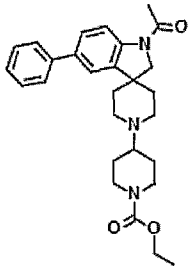
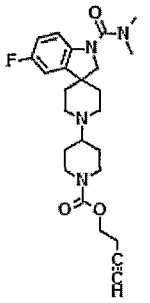
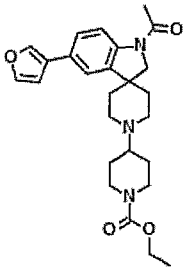
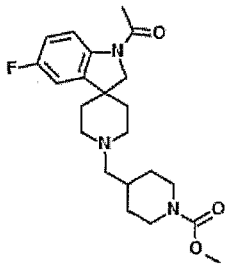
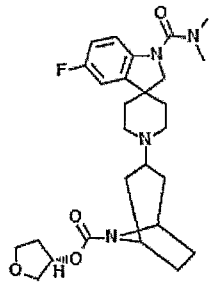
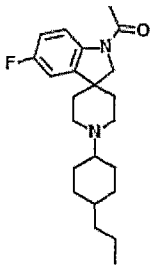
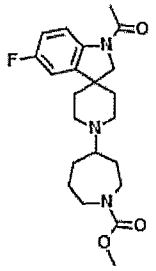
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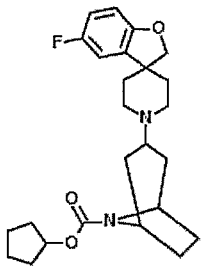
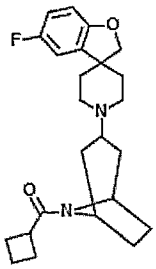
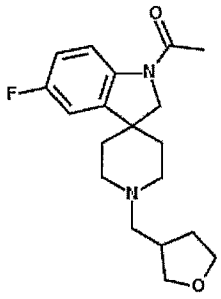
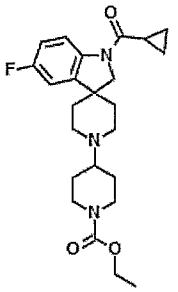
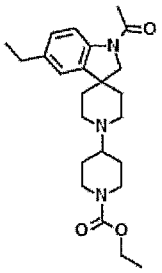
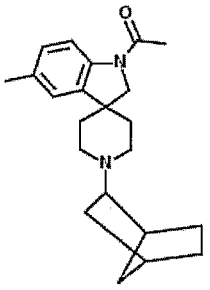
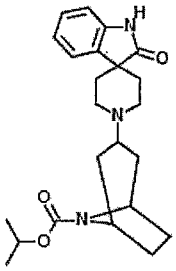
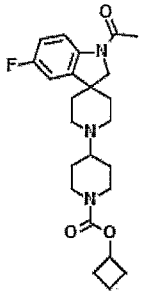
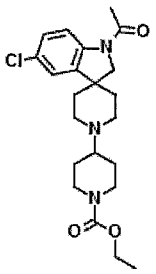
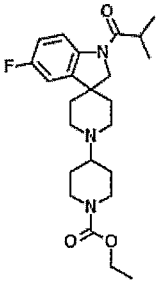
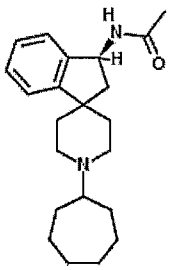
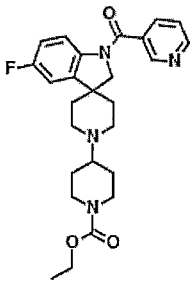
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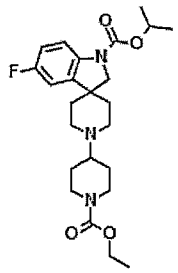
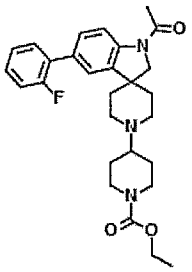
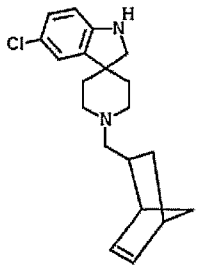
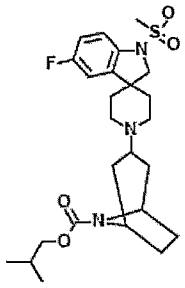
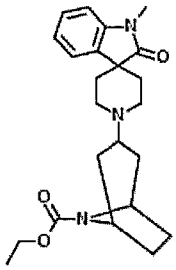
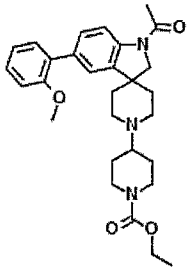
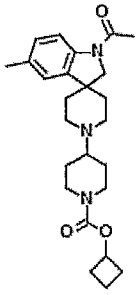
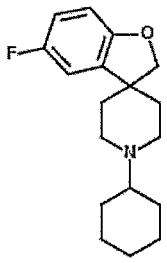
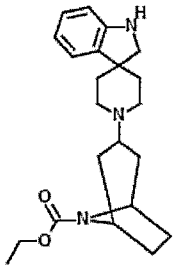
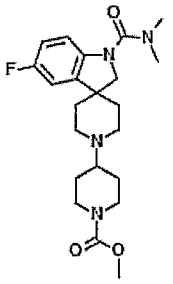
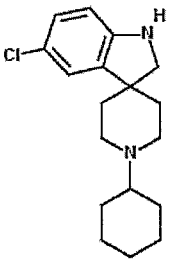
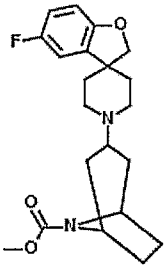
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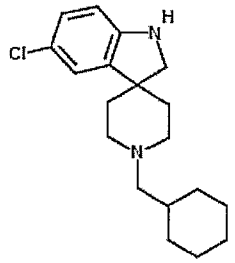
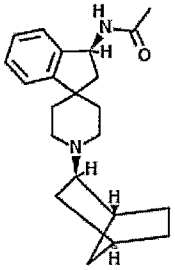
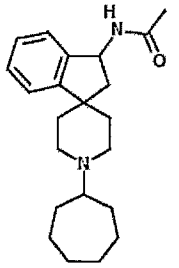
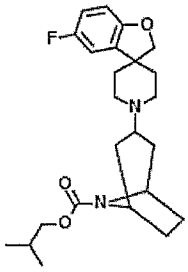
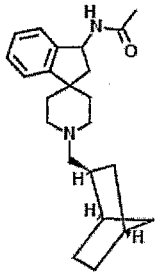
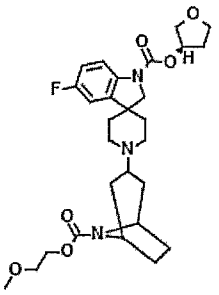
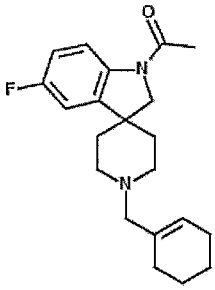
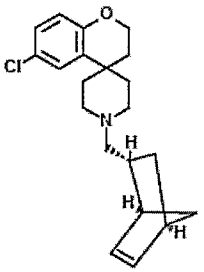
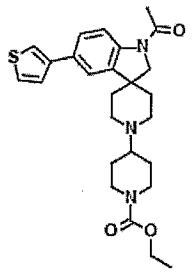
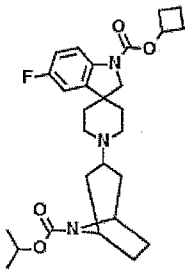
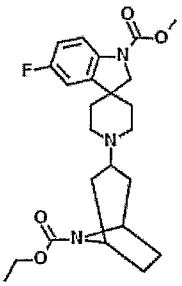
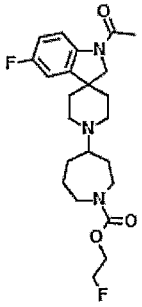
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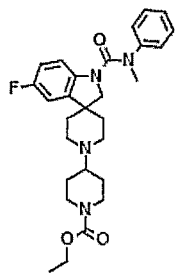
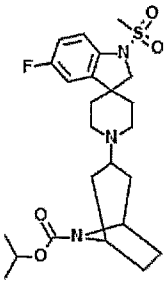
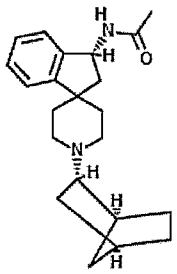
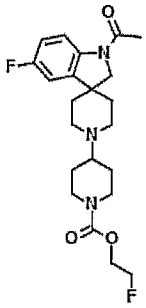
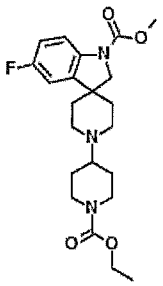
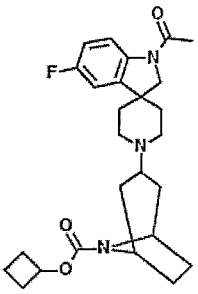
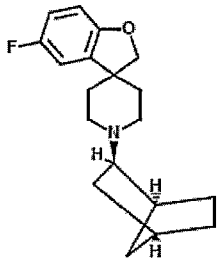
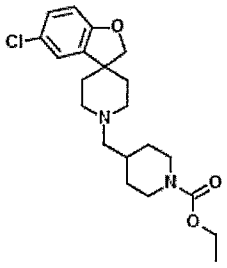
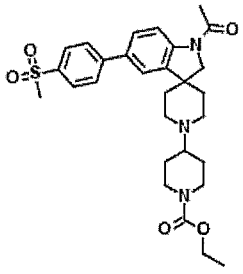
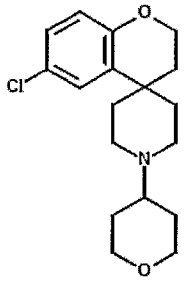
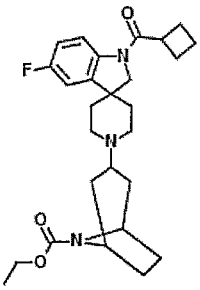
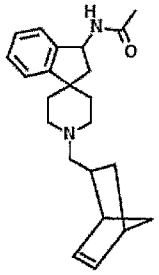
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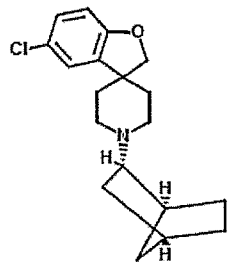
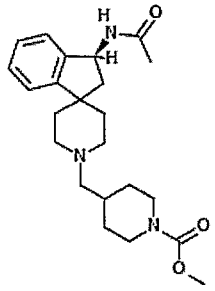
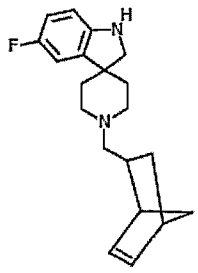
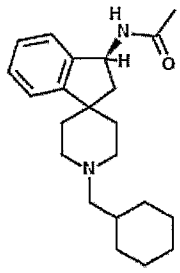
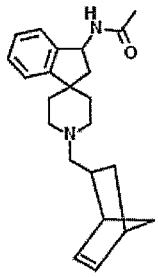
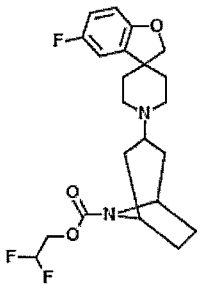
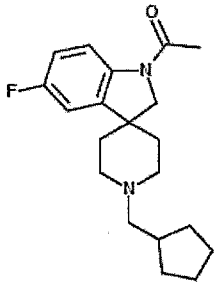
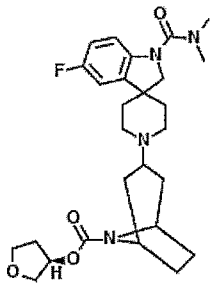
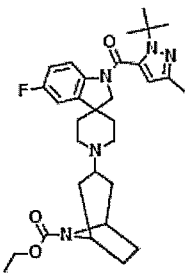
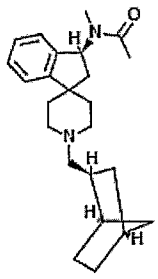
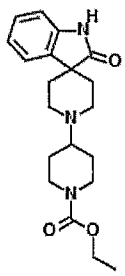
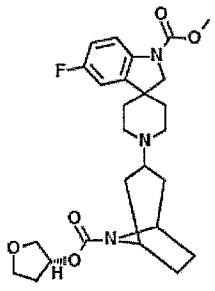
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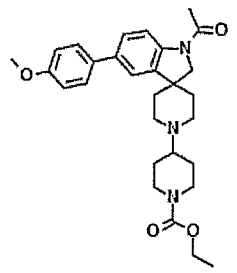
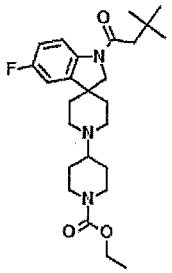
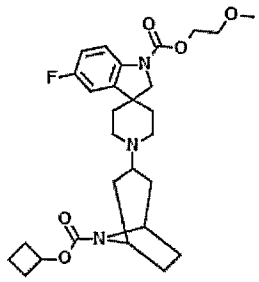
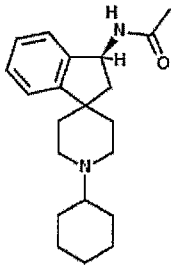
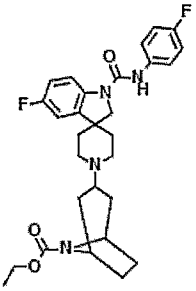
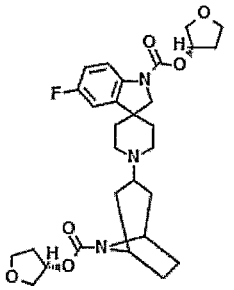
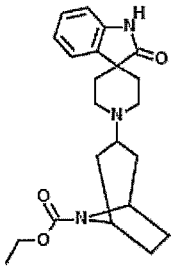
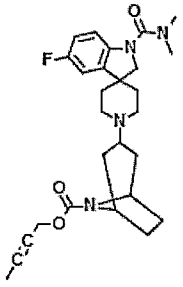
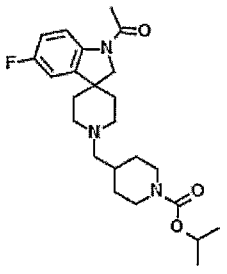
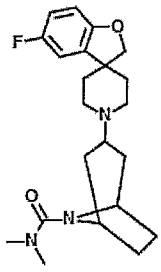
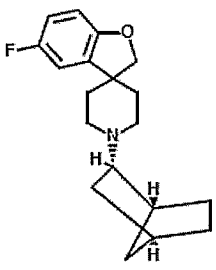
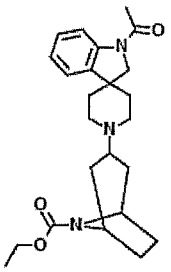
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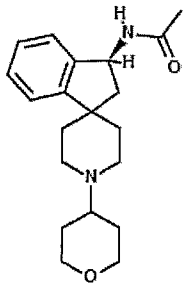
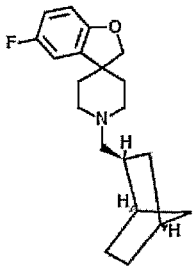
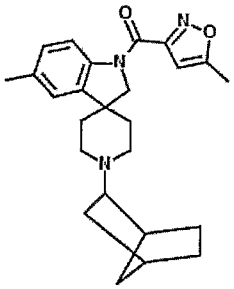
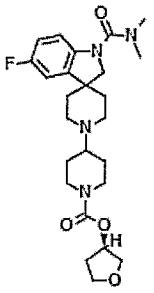
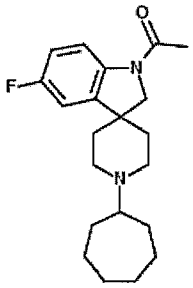
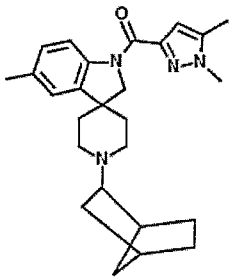
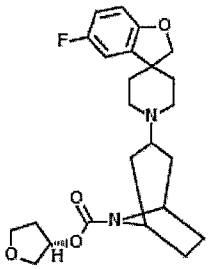
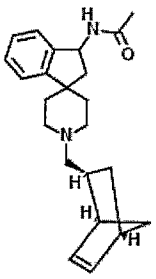
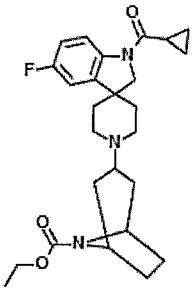
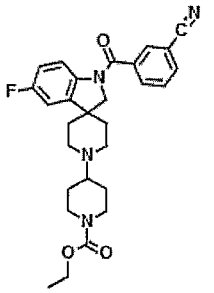
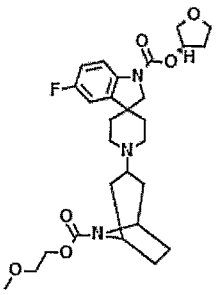
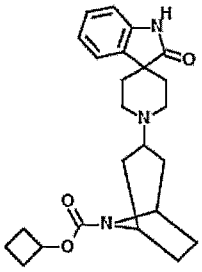
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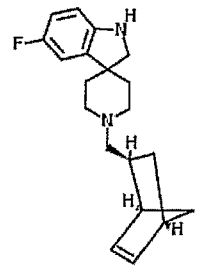
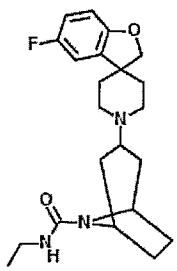
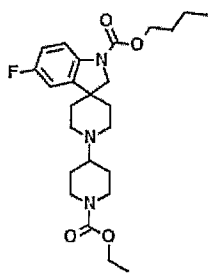
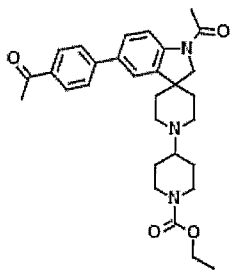
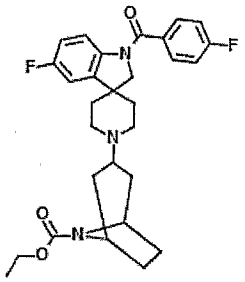
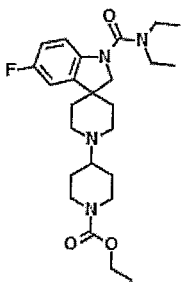
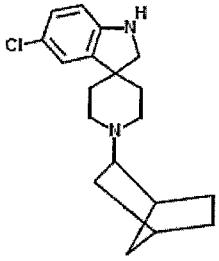
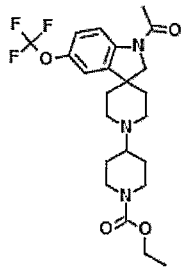
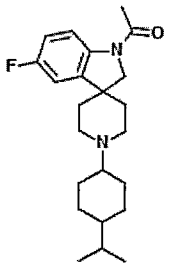
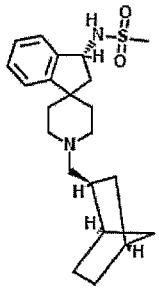
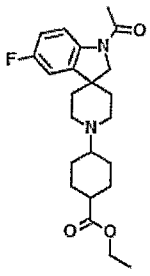
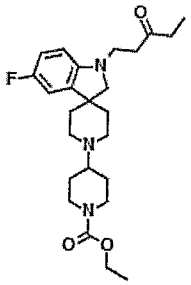
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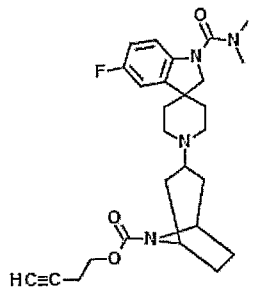
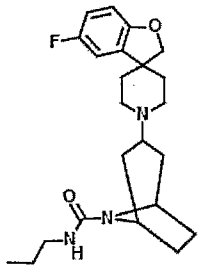
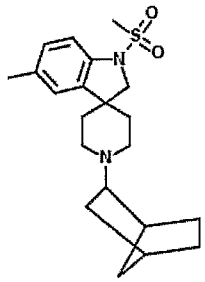
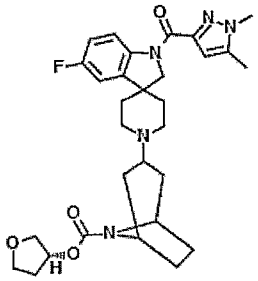
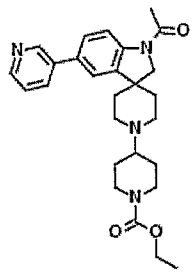
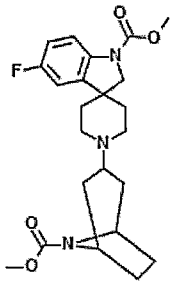
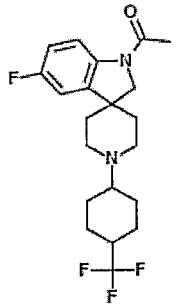
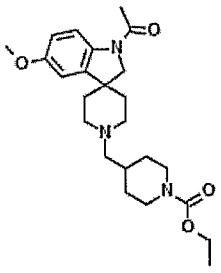
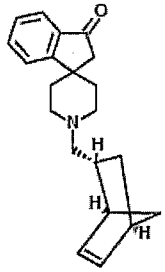
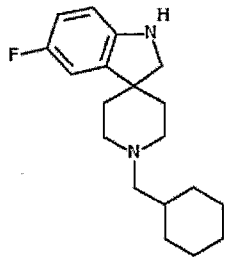
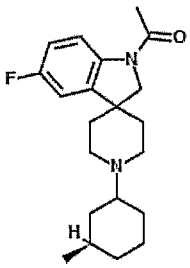
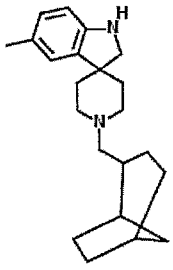
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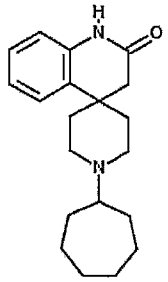
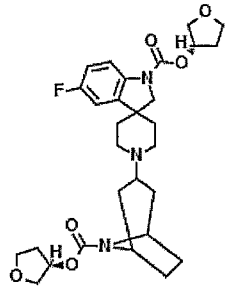
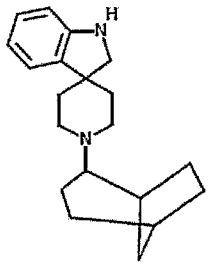
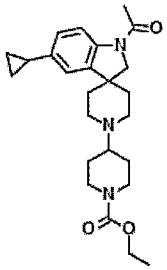
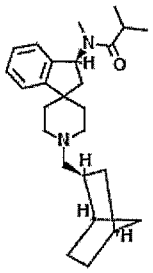
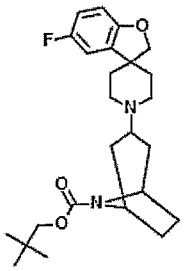
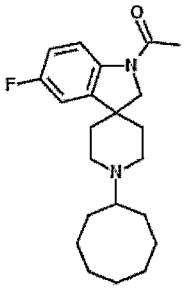
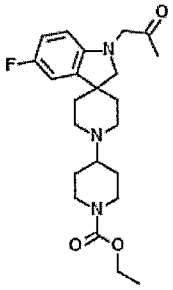
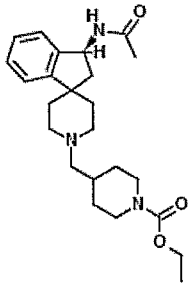
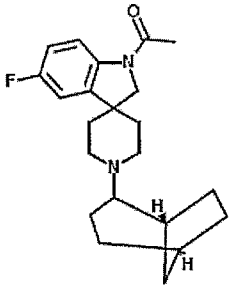
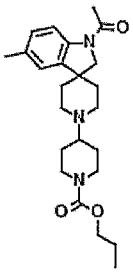
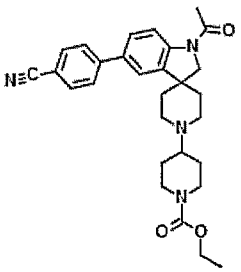
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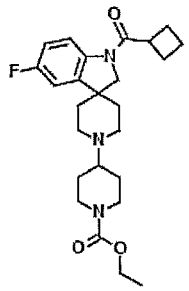
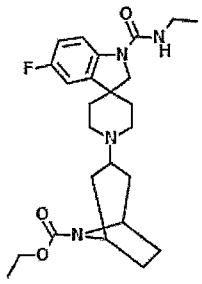
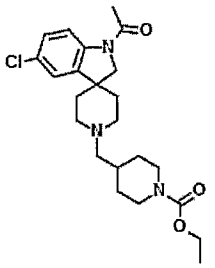
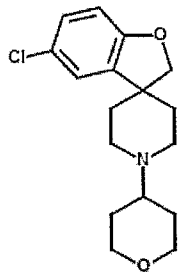
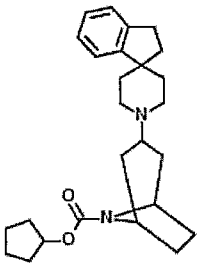
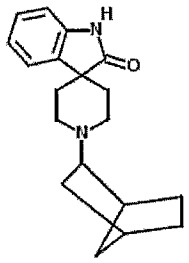
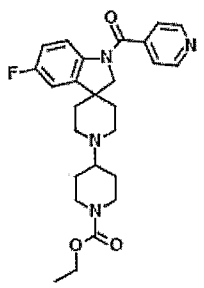
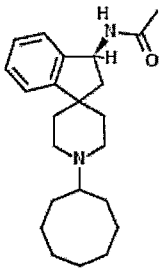
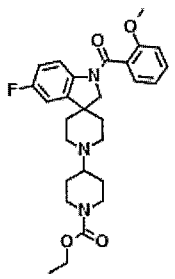
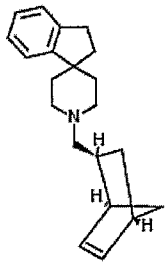
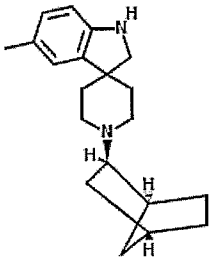
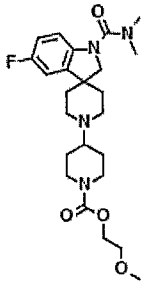
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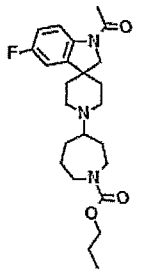
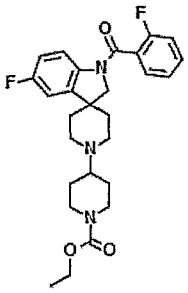
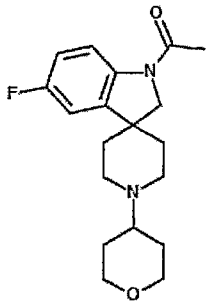
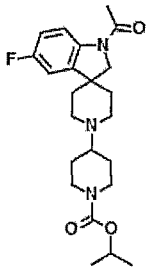
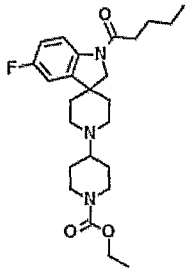
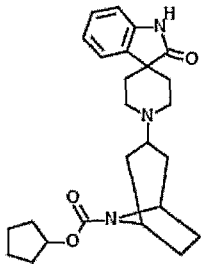
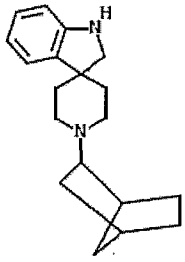
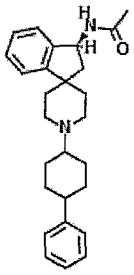
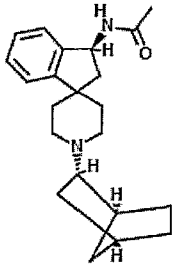
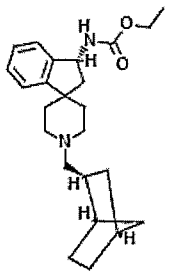
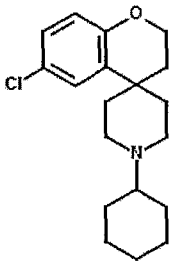
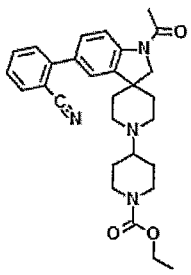
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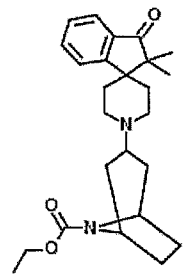
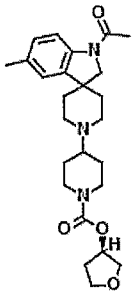
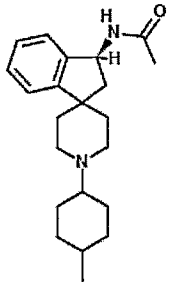
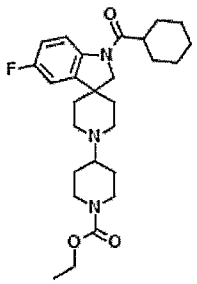
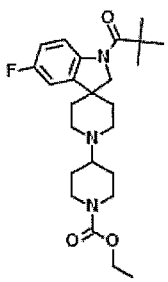
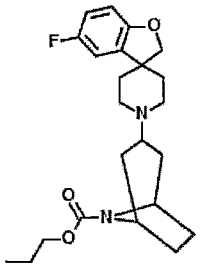
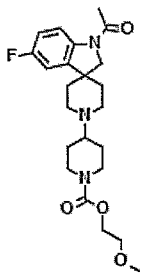
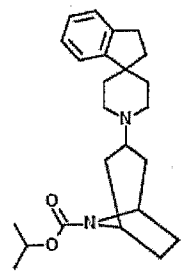
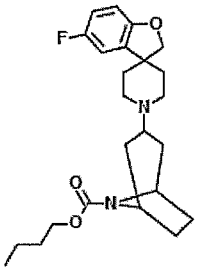
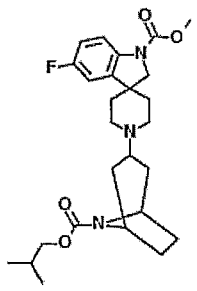
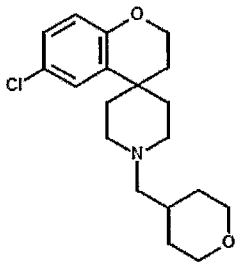
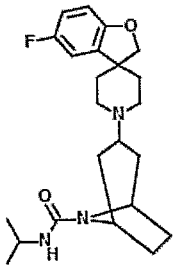
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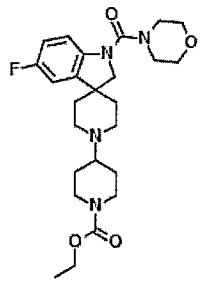
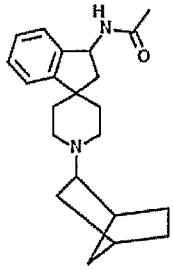
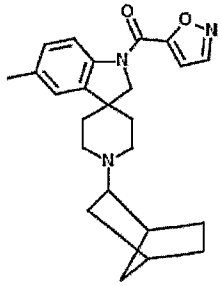
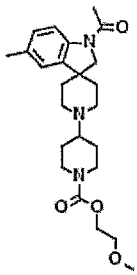
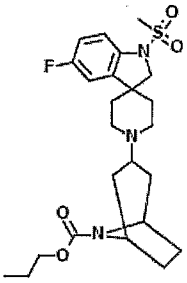
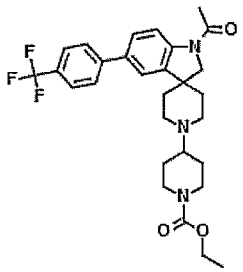
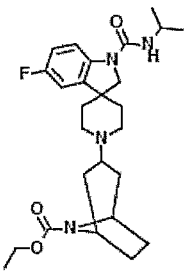
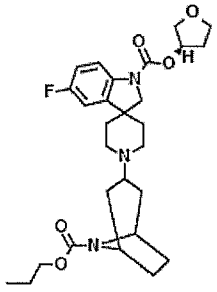
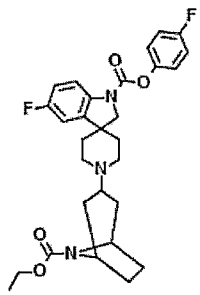
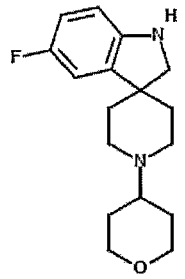
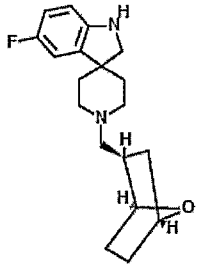
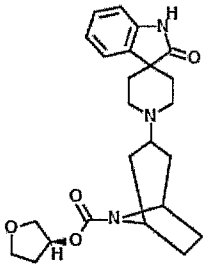
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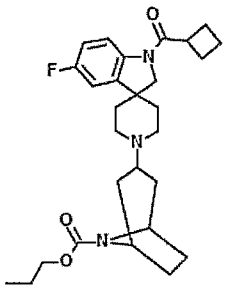
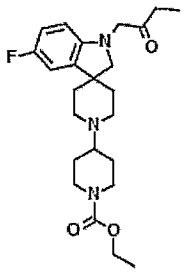
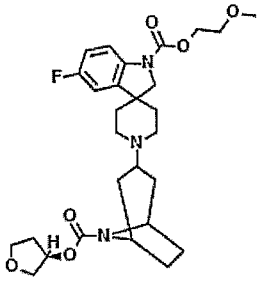
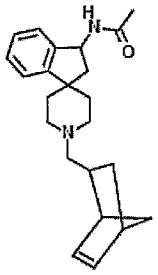
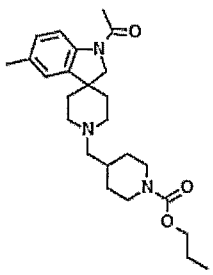
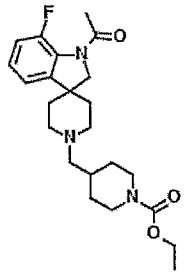
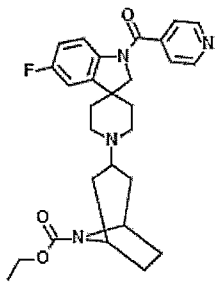
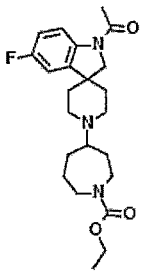
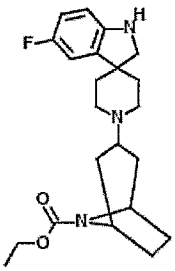
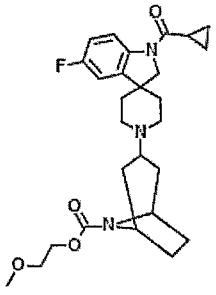
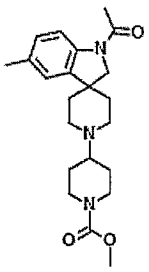
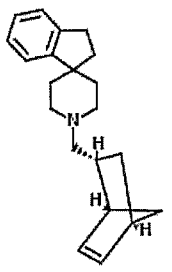
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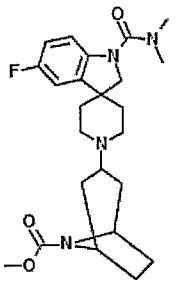
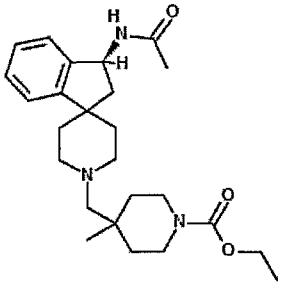
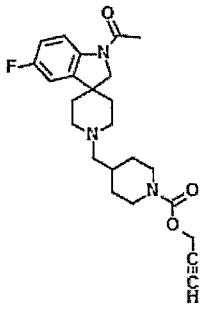
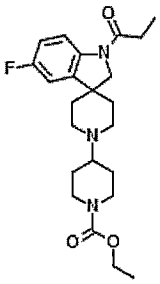
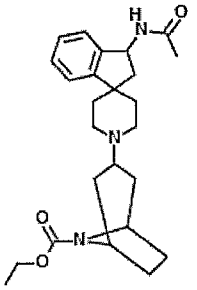
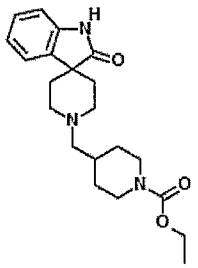
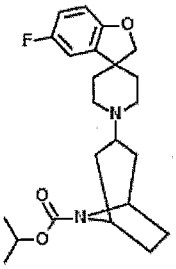
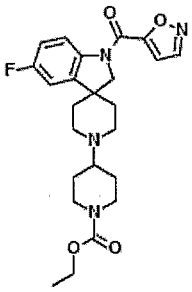
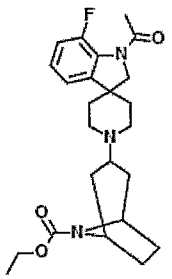
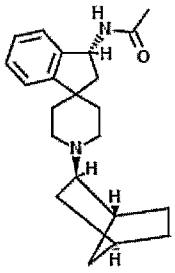
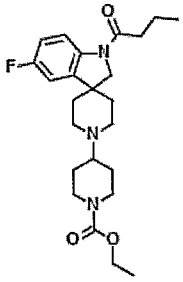
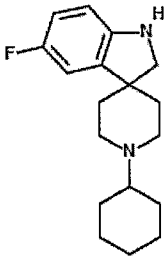
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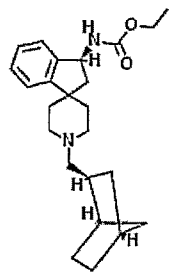
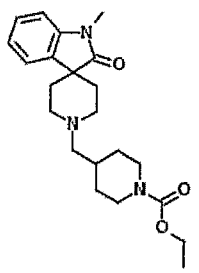
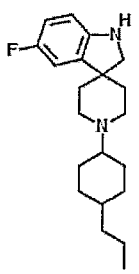
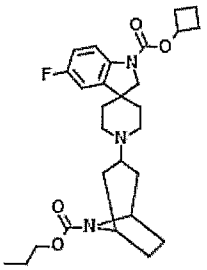
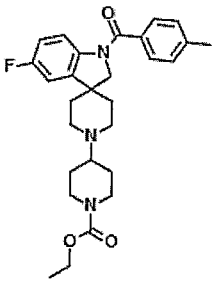
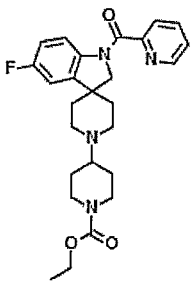
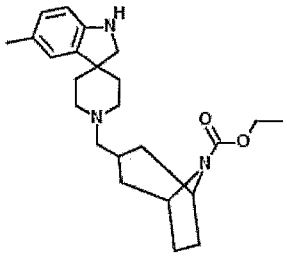
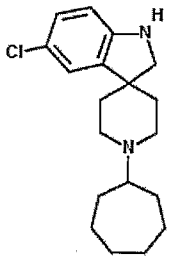
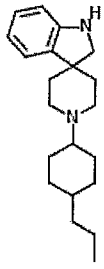
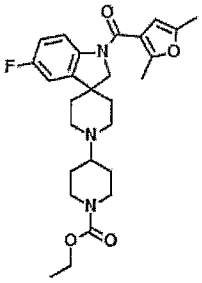
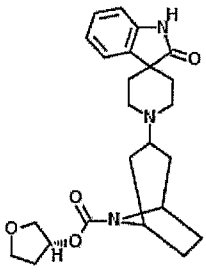
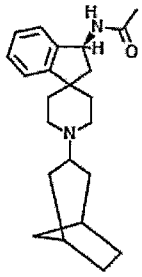
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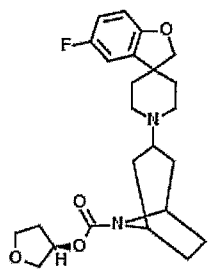
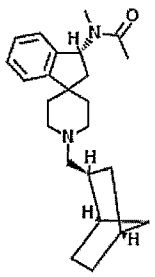
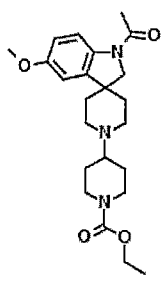
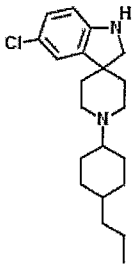
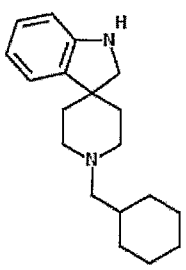
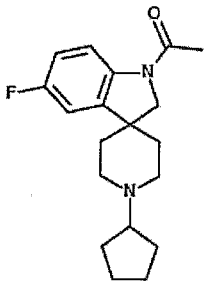
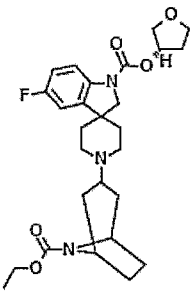
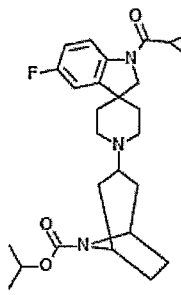
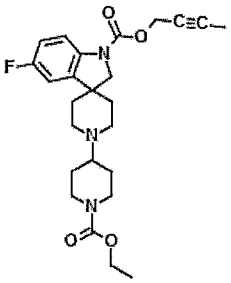
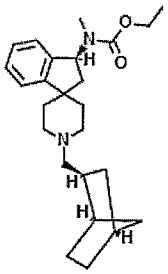
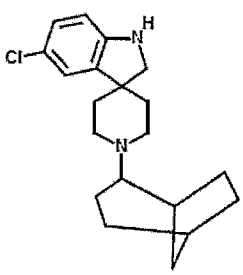
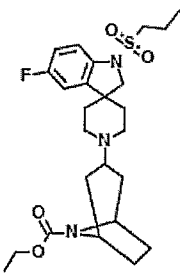
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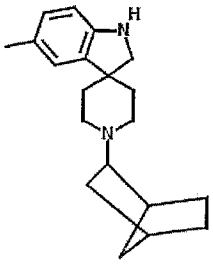
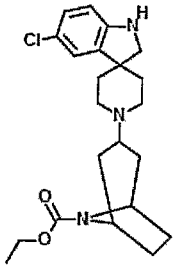
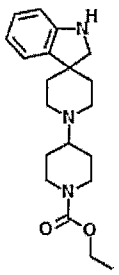
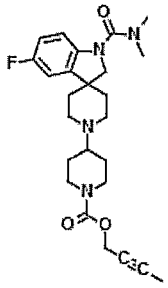
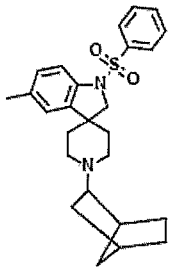
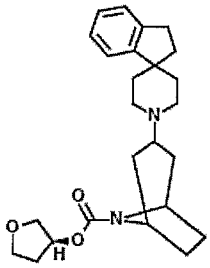
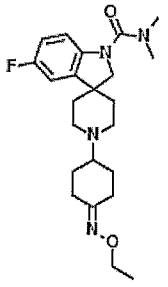
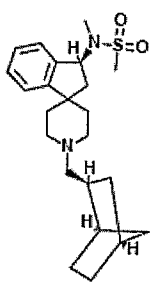
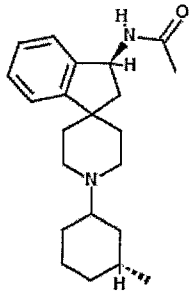
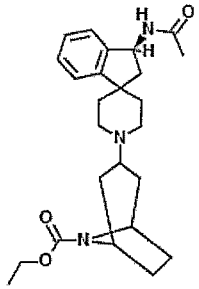
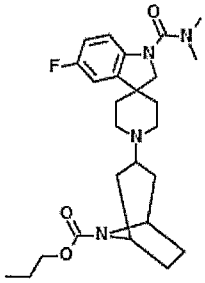
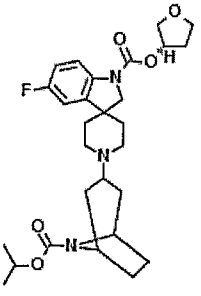
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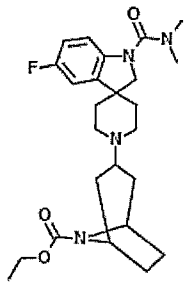
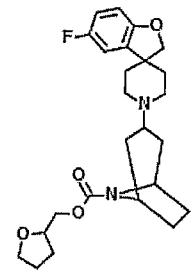
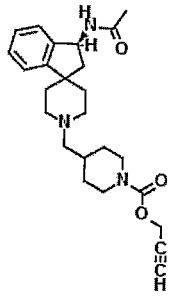
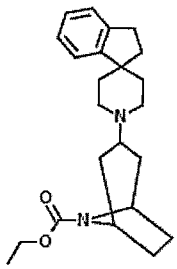
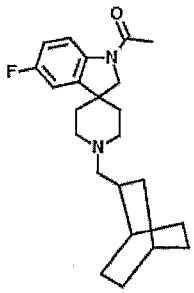
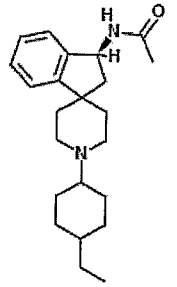
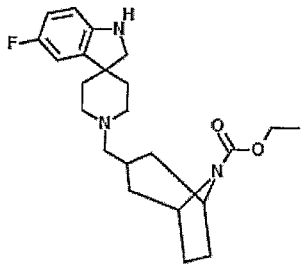
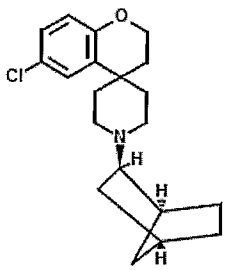
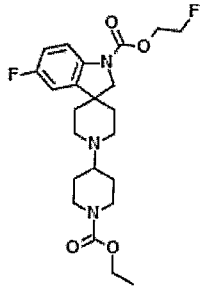
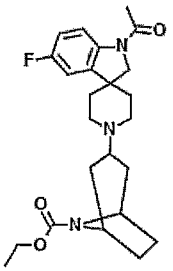
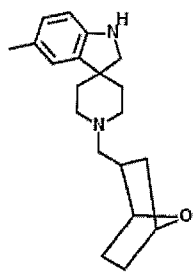
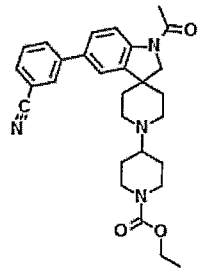
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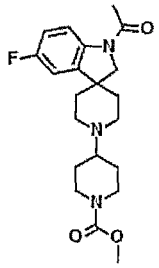
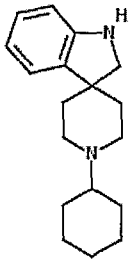
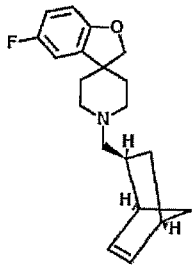
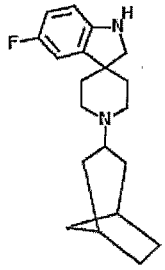
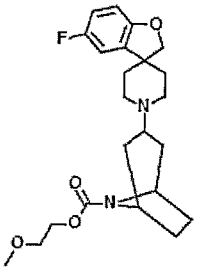
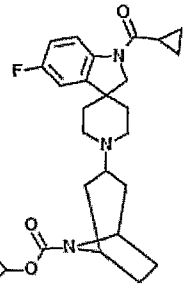
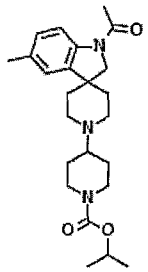
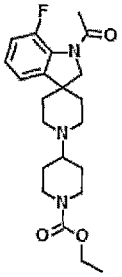
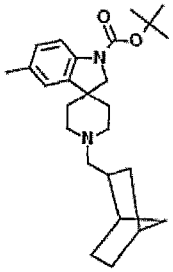
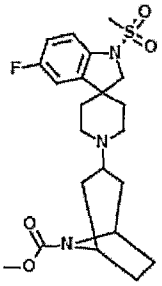
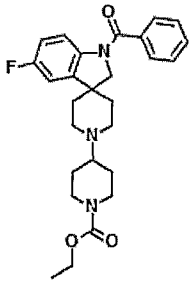
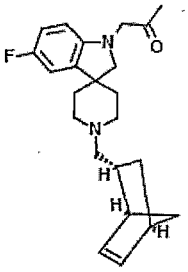
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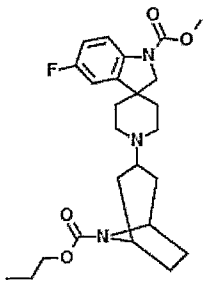
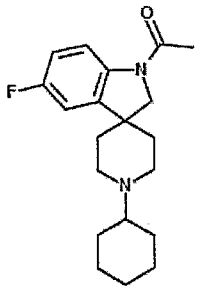
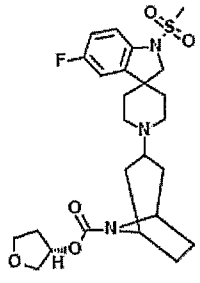
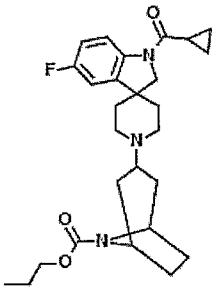
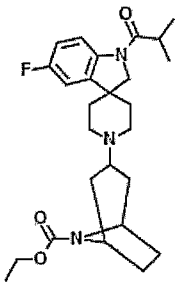
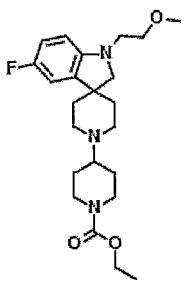
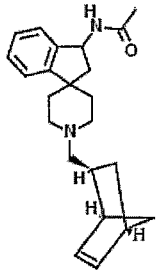
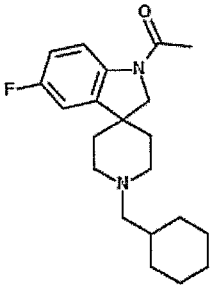
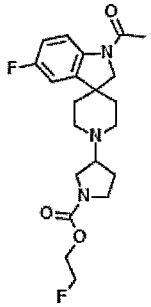
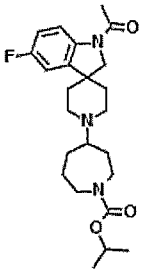
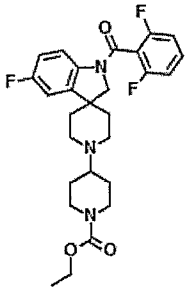
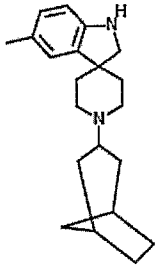
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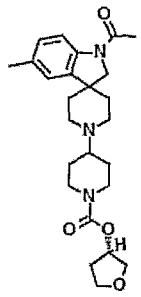
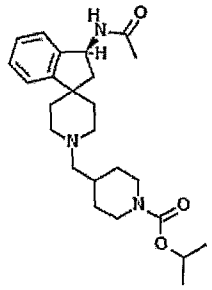
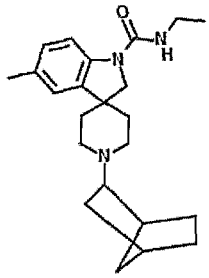
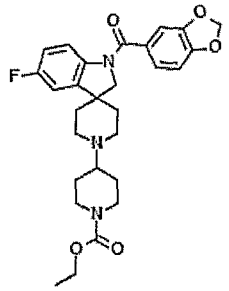
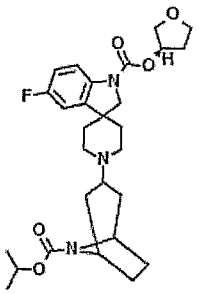
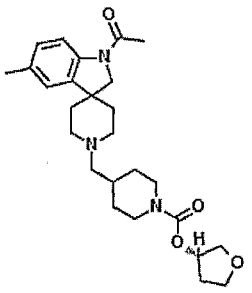
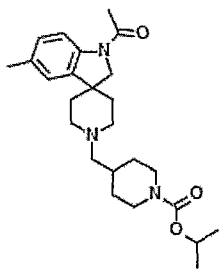
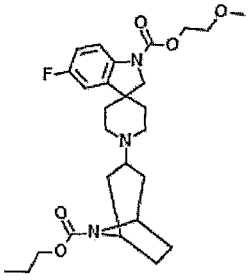
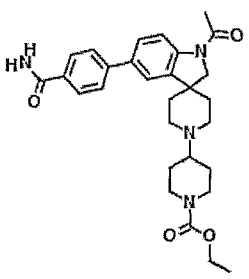
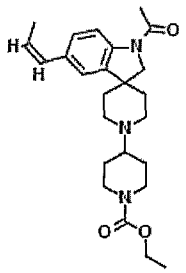
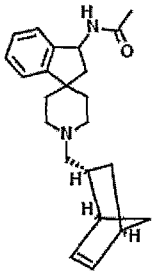
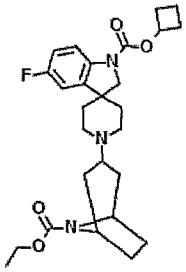
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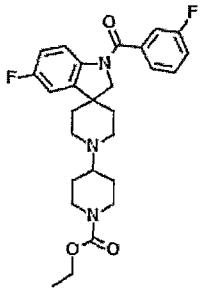
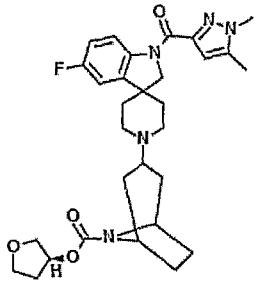
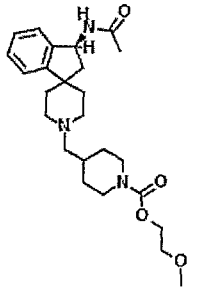
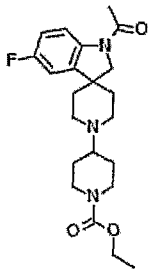
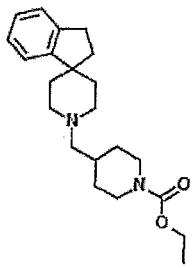
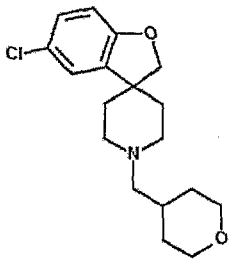
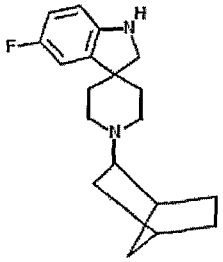
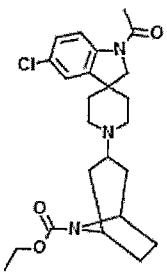
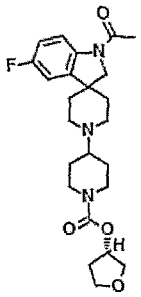
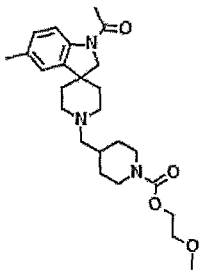
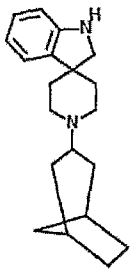
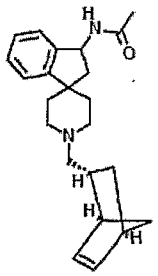
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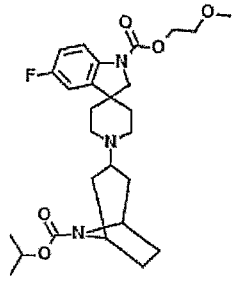
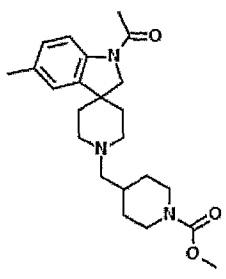
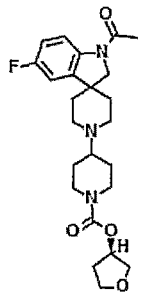
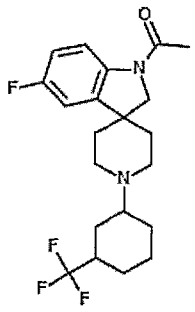
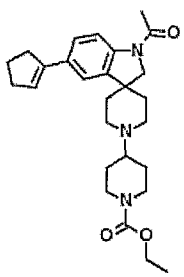
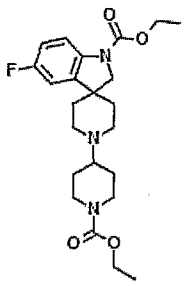
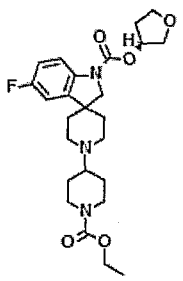
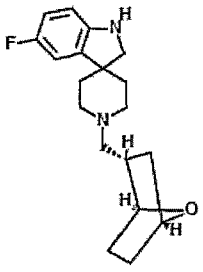
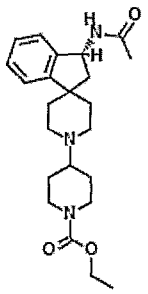
362	363	364
		
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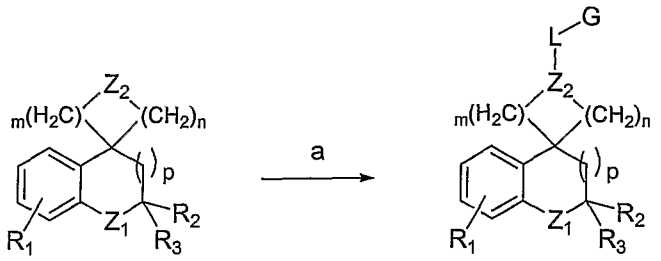
422	423	424
		
425	426	427
		
428	429	430
		

IV. SYNTHETIC SCHEMES

[0154] The compounds of formulae (I and II) may be readily synthesized from commercially available starting materials using methods known in the art. Exemplary synthetic routes to produce compounds of formulae (I and II), are provided below in Preparations A-F and Schemes 1-10. For simplicity of illustration, schemes 1-10 depict only a single R_1 substituent on the fused phenyl ring of formulae I and II, the compounds of this invention may include 1 to 4 R_1 substituents on the fused phenyl ring.

[0155] Scheme 1 below depicts general conditions for the synthesis of compounds of formula (I).

Scheme 1:



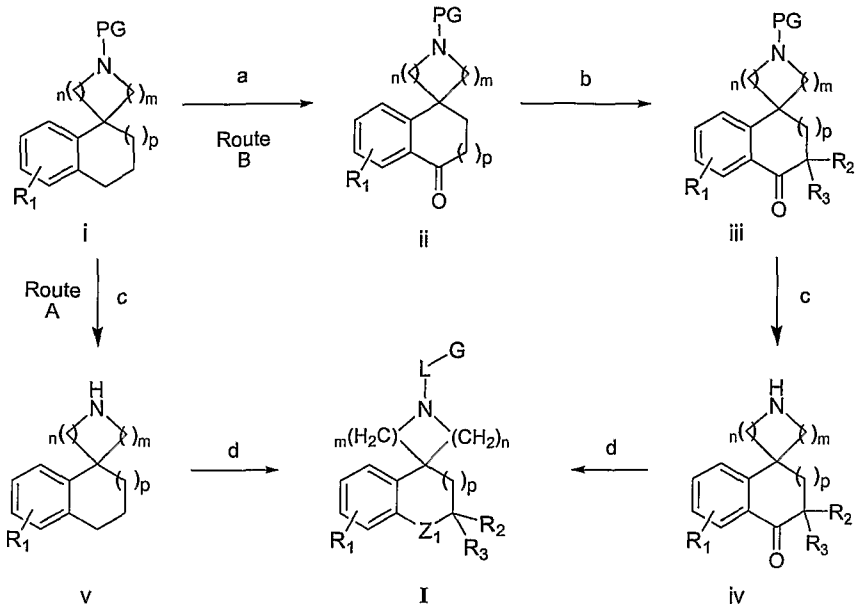
A (I)

[0156] The reaction of amine (A) with an appropriate aldehyde or ketone under reductive amination conditions (step a), typically using $NaBH(OAc)_3$ in DCE/AcOH/TEA at room temperature, may be used to provide the desired compounds of formula I. For less reactive ketones, more forcing conditions may be used. For example, the treatment of the amine (A) and the ketone in a neat solution of $Ti(OiPr)_4$, followed by treatment with $NaBH_4$ in MeOH, may be used to provide the desired compounds of formula I. See Abdel-Magid, A.F. et al., "Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures," *J. Org. Chem.*, 61, pp. 3849-3862 (1996) and the references sited therein.

[0157] Alternatively, the of spiroamine of type A may be alkylated with an alkyl halide in the presence of an appropriate base to provide the desired compounds of formula I. Typically, the amine (A) is reacted with an alkyl iodide, bromide, or chloride in the presence of an appropriate base to yield compounds of formula I. Bases may be organic such as triethylamine, or inorganic such as Na_2CO_3 or Cs_2CO_3. Typical reaction solvents include but are not limited to DMF, acetone, and acetonitrile.

[0158] Scheme 2 illustrates alternative conditions for the synthesis of compounds of formula I in which Z_1 is $-C(H)_2-$ and R_2 and R_3 are hydrogen (Synthetic route A), or in which Z_1 is $-C(O)-$ (Synthetic route B).

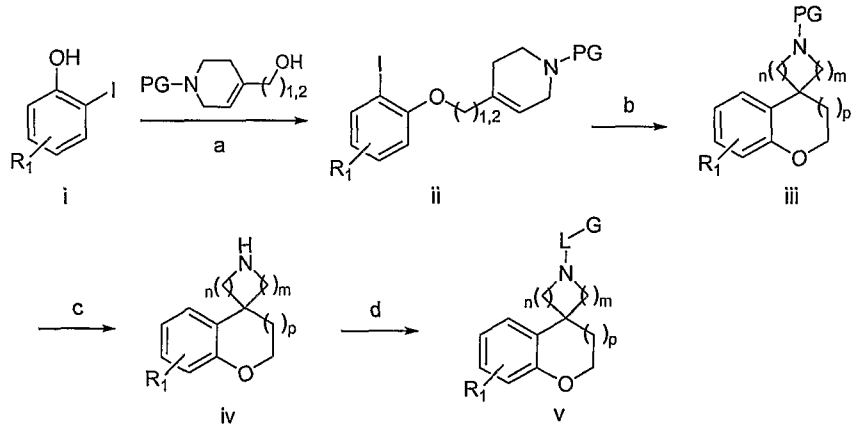
Scheme 2:



[0159] Compounds of type i in Scheme 2 may be prepared using procedures as described in Evans, B.E, et al., *J. Med. Chem.* **1992**, *35*, 3919 and M.S. Chambers *J. Med. Chem.* **1992**, *35*, 2033. Intermediate compounds may be produced from compound of type i using the following conditions: (a) $KMnO_4$ oxidation, TBAB, aqueous KOH (b) NaH, X-R_2 and/or X-R_3, THF (c) Ammonium formate, MeOH, Pd/C, room temperature or heat; or Pd/C, MeOH, H_2; or if PG = Boc, then TFA, CH_2Cl_2, -10°C; (d) $NaBH(OAc)_3$, DCE, AcOH, TEA, appropriate ketone or aldehyde; or i. neat $Ti(OiPr)_4$, appropriate ketone; ii. $NaBH_4$, MeOH; or the appropriate alkyl halide, Cs_2CO_3, acetonitrile, heat.

[0160] Scheme 3 illustrates alternative conditions for the synthesis of compounds of formula I in which Z_1 is -O- and R_2 and R_3 are hydrogen.

Scheme 3:

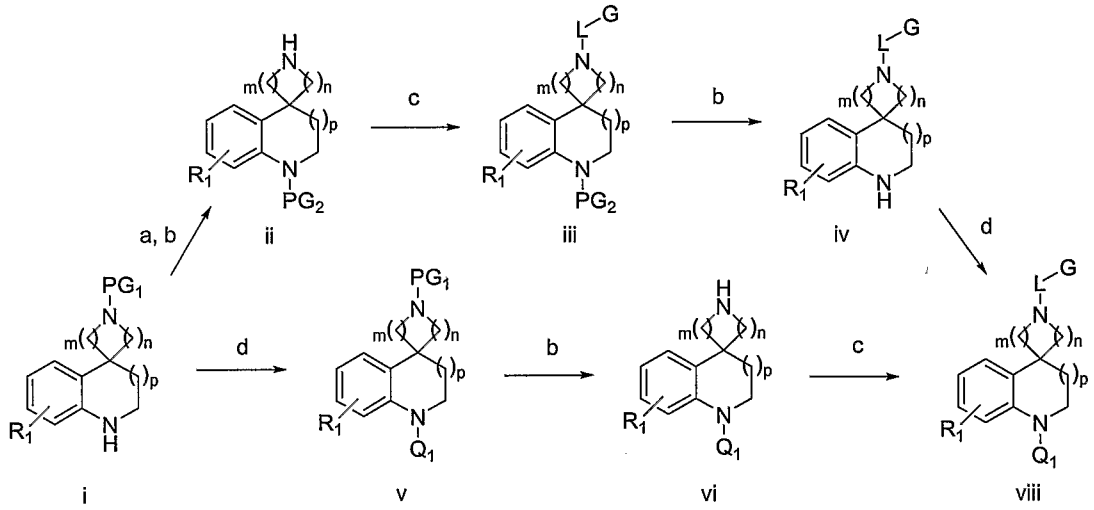


[0161] Amines of type iv in Scheme 3 were prepared using procedures analogous to those found in the following references: WO 96/11934 "Tricyclic spiro compounds process for their preparation" and US006013652A "Spiro-substituted azacyclics as neurokinin antagonists".

Conditions: (a) Ph_3P/DEAD (b) Bu_3SnH, AIBN (c) Ammonium formate, MeOH, Pd/C, room temperature or heat; or Pd/C, MeOH, H_2; or if PG = Boc, then TFA, CH_2Cl_2, -10°C; (d) $NaBH(OAc)_3$, DCE, AcOH, TEA, appropriate ketone or aldehyde; or i. neat $Ti(OiPr)_4$, appropriate ketone; ii. $NaBH_4$, MeOH; or the appropriate alkyl halide, Cs_2CO_3, acetonitrile, heat.

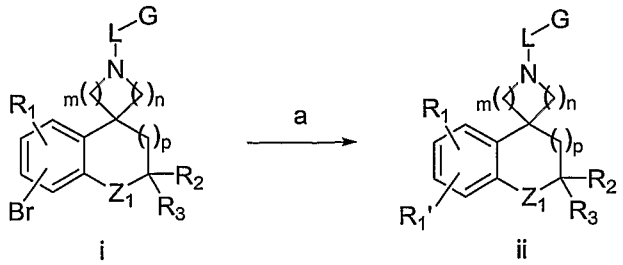
[0162] Scheme 4 illustrates alternative conditions for the synthesis of compounds of formula I in which Z_1 is -N(Q1)- and R_2 and R_3 are hydrogen.

Scheme 4:



[0163] Amines of type i in Scheme 4 may be prepared from methods known in the art and by using procedures analogous to those found in the following references: WO 03/106457 "Spiroindolinepiperidine Derivatives"; Maligres, P.E., et al., *Tetrahedron*, **1997**, *53*, 10983-10992; Cheng, Y. and Chapman, K.T., *Tet. Lett.* **1997**, *38*, 1497-1500; US006013652A "Spiro-substituted azacyclics as neurokinin antagonists". Conditions: (a) amine protection orthoganol to PG_1; (b) amine deprotection of PG_1 (e.g. PG_1 = Boc: TFA, CH_2Cl_2, -10°C); (c) $NaBH(OAc)_3$, DCE, AcOH, TEA, appropriate ketone or aldehyde; or i. neat $Ti(OiPr)_4$, appropriate ketone; ii. $NaBH_4$, MeOH; or the appropriate alkyl halide, Cs_2CO_3, acetonitrile, heat; (d) Q_2X (Q_2 may be, for example, H and aliphatic, X is halogen), K_2CO_3, DMF/THF, RT to 60 °C; or electrophile (e.g. RSO_2Cl, RCOCl, ROC(=O)Cl, where R is H or Q_2, TEA, CH_3CN.

Scheme 5:

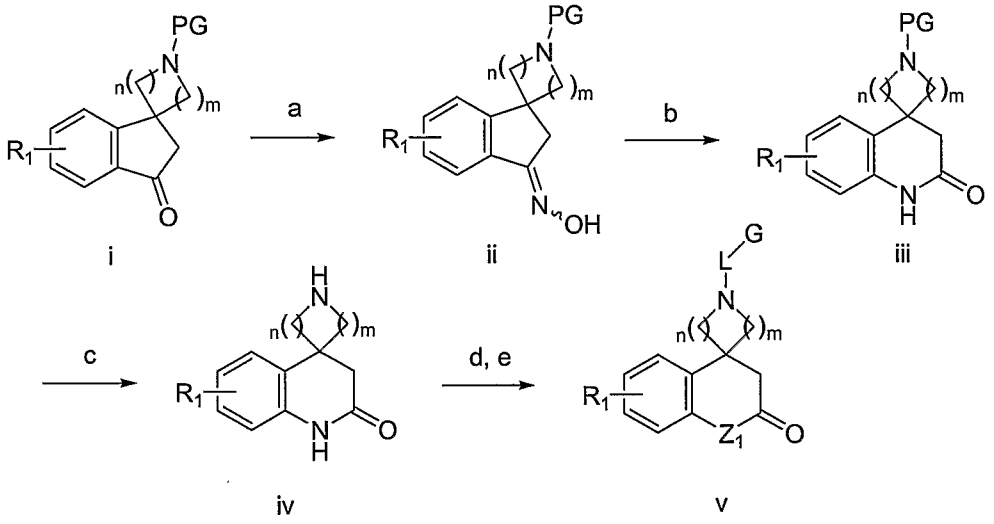


i ii

[0164] Reaction of i with intermediate under palladium cross coupling conditions (step a) Pd(dppf)Cl2 or $(Ph_3P)_4Pd$, 2M K_2CO_3, and acetonitrile under microwave irradiation at 150^{0}C for 10-20 minutes yields compound ii. Unsaturated compounds of type ii may be further elaborated (e.g. reduction; oxidation) to provide additional compounds of formula (I).

[0165] Scheme 6 illustrates alternative conditions for the synthesis of compounds of formula I in which Z_1 is -N(Q_1)- or -N(Q_2)-, R_2 and R_3 together form oxo, and p=1.

Scheme 6:

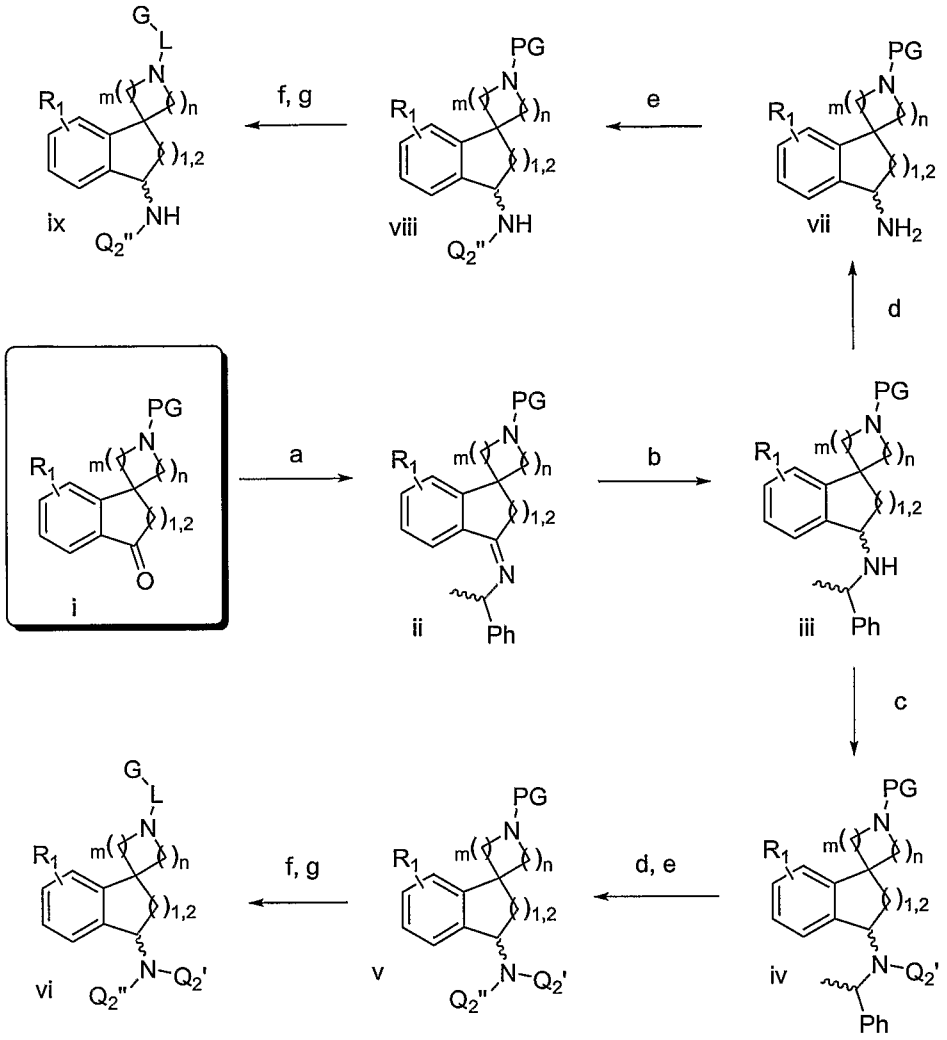


i ii iii iv v

[0166] Compound i may be produced by methods disclosed above and by those known in the art. Intermediate compounds may be produced from compounds of type i using the following conditions: (a) $NH_2OH.HCl$; (b) 2,4,6-trichloro-1,3,5-triazine; (c) PG = Bn or Cbz; Ammonium formate, MeOH, Pd/C, room temperature; or Pd/C, MeOH, H_2; (d) $NaBH(OAc)_3$, DCE, AcOH, TEA, appropriate ketone or aldehyde; or i. neat $Ti(OiPr)_4$, appropriate ketone; ii. $NaBH_4$, MeOH; or the appropriate alkyl halide, Cs_2CO_3, acetonitrile, heat; (e) optional alkylation, NaH, THF, appropriate alkyl halide.

[0167] Scheme 7 illustrates alternative conditions for the synthesis of compounds of formula I in which Z_1 is -CH(Q_1)- and R_2 and R_3 are hydrogen.

Scheme 7:

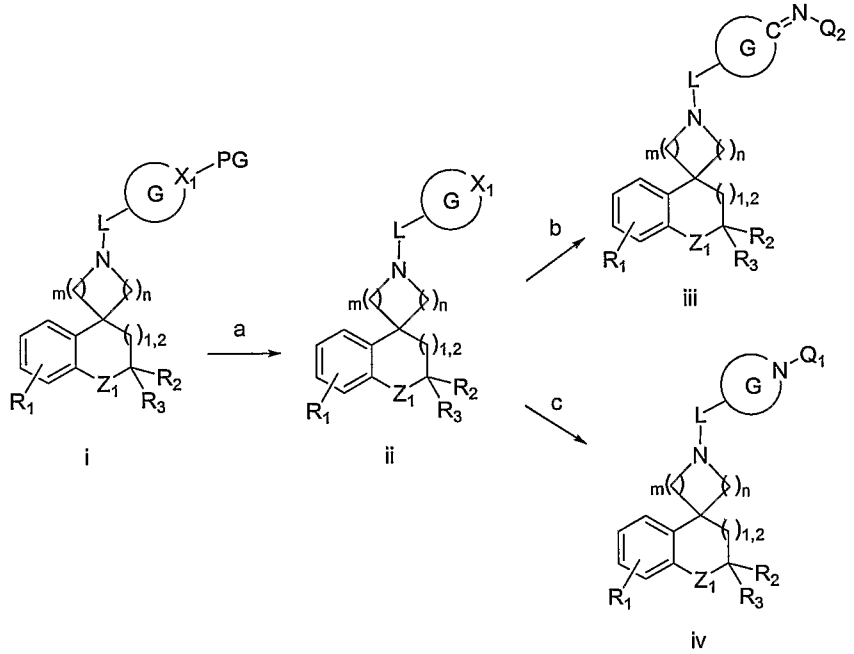


[0168] Compound i may be produced by methods disclosed above and by those known in the art. Compounds ii through ix may be produced from compound i using the following conditions: (a) $ZnCl_2$ or other Lewis acid, (R)- or (S)-1-phenylethanamine, $PhCH_3$ reflux, Dean-Stark; (b) $NaBH_4$, MeOH, -30 °C; (c) Q_2'X (Q_2' may be, for example, H and aliphatic, X is halogen), K_2CO_3, DMF/THF, RT to 60 °C (d) Ammonium formate, MeOH, Pd/C, room temperature; or Pd/C, MeOH, H_2; (e) electrophile (e.g. RSO_2Cl, RCOCl, ROC(=O)Cl, where R is H or alkyl, and Q_2'' is RSO_2-, RC(O)-, ROC(O)-, TEA, CH_3CN; (f) PG = Boc: TFA, CH_2Cl_2, -10°C; (g) $NaBH(OAc)_3$, DCE, AcOH, TEA, appropriate ketone or aldehyde; or i. neat $Ti(OiPr)_4$, appropriate ketone; ii. $NaBH_4$, MeOH; or the appropriate alkyl halide, Cs_2CO_3, acetonitrile, heat.

[0169] Scheme 8 illustrates alternative conditions as example for the synthesis of compounds of formula I in which Ring G contains or is substituted with a protected functionality which may be

either be retained, deprotected and retained, or deprotected and further elaborated to produce additional compounds of formula I.

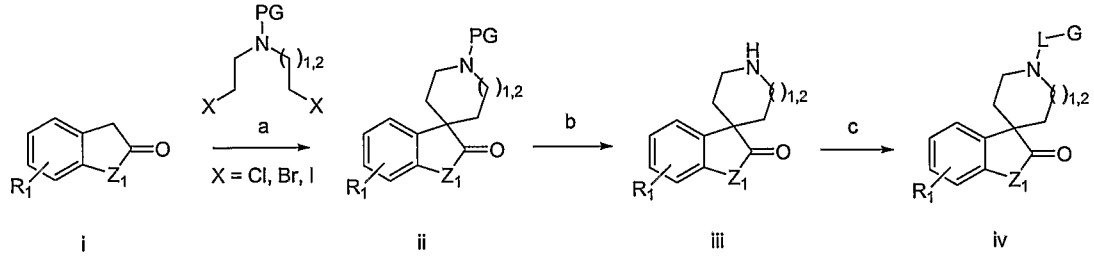
Scheme 8:



[0170] Compound i may be produced by methods disclosed above and by those known in the art. Compounds ii through iv may be produced from compound i using the following conditions: (a) e.g. PG=ketal: AcOH/H_2O, heat; PG=Boc: TFA, CH_2Cl_2; (b) e.g. if ring G is substituted by oxo, the compound of formula I may be further elaborated to the oxime: NH_2-O-Q_2, pyridine; (c) e.g. if ring G contains or is substituted by –NH- or –N(Q_2)-, it may be elaborated with an appropriate electrophile to produce iv.

[0171] Scheme 9 illustrates alternative conditions for the synthesis of compounds of formula I in which Z_1 is -N(Q_1)- or -N(Q_2)-, and R_2 and R_3 are oxo, and p=0.

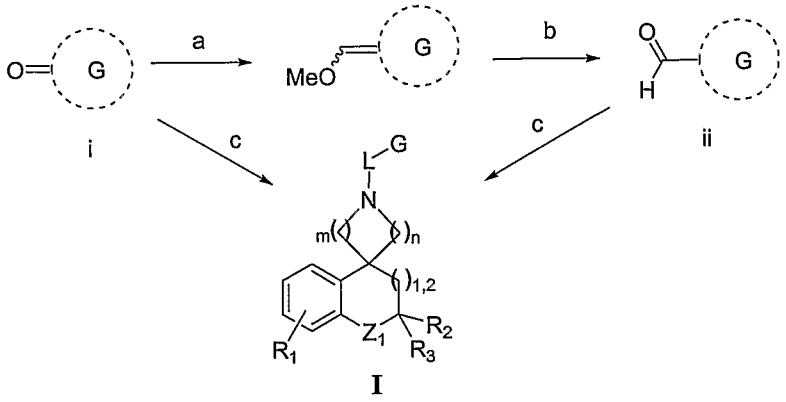
Scheme 9:



[0172] Compounds of type i may be purchased commercially or produced by methods known in the art. Conditions: (a) NaH/HMDS/THF; (b) e.g. PG=Bn: $Pd(OH)_2$; (c) $NaBH(OAc)_3$, DCE, AcOH, TEA, appropriate ketone or aldehyde; or i. neat $Ti(OiPr)_4$, appropriate ketone; ii. $NaBH_4$, MeOH; or the appropriate alkyl halide, Cs_2CO_3, acetonitrile, heat.

[0173] Scheme 10 outlines the general preparation of the appropriate aldehydes from the corresponding ketone.

Scheme 10:



I

[0174] Ketone electrophiles of type i may be purchased commercially or produced by methods disclosed above and by those known in the art. Aldehydes of type ii may be purchased commercially or produced from compounds of type i using the following conditions: (a) $Ph_3P^+CH_2OMeCl^-$, $NaN(SiMe_3)_2$; (b) aqueous HCl, CH_3CN. The following conditions may be used for the synthesis of compounds of formula I using ketones of type i and aldehydes of type ii: (c) Spiro-amine of type A (see Scheme 1), $NaBH(OAc)_3$, DCE, AcOH, TEA, appropriate ketone or aldehyde; or i. neat $Ti(OiPr)_4$, appropriate ketone; ii. $NaBH_4$, MeOH.

V. FORMULATIONS, ADMINISTRATIONS, AND USES

[0175] The present invention includes within its scope pharmaceutically acceptable prodrugs of the compounds of the present invention. A "pharmaceutically acceptable prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of the present invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an active metabolite or residue thereof. Preferred prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal or which enhance delivery of the parent compound to a biological compartment relative to the parent species.

[0176] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate,

disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0177] Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0178] Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4}\ alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[0179] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0180] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0181] The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0182] Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0183] The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0184] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[0185] For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol,

polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0186] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[0187] The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0188] Most preferably, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[0189] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01-100 mg/kg body weight/day of the modulator can be administered to a patient receiving these compositions.

[0190] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

[0191] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic

agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[0192] According to a preferred embodiment, the compounds of formulae (I and II) are selective modulators of M_1, M_2 and M_4. More preferably, the compounds of formulae (I and II) are selective modulators of M_1 and/or M_4. Yet more preferably, certain compounds of formulae (I and II) are selective modulators of M_1. Or, preferably, certain compounds of formulae (I and II) are selective modulators of M_4.

[0193] Applicants believe that the ability of the compounds of the present invention to modulate the activity of muscarinic receptors is derived from the affinity of these compounds to the muscarinic receptors. Such affinity, applicants believe, activates a muscarinic receptor (i.e., an agonist) or inhibits the activity of a muscarinic receptor.

[0194] The term "selective" as used herein means a measurably greater ability to modulate one muscarinic receptor subtype when compared to the other muscarinic receptor subtypes. E.g., the term "selective M_4 agonist" means a compound that has a measurably greater ability to act as an M_4 agonist when compared to that compound's agonist activity with the other muscarinic receptor subtype(s).

[0195] According to an alternative embodiment, the present invention provides a method of treating a muscarinic receptor mediated disease in a mammal, such as a human, including the step of administering to said mammal a composition comprising a compound of formulae I and II, or an embodiment thereof as set forth herein.

[0196] According to another embodiment, the present invention provides a method of treating a disease mediated by a muscarinic receptor including the step of administering to said mammal a composition comprising a compound of formulae (I and II), or other embodiments thereof as set forth above. Preferably, said disease is mediated by M_1, or said disease is mediated by M_4.

[0197] According to yet another embodiment, the present invention provides a method of treating or reducing the severity of a disease in a patient, wherein said disease is selected from CNS derived pathologies including cognitive disorders, Attention Deficit Hyperactivity Disorder (ADHD), obesity, Alzheimer's disease, various dementias such as vascular dementia, psychosis including schizophrenia, mania, bipolar disorders, pain conditions including acute and chronic syndromes, Huntington's Chorea, Friederich's ataxia, Gilles de la Tourette's Syndrome, Downs Syndrome, Pick disease, clinical depression, sudden infant death syndrome, Parkinson's disease, peripheral disorders such as reduction of intra ocular pressure in Glaucoma and treatment of dry eyes and dry mouth including Sjögren's Syndrome, wherein said method comprises the step of contacting said patient with a compound according to the present invention.

[0198] According to an alternative embodiment, the present invention provides a method of treating or reducing the severity of a disease in a patient, wherein said disease is selected from pain, psychosis (including schizophrenia, hallucinations, and delusions), Alzheimer's disease, Parkinson's disease, glaucoma, bradhycardia, gastric acid secretion, asthma, or GI disturbances.

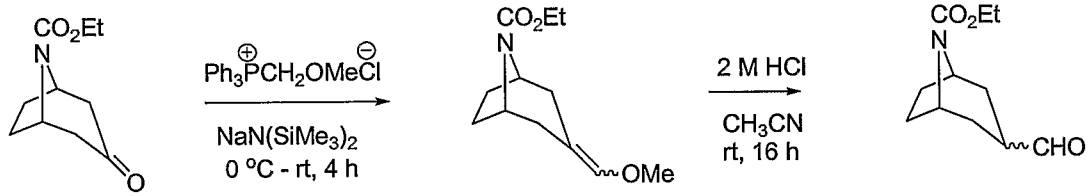
[0199] According to a preferred embodiment, the present invention is useful for treating or reducing the severity of psychosis, Alzheimer's disease, pain, or Parkinson's disease.

[0200] All references cited within this document are incorporated herein by reference.

VII. PREPARATIONS AND EXAMPLES

[0201] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

Preparation A: Synthesis of *N*-(ethoxycarbonyl)-8-aza-bicyclo[3.2.1]octane-3-carbaldehyde



[0202] Sodium bis(trimethylsilyl)amide (6 mmol, 6 mL of 1 M solution in THF) was added to a suspension of 2.06 g (6.0 mmol) of methoxymethyltriphenylphosphonium chloride in 6 mL of THF at 0 °C under argon. After stirring at 0 °C for 15 min, the resulting dark red solution was added via syringe to a solution of 0.79 g (4.0 mmol) of *N*-(ethoxycarbonyl)tropinone (6) in 8 mL of THF at 0 °C and then stirred at room temerature for 4 h (an orange color persisted). The reaction mixture was quenched by adding sat. aq. NaCl (15 mL) and then extracted with ether (25 mL x 3). The combined organic extracts were dried over Na_2SO_4. The solid residue obtained after solvent evaporation was loaded onto a short silica gel column (3.5 cm x 4 cm) to remove the phosphorous impurities. The product was eluted with ether. After the solvent was evaporated, the product enol ether was obtained as a brown oil which was used in the next step without further purification.

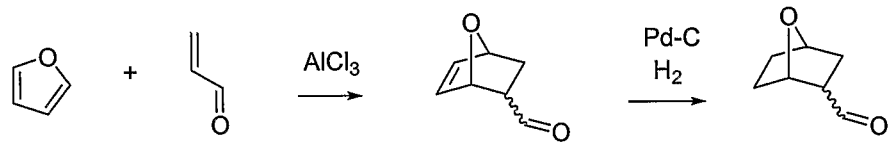
[0203] The enol ether intermediate was dissolved in a solution of 12 mL of 2 N HCl and 20 mL of acetonitrile, and stirred at room temperature for 16 h. After removing the acetonitrile on a rotary evaporator, the aqueous solution was extracted with ether (25 mL x 3). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (15 mL x 2), sat. aq. NaCl (15 mL) and then dried over Na_2SO_4. After the solution was evaporated to dryness, the residue was purified by chromatography (SiO_2, 10%-20% EtOAc in Hexane as eluent). *N*-(ethoxycarbonyl)-8-aza-bicyclo[3.2.1]octane-3-carbaldehyde (0.65 g) was obtained as a colorless oil in an approximately

1:1 ratio of endo and exo isomers (77%). ESI-MS *m/z* 212.1 (MH^+); ^1H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 4.54 (br s, 1H), 4.38 (br s, 1H), 4.16 (m, 2H), 2.72 (m, 2H), 2.38 (s, 1H), 2.32 (s, 1H), 2.10 (m, 3H), 1.69 (m, 2H), 1.29 (m, 3H).

Preparation B: Synthesis of bicyclo[3.2.1]octane-2-carbaldehyde

[0204] Bicyclo[3.2.1]octane-2-carbaldehyde was prepared using an analogous procedure as for Intermediate 1 from commercially available bicyclo[3.2.1]octan-2-one. The crude products were used in the next step without further purification.

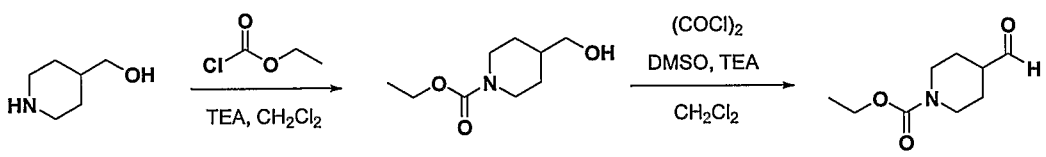
Preparation C: Synthesis of 7-oxa-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde



[0205] To a stirred solution of furan (9) (15 mL, 200 mmol) and acrolein (13) (6.7 mL, 100 mmol) in DCM (25 mL) was slowly added $AlCl_3$ (666 mg, 5 mmol) under argon at -43 °C (dry ice/isopropanol bath). The reaction mixture was stirred at -43 °C under argon for 30 min, and then quenched with sat. aq. K_2CO_3 (50 mL). After the reaction mixture was gradually warmed to room temperature, it was extracted with ether (200 mL x 5). The combined ether extracts were washed with sat. aq. K_2CO_3 (200 mL x 2) and sat. aq. NaCl (200 mL x 2), dried over $MgSO_4$, filtered, and concentrated to give 2.6 g of oily crude product 7-oxa-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde which was used in the next step without further purification. See references Laszlo, P.; Lucchetti, J. *Tetrahedron Lett.* **1984**, *25*, 4387-4388. Moore, J. A., Partain, E. M. III. *J. Org. Chem.* **1983**, *48*, 1105-1106. Dauben, W. G.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992-1993. Nelson, W. L.; Allen, D. R.; Vincenzi, F. F. *J. Med. Chem.* **1971**, *14*, 698-702.

[0206] To a stirred solution of crude product 7-oxa-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (2.6 g. 20 mmol) in 95% EtOH (200 mL) was added 10% Pd-C (0.25 g) at room temperature under argon. The mixture was shaken on a Parr hydrogenation apparatus for 4 h at room temperature under 30 psi of hydrogen. After the Pd catalyst was removed by filtration through a Celite pad, the Celite was washed with MeOH (15 mL x 2), the combined extracts were concentrated under vacuum to yield 2.5 g of crude 7-oxa-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde as a pale yellow oil, which was used in the next step without further purification.

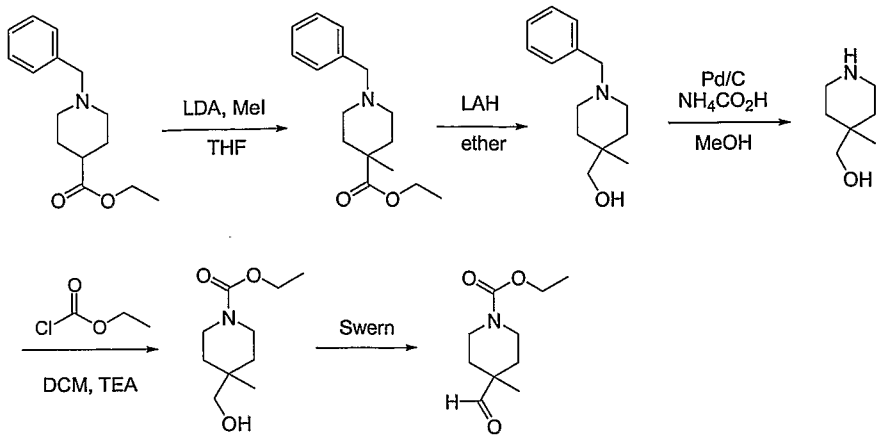
Preparation D: Synthesis of ethyl 4-formylpiperidine-1-carboxylate



[0207] 1.0 eq 4-piperidinemethanol (10.00 g, 86.8 mmol) was dissolved in dichloromethane (350 mL), cooled in an ice-H_2O bath and treated dropwise with a solution of 1.05 eq ethyl chloroformate (9.89 g, 91.1 mmol) in dichloromethane (50 mL), followed by the dropwise addition of a solution of 1.0 eq triethylamine (8.78 g) in dichloromethane (50 mL). The reaction was stirred at ~0^0C for 15 minutes, then at room temperature for 10 minutes. The reaction was diluted with dichloromethane (250 mL) and washed successively with (150 mL each) H_2O, 0.1 *N* HCl (aq) (x2), saturated brine, then dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo* to afford 15.60 g ethyl 4-(hydroxymethyl)-piperidine-1-carboxylate as a viscous, pale bluish-green oil. Yield = 96%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.15 (br m, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.46 (d, J = 6.4 Hz, 2H), 2.72 (br t, J = 12.4 Hz, 2H), 2.07 (s, 1H), 1.70 (m, 2H), 1.63 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.12 (m, 2H); t_R = 1.56 min [10-99% CH_3CN gradient over 5 mins with 0.1% TFA (aq)]; Theoretical $(M+H)^+$ *m/z* for $C_9H_{17}NO_3$ = 188.1; Found 188.0.

[0208] A solution of 1.2 eq oxalyl chloride (12.69 g, 0.10 mol) in dichloromethane (150 mL) was cooled to approximately -78^0C and treated dropwise, under nitrogen, with a solution of 2.4 eq anhydrous dimethylsulfoxide (15.63 g, 0.20 mol) in dichloromethane (50 mL). 15 minutes after the addition was complete, a solution of 1.0 eq ethyl 4-(hydroxymethyl)-piperidine-1-carboxylate (15.60 g, 83.3 mmol) in dichloromethane (50 mL) was added dropwise. 30 minutes after the addition was complete, a solution of 3.0 eq triethylamine (25.30 g, 0.25 mol) in dichloromethane (50 mL) was added dropwise and the reaction warmed to room temperature. The reaction was stirred at room temperature for 1 hour, then quenched with saturated sodium bicarbonate (500 mL). The layers were separated and the aqueous layer extracted once with dichloromethane (200 mL). The pooled organic layers were washed with H_2O (3 x 100 mL), saturated sodium bicarbonate (1 x 100 mL) and saturated brine, then dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo* to afford 13.84 g ethyl 4-formylpiperidine-1-carboxylate as a viscous amber oil. Yield = 90%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.00 (br m, 2H), 2.97 (m, 2H), 2.40 (m, 1H), 1.87 (br m, 2H), 1.54 (m, 2H), 1.23 (t, J = 7.0 Hz, 3H).

Preparation E: Synthesis of ethyl 4-formyl-4-methylpiperidine-1-carboxylate



[0209] Diisopropylamine (3.14 mL; 22.23 mmol; 1.1 eq.) was dissolved in THF (60 mL) and cooled to –78 °C. Butyl lithium (2.5 M in hexane; 8.89 mL; 22.23 mmol; 1.1 eq.) was then added and the solution was stirred for 30 minutes at –78 °C. Ethyl 1-benzylpiperidine-4-carboxylate (5 g; 20.21 mmol; 1 eq.) was dissolved in THF (40 mL) and added to the LDA solution at –78 °C. The solution was stirred at –78 °C for 30 minutes and iodomethane (1.32 mL; 21.22 mmol; 1.05 eq.) was added. The solution was slowly warmed to room temperature and stirred at room temperature for 1 hour. Water (100 mL) was then added to the reaction followed by EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the product (5.0 g, 94% yield) as an oil. The product was analytically pure and used without further purification. LC/MS m/z (M+1) 262.0, Retention time 1.78 minutes; (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min). ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.14 (m, 5H), 4.08 (q, J = 7.1 Hz, 2H), 3.40 (s, 2H), 2.60-2.57 (m, 2H), 2.08-2.02 (m, 4H), 1.47-1.40 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H), 1.10 (s, 3H).

[0210] 1-Benzyl-4-methylpiperidine-4-carboxylate (5.0 g; 19.15 mmol) was dissolved in Et_2O (50 mL) and cooled to 0 °C. $LiAlH_4$ (1.0 g; 26.3 mmol) was slowly added portion-wise to the solution. After the addition was complete, the solution was slowly warmed to room temperature and stirred for 1 h. The solution was then cooled to 0 °C and slowly quenched with 1N NaOH (6 mL). The resultant white precipitates were filtered and washed with EtOAc (100 mL). The combined organic layers were concentrated under reduced pressure to provide the product (3.9 g, 90% yield) as an oil which was used without further purification. LC/MS m/z M+1 220.0, retention time 0.64 minutes; (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.16 (m, 5H), 3.46 (s, 2H), 3.30 (d, *J* = 3.9 Hz, 2H), 2.51-2.46 (m, 2H), 2.26-2.20 (m, 2H), 1.52-1.45 (m, 3H), 1.30-1.25 (m, 2H), 0.87 (s, 3H).

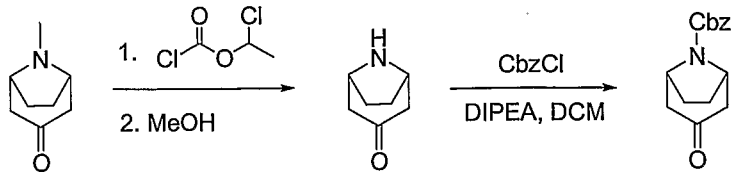
[0211] (1-benzyl-4-methylpiperidin-4-yl)methanol (3.9 g; 17.8 mmol) was dissolved in MeOH (50 mL) and NH_4CO_2H (12.5 g; 178.0 mmol) was added. Pd/C (10% by weight, wet; 5.5 g) was then added and the system was flushed with nitrogen and then with hydrogen. The reaction was stirred at room temperature overnight (18 h) and then filtered through a pad of Celite. The solvent was removed under high vacuum to provide a solid that was a mixture of the amino alcohol and NH_4CO_2H. The crude product (2.4 g as a mixture with NH_4COOH) was used in the next step without further purification. LC/MS m/z (M+1) 130.0, retention time 0.35 min; (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min). ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 2H), 3.03-2.98 (m, 2H), 2.95-2.88 (m, 2H), 1.64-1.57 (m, 2H), 1.36-1.31 (m, 2H), 0.89 (s, 3H).

[0212] (4-methylpiperidin-4-yl)methanol (2.4 g, a mixture of the amino alcohol and NH_4CO_2H) was suspended in DCM (70 mL). Et_3N (5 mL; 37.2 mmol) was then added followed by the drop-wise addition of ethyl chloroformate (1.05 mL, 13 mmol, 1.4 eq.). After 1 hour at room temperature, 1N HCl (70 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (70 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under high vacuum. The product (1.7 g, 47% yield over 2 steps) is obtained analytically pure as an oil and used without further purification. LC/MS m/z (M+1) 202.2, retention time 1.89 minutes; (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min). ^1H NMR (400 MHz, DMSO-d_6) δ 4.05 (q, J = 7.1 Hz, 2H), 3.66 (dt, J = 13.6, 4.7 Hz, 2H), 3.32 (s, 2H), 3.11 (t, J = 5.2 Hz, 1H), 3.11 (dd, J = 23.9, 3.5 Hz, 1H), 1.44-1.37 (m, 3H), 1.26-1.22 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H), 0.93 (s, 3H).

[0213] To a 100 mL round bottom flask was added DCM (30 mL) and oxalyl chloride (0.88 mL; 10.13 mmol). The solution was cooled to –78 °C and treated with DMSO (1.19 mL; 16.88 mmol). The solution was stirred at –78 °C for 20 minutes and then treated with ethyl 4-(hydroxymethyl)-4-methylpiperidine-1-carboxylate (1.7 g; 8.44 mmol, dissolved in 10 mL of DCM). The solution was stirred for 30 minutes at –78 °C and then treated with Et_3N (3.53 mL; 25.32 mmol). The solution was stirred at –78 °C for 20 min and then slowly warmed to room temperature and stirred at room temperature for an additional 2 h. The solution was then treated with saturated aqueous $NaHCO_3$ (50 mL), diluted with DCM (50 mL), and the layers were separated. The organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 1.6 g (95% yield) of the product as an oil which was used without further purification. LC/MS m/z (M+1) 200.0, retention time 2.23 minutes; (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min). ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.66 (dt, J = 13.6, 4.7 Hz, 2H), 3.09 (dd, J = 10.1, 3.5 Hz, 1H),

3.06 (dd, J = 10.2, 3.4 Hz, 1H), 1.86 (dt, J = 13.6, 4.4 Hz, 2H), 1.42-1.30 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H), 1.02 (s, 3H).

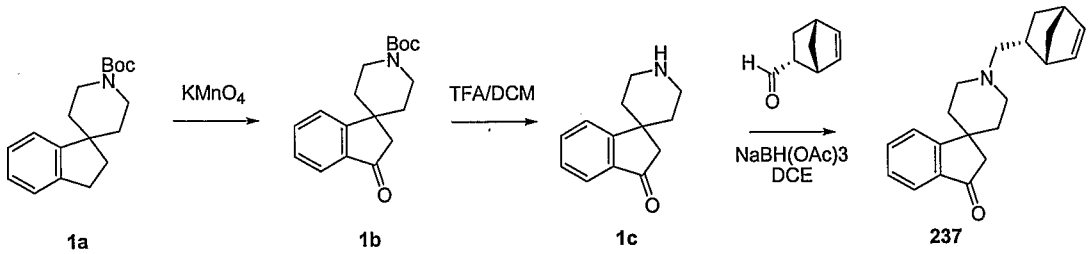
Preparation F: Synthesis of benzyl 4-oxotropane-*N*-carboxylate



[0214] Tropinone (10.0 g; 71.84 mmol) was dissolved in DCE (60 mL) and treated drop-wise with 1-chloroethyl chloroformate ACE-Cl (14.5 mL; 19.11 g; 133.7 mmol). The reaction was allowed to stir at room temperature overnight and was then diluted with Et_2O (400 mL) and filtered. The filtrate was concentrated under reduced pressure to provide the crude chloroethyl carbamate. This compound was taken in MeOH (200 mL) and stirred at room temperature for 1 h, then concentrated under reduced pressure (at 55°C) to provide the crude des-methyltropinone as the HCl salt (tan solid, 11.4 g, 98% yield). The crude material was recrystallized from acetonitrile to furnish the pure product as a white crystalline solid (5 g, 43% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 1.79 (dd, J = 15.0, 6.9 Hz, 2H), 2.09 (m, 2H), 2.40 (d, J = 16.7 Hz, 2H), 3.02 (dd, J = 17.1, 4.3 Hz, 2H), 4.23 (s, 2H), 10.00 (br s, 2H)

Des-methyl tropinone (5.10 g; 31.55 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated with benzyl chloroformate (4.29 mL; 5.11 g; 29.98 mmol) DIPEA (16.48 mL; 12.23 g; 94.66 mmol) was added drop-wise (exothermic reaction). The resulting clear solution was allowed to stir at room temperature for 30 min and was subsequently diluted with 100 mL CH_2Cl_2. The organic phase was washed with 1 N HCl (2 x 100 mL), dried on Na_2SO_4 and concentrated to provide the crude product (7.2 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (dd, J = 15.0, 7.2 Hz, 2H), 2.12 (m, 2H), 2.38 (d, J = 15.9 Hz, 2H), 2.67 (m, 2H), 4.62 (s, 2H), 5.22 (s, 2H), 7.38 (m, 5H).

Example 1:



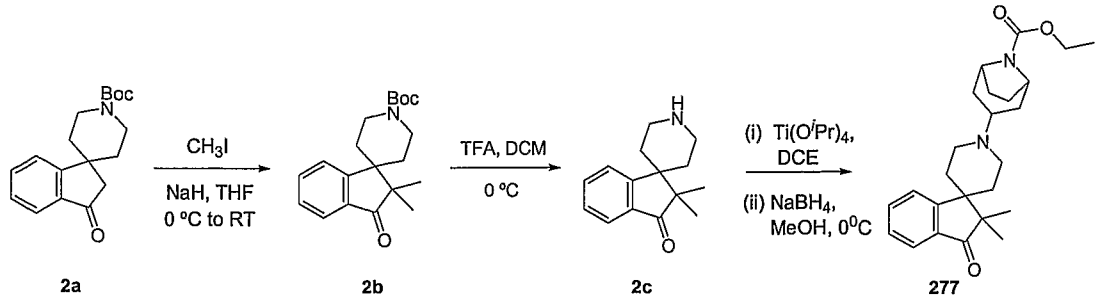
[0215] To a solution of compound *N*-Boc Spiroindane **1a** (60.0 g, 0.21 mol) in CH_2Cl_2 (1000 mL) was added H_2O (500 mL), TBAB (6.9 g, 0.02 mol) and KOH (3.5 g, 0.06 mol) and followed by addition of $KMnO_4$ (70.0 g, 0.45 mol) in several portions. After stirring for two days at 35 °C, another quantity of $KMnO_4$ (70.0 g, 0.45 mol) was added and the mixture was

continued to stir for 2 days. After Na_2SO_3 (103.0 g, 1.0 mol) was added in portions at 5 °C, the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography (PE/EtOAc: 5/1) to yield **1b** (30.0 g, 47.7%). ^{1}H NMR ($CDCl_3$) δ: 7.74-7.72 (m, 1 H), 7.66-7.64 (m, 1 H), 7.62-7.61 (m, 1 H), 7.49-7.38 (m, 1 H), 4.22-4.20 (m, 2 H), 2.89-2.82 (m, 2 H), 2.63 (s, 2 H), 2.02-1.94 (m, 2 H), 1.56-1.52 (m, 2 H), 1.49 (s, 9 H). MS (ESI) *m/z* ($M+H^+$) 246.0/202.1.

[0216] Boc-protected starting material **1b** (400.0 mg; 1.33 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and treated with TFA (1.5 mL). The reaction was allowed to stir at room temperature for 1 h and was then quenched by adding H_2O (5 mL) and Et_2O (7 mL). The layers were separated, and the aqueous layer was brought to a basic pH by addition of solid KOH. The resulting emulsion was extracted with Et_2O (3 x 10mL). The combined organic extracts were dried on Na_2SO_4 and concentrated to yield the desired product **1c** as a colorless oil that solidifies upon standing (220 mg, 82% yield). LC/MS m/z 202.2 $[M+H]^+$, retention time 0.72 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min).

[0217] Intermediate **1c** (40 mg; 0.2 mmol) was suspended in DCE (1 mL) and treated with (1R,2R,4R)-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (31 mg; 0.26 mmol; 1.300eq.) in DCE (0.5 mL), followed by portion-wise addition of $NaBH(OAc)_3$ (127 mg; 0.6 mmol) The reaction was allowed to stir at room temperature for 1 h and was then quenched with MeOH (1 mL) and allowed to stir for another 30 min. The crude reaction mixture was purified by HPLC (10-99% CH_3CN gradient with 0.03% TFA, 15 min) to provide the purified compound no. 237. LC/MS m/z 308.2 $[M+H]^+$, retention time 2.08 (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (br s, 1H), 7.81-7.77 (m, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.59 (d, J = 7.8 Hz, 7.53-7.49 (m, 1H), 6.27 (dd, J = 5.7, 3.0 Hz, 1H), 6.05 (dd, J = 5.7, 2.8 Hz, 1H), 3.60 (t, J = 12.7 Hz, 3H), 3.11-2.90 (m, 4H), 2.85-2.74 (m, 4H), 2.29 (t, J = 13.0 Hz, 2H), 2.05-1.99 (m, 1H), 1.76 (d, J = 14.2 Hz, 2H), 1.39-1.35 (m, 1H), 1.29 (d, J = 8.2 Hz, 1H), 0.71-0.66 (m, 1H).

Example 2:



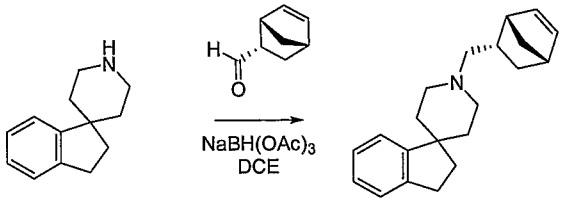
[0218] 1.0 eq of the Boc-protected spiroindanone **2a** (2.06 g, 6.84 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL) and added drop-wise, under nitrogen, to an ice-cold (~0^0C) suspension of 2.2 eq sodium hydride (600 mg, 60% dispersion in mineral oil, 15.0 mmol) in anhydrous tetrahydrofuran (10 mL). A solution of 10.0 eq iodomethane (9.71 g, 68.4 mmol) in anhydrous tetrahydrofuran (5 mL) was then added drop-wise over 20 min. The reaction was warmed to room temperature and stirred for 2 hours under nitrogen. The reaction mixture was concentrated under reduced pressure and slowly treated with H_2O (25 mL). The product was extracted with ethyl acetate (2 x 50 mL) and the pooled extracts washed with saturated sodium bicarbonate and saturated brine, then dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo* to afford 2.41 g crude product **2b** as a viscous, pale yellow oil. Yield = ~100%. ^{1}H-NMR (400 MHz, acetone-d_6) δ 7.90 (d, J = 6.8 Hz, 1H), 7.71 (m, 2H), 7.49 (t, J = 7.4 Hz, 1H), 3.75 (m, 2H), 3.56 (br m, 2H), 1.89 (m, 2H), 1.64 (br m, 2H), 1.48 (s, 9H), 1.12 (s, 6H); t_R = 3.50 min [10-99% CH_3CN gradient over 5 min with 0.1% TFA (aq)]; Theoretical $(M+H)^+$ *m/z* for $C_{20}H_{27}NO_3$ = 330.2; Found 330.2.

[0219] The gem-dimethyl spiroindanone **2b** (379 mg, 1.15 mmol) was dissolved in dichloromethane (2.5 mL), cooled in an ice-H20 bath and treated slowly with trifluoroacetic acid (2.5 mL). The reaction was stirred for 30 min at ~0 ^{0}C, then concentrated under reduced pressure. The oil obtained was dissolved in acetonitrile and re-concentrated under reduced pressure. The crude TFA salt was treated with 1.0 N NaOH (5 mL) and extracted with ethyl acetate (2 x 30 mL). The pooled extracts were washed with H2O and saturated brine, then dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to afford 210 mg of the crude free base **2c** as a colorless semi-solid. Yield = 80%. t_R = 1.52 min [10-99% CH_3CN gradient over 5 min with 0.1% TFA (aq)]; Theoretical (M+H)+ m/z for $C_{15}H_{19}NO$ = 230.2; Found 230.2

[0220] The crude free base **2c** (53 mg, 0.23 mmol) was dissolved in anhydrous 1,2-dichloroethane (1.0 mL) and treated with *N*-(carbethoxy)-4-tropinone (55 mg, 0.28 mmol), followed by titanium tetraisopropoxide (202 μL, 196 mg, 0.69 mmol). The vial was flushed

with nitrogen and stirred at room temperature for 2.5 days. The reaction was diluted with methanol (1.0 mL), cooled in an ice-H_2O bath and treated with sodium borohydride (17 mg, 0.46 mmol). The reaction was warmed to room temperature and stirred thereafter for 30 min. The reaction was then quenched with 1.0 *N* NaOH (750 μL), diluted with methanol (1.5 mL) and stirred at room temperature for 10 min. The suspension obtained was centrifuged (3K rpm, 10 min) and the supernatant concentrated under reduced pressure. The residue obtained was dissolved in DMSO:methanol (1.5 mL, 1:1 v/v), filtered, and purified by reverse-phase HPLC (2-40% CH_3CN gradient over 10 min with 0.1% TFA (aq), 35 mL/min, 1.0 mL injected) to produce the compound no. 277 as a TFA salt. t_R = 2.12 min [10-99% CH_3CN gradient over 5 min with 0.1% TFA (aq)]; Theoretical $(M+H)^+$ *m/z* for $C_{25}H_{34}N_2O_3$ = 411.3; Found 411.2.

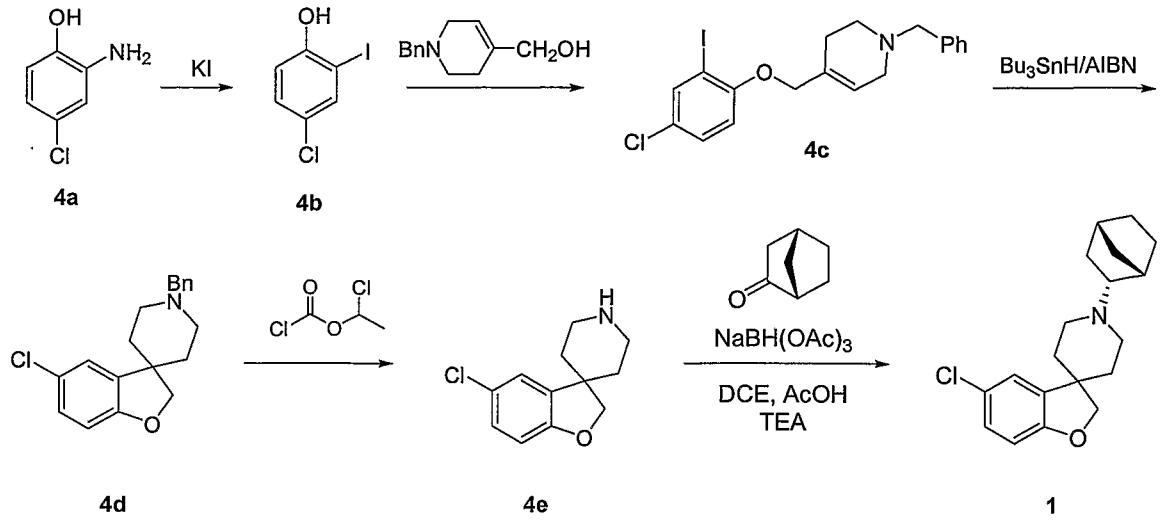
Example 3:



3a 312

[0221] The starting Spiroindane **3a** (45 mg, 0.2 mmol) was suspended in DCE (1 mL) and treated with (1S,2S,4S)-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (25 mg, 0.2 mmol) in DCE, followed by the addition of $NaBH(OAc)_3$ (63 mg, 0.3 mmol). The reaction was allowed to stir at room temperature for 1 h and was then quenched with MeOH (0.5 mL) and allowed to stir for another 30 min (until gas evolution stopped). The crude reaction mixture was filtered, then purified by HPLC (10-99% CH_3CN/0.05% TFA gradient) to yield compound no. 312. LC/MS *m/z* 294.4 $[M+H]^+$, retention time 2.33 min (RP-C_{18}, 10-99% CH_3CN/0.05% TFA); ^1H NMR (400 MHz, DMSO-d_6) δ 9.33 (br s, 1H), 7.25-7.17 (m, 3H), 7.13 (d, *J* = 6.9 Hz, 1H), 6.27-6.26 (m, 1H), 6.06-6.04 (m, 1H), 3.56-3.40 (m, 3H), 3.11-3.03 (m, 2H), 2.98-2.78 (m, 6H), 2.09-1.98 (m, 5H), 1.67 (d, *J* = 13.9 Hz, 2H), 1.36 (t, *J* = 8.0 Hz, 1H), 1.29 (d, *J* = 8.2 Hz, 1H), 0.70-0.66 (m, 1H).

Example 4:



4a 4b 4c

4d 4e 1

[0222] To a solution of 2-amino-4-chloro-phenol **4a** (50 g, 0.35 mol) in HCl (2.5 mol, 500 mL) was added drop-wise a solution of sodium nitrite (25.25 g, 0.35 mol) in water (50 mL) at 0 °C. The mixture was stirred at this temperature for 30 min. Then a cooled solution of KI (70 g, 0.42 mol) in H_2O (100 mL) was slowly added at 0 °C. After addition, the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate (200 mL) and the separated aqueous phase was extracted with ethyl acetate (100 mL x 3). The combined organic fraction was washed with $Na_2S_2O_3$ (10%, 100 mL), water (100 mL x 2) and brine (200 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column on silica gel to afford 4-chloro-2-iodo-phenol **4b** as a yellow solid (46 g, yield 51.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 2.4 Hz, 1 H), 7.21 (dd, J = 2.4, 8.4, Hz, 1 H), 6.91 (d, J = 8.4 Hz, 1 H), 5.33 (s, 1 H).

[0223] To a solution of 4-chloro-2-iodo-phenol **4b** (20.32 g, 0.08 mol), (1-benzyl- 1, 2, 3, 6-tetrahydro-pyridin-4-yl)-methanol (20.5 g, 0.08 mol) and triphenylphosphine (23.58 g, 0.09 mol) in dry THF (150 mL) was added DEAD (17.4 g, 0.09 mol) at 0 °C under nitrogen atmosphere. After addition, the mixture was stirred at room temperature overnight. The mixture was concentrated to dryness and the residue was basified by Na_2CO_3 solution (10% 100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with water (100 mL x 2) and brine (200 mL), dried over Na_2SO_4, concentrated to dryness. The residue was purified by column on silica gel to afford 1-benzyl-4-(4- chloro-2-iodo-phenoxymethyl)-1, 2, 3, 6-tetrahydro-pyridine **4c** (30 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 2.4 Hz, 1 H), 7.22-7.38 (m, 6 H), 6.70 (d, J = 8.8 Hz, 1 H), 5.82 (s, 1 H), 4.43 (s, 2 H), 3.63 (s, 2 H), 3.05 (s, 2 H), 2.67 (t, J = 5.6 Hz, 2 H), 2.28 (s, 2 H).

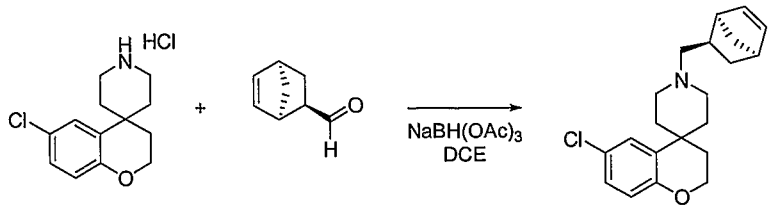
[0224] To a refluxing solution of 1-benzyl-4-(4-chloro-2-iodo-phenoxymethyl)-1, 2, 3, 6-tetrahydro- pyridine **4c** (26.7 g, 0.06 mol) and AIBN (0.05g, 0.003 mol) in dry benzene was added a solution of Bu_3SnH (40 g, 0.137 mol) in benzene (100 mL) over 1h under nitrogen atmosphere. After addition, the mixture was refluxed for 3 hr and additional AIBN (0.5g, 0.003 mol) and Bu_3SnH (20 g, 0.68 mol) were added. After refluxing for 4 hr, the mixture was concentrated to dryness, and EtOAc (100 mL) and HCl (10%, 40 mL) were added. The precipitate was filtered and washed with petroleum ether to give 2, 3-dihydro-1'-benzyl-5-chlorospiro (benzofuran-3, 4'-piperidine) as its HCl salt, which was basified by $NaHCO_3$ solution to give 2, 3-dihydro-1'-benzyl-5-chlorospiro (benzofuran-3, 4'-piperidine) **4d** (13 g, 68%).

[0225] To a solution of 2, 3-dihydro-1'-benzyl-5-chlorospiro (benzofuran-3, 4'-piperidine) **4d** (13g, 0.04 mol) in CH_2Cl_2 (130 mL) was added drop-wise 1-chloroethyl chloroformate (7.2 g, 0.05 mol). The mixture was stirred for 3 hr at room temperature and then concentrated to dryness. The residue was dissolved in CH_3OH (30 mL) and the solution was heated to reflux for 30 min. After removing of the solvent, ether was added. The resulted solid was filtered and washed with ether to the debenzylated product **4e** as the HCl salt (5.5g, yield 48%). ^1H NMR (400 MHz, DMSO-d_6): δ 9.08 (br s, 1 H), 7.16-7.19 (m, 2 H), 6.82 (d, J= 8.4 Hz, 1 H), 4.50 (s, 2 H), 3.25-9.29 (m, 2 H), 2.98-2.92 (m, 2 H), 2.12-2.05 (m, 2 H), 1.83-1.8 (m, 2 H).

[0226] The chloro-dihydrobenzofuran spiro amine **4e** (3.18 mmol) was dissolved in anhydrous DCE (15 mL) and treated with triethylamine (322 mg, 3.18 mmol), followed by (+)-2-norcamphor (421 mg, 3.82 mmol), acetic acid (382 mg, 6.36 mmol) and $NaBH(OAc)_3$ (1.35 g, 6.37 mmol). The reaction was stirred vigorously under nitrogen at room temperature for ~36 hours. The reaction was quenched with methanol (15 mL) and stirred vigorously for 10 min at room temperature. The reaction mixture was then concentrated under reduced pressure and the residue obtained dissolved in a mixture of DMSO:CH_3OH (20 mL, 1:3 v/v). The solution was filtered and purified by reverse-phase HPLC (2-99% CH_3CN/0.05% TFA, 35 mL/min). The combined pure fractions were concentrated under reduced pressure until ~25 mL of solvent remained. The suspension was treated with 1 N NaOH (25 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with H_2O, saturated brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford 522 mg pure free base (1.64 mmol) as a crystalline white solid. The free base was readily dissolved in anhydrous diethyl ether (10 mL) and treated with 1.0 eq 1 N ethereal HCl (1.7 mL). The thick, gelatinous suspension obtained was cooled in an ice/H_2O bath for 1 hour, filtered, rinsed with Et_2O (3 × 10 mL), and dried overnight under reduced pressure to yield compound no. 1 as a fine

white powder. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.1 (br s, 1 H), 7.77 (d, J = 2.2 Hz, 0.2 H), 7.21 (dd, J = 2.3 Hz, 8.5 Hz, 1H), 7.08 (d, J = 2.3 Hz, 0.8 H), 6.85 (d, J = 8.5 Hz, 0.8 H), 6.84 (d, J = 8.5 Hz, 0.2H), 4.52 (s, 1.6 H), 4.45 (s, 0.4 H), 3.41 (m, 1.8 H), 3.24 (m, 0.8 H), 3.01 (br m, 1.6 H), 2.63 (br m, 2H), 2.44 (m, 0.9 H), 2.27 (br s, 1.1H), 1.86 (br m, 4H), 1.51 (br m, 3.3H), 1.39 (br m, 2.7H), 1.24 (br m, 0.7H); LC/MS *m/z* 318.0 $[M+H]^+$, retention time 2.14 min (RP-C_{18}, 10-99% CH_3CN/0.05% TFA).

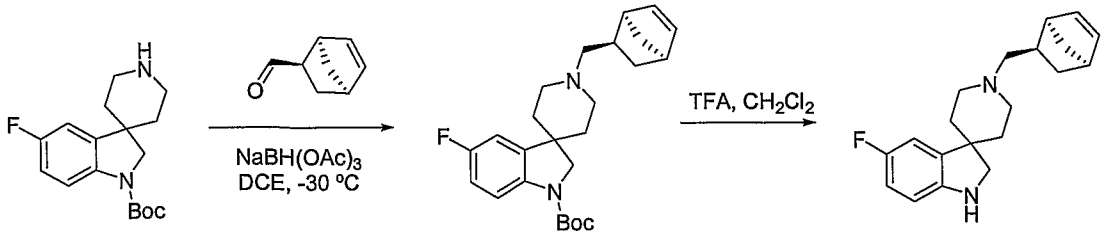
Example 5:



5a 64

[0227] The starting material **5a** (54 mg, 0.2 mmol, 1.0 eq) was suspended in DCE (1 mL) and treated with (1R,2R,4R)-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (31 mg, 0.26 mmol, 1.3 eq) in DCE (0.5 mL), followed by portion-wise addition of $NaBH(OAc)_3$ (127 mg, 0.6 mmol). The reaction was allowed to stir at room temperature for 3 h and was then quenched with MeOH (2 mL) and allowed to stir for another hour (until gas evolution stopped). The reaction mixture was then diluted with H_2O (5 mL) and extracted with Et_2O (10 mL). The organic layer was treated with 1 N HCl (5 mL) and formation of an insoluble precipitate was observed. The biphasic emulsion was filtered, and the white precipitate was washed with Et_2O (3 × 5mL) and hexanes (2 × 10 mL) and dried under vacuum to provide the pure HCl salt of compound no. 64 as white shiny platelets. LC/MS *m/z* 344.0 $[M+H]^+$, retention time 2.56 min (RP-C_{18}, 10-99% CH_3CN/0.05% TFA). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 6.18 (q, J = 2.8 Hz, 1H), 6.02 (q, J = 2.7 Hz, 1H), 4.05-4.03 (m, 2H), 3.37-3.32 (m, 2H), 3.08-2.97 (m, 3H), 2.85-2.77 (m, 2H), 2.72-2.65 (m, 1H), 2.49-2.45 (m, 3H), 1.98-1.90 (m, 3H), 1.72-1.70 (m, 2H), 1.26 (dd, J = 33.4, 7.3 Hz, 2H), 0.63 (d, J = 10.5 Hz, 1H).

Example 6:



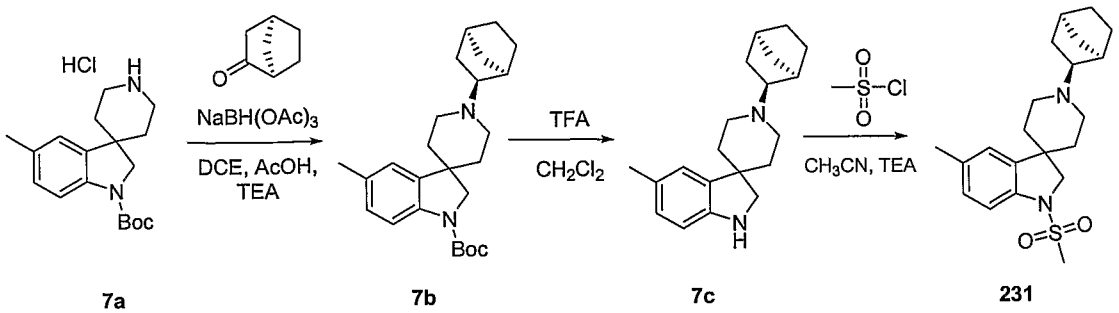
6a 6b 147

[0228] The fluoroindoline **6a** (1.22g; 4.0 mmol) was suspended in DCE (10 mL) and cooled to -30°C. A solution of (1R,2R,4R)-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (635 mg; 5.2 mmol) in dry DCE (2 mL) was added, followed by portion-wise addition of $NaBH(OAc)_3$ (1.18 g; 5.6 mmol). The reaction was stirred at -30 °C under nitrogen for 90 min then at room temperature until complete consumption of starting material was observed by LC/MS (30 h). The reaction was quenched with MeOH (10 mL) and allowed to stir vigorously for 30 min (until gas evolution stopped). The reaction was diluted with 1N HCl (80 mL) and Et_2O (50 mL). Formation of a white precipitate can be observed as the HCl salt of the desired product is insoluble in both phases. The biphasic mixture was filtered, and the precipitate was washed with Et_2O (2 × 20 mL) and hexanes (2 × 30 mL) and dried under high vacuum to provide the product **6b** as the corresponding HCl salt (white powder, 1.41g, 78.5% yield).

[0229] The HCl salt **6b** (1.4 g; 3.1 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (10 mL) was added. The reaction mixture was allowed to stir at room temperature for 1 h. The reaction was quenched with water (100 mL) and diluted with hexanes (40 mL) and Et_2O (50 mL). The layers were separated, and the organic layer was extracted with H_2O (2 × 100mL). The combined aqueous layers were washed with Et_2O (50 mL) then neutralized with solid KOH (under dry-ice bath cooling) until formation of an oily suspension was observed. The suspension was extracted with EtOAc (3 × 100mL) and CH_2Cl_2 (100 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated to provide the crude product as a light brown oil. The amine was dissolved in 15 mL Et_2O and treated with 2 N HCl in ether (1.5 mL, 3.0 mmol, 0.96 eq). After 20 min of stirring the resulting precipitate was vacuum filtered under a nitrogen atmosphere, washed with 50 mL Et_2O, 30 mL Et_2O:CH_3CN (5:1) and 40 mL hexanes and dried under high vacuum to provide the HCl salt of compound no. 147 as an off-white powder. LC/MS *m/z* 313.30 $[M+H]^+$, retention time 1.73 min (RP-C_{18}, 10-99% CH_3CN/0.05% TFA). ^1H NMR (400 MHz, MeOD) δ 0.83 (ddd, J = 5.8, 2.6 Hz, 1H), 1.41 (d, J = 8.4 Hz, 1H), 1.54 (m, 1H), 2.01 (s, 1H), 2.05 (d, J = 3.9 Hz, 1H), 2.15 (ddd, J = 6.1, 3.1 Hz, 1H), 2.23 (m, 2H), 2.60 (m, 1H), 2.86 (dd, J = 13.0, 7.4 Hz, 1H), 2.93 (s, 1H), 3.11 (m, 4H), 3.66 (m, 4H),

6.09 (d, J = 2.8 Hz, 1H), 6.33 (d, J = 3.0 Hz, 1H), 6.90 (m, 3H).

Example 7:



7a 7b 7c 231

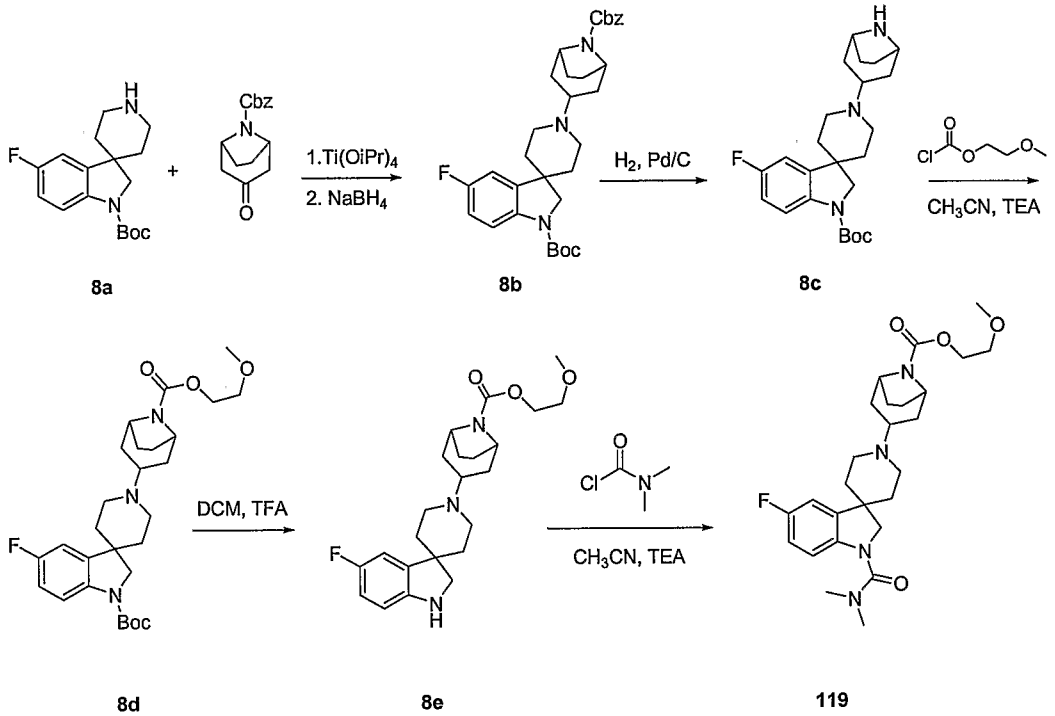
[0230] Starting material **7a** hydrochloride (2.17 g, 6.40 mmol) was suspended in anhydrous DCE (30 mL) and treated with triethylamine (648 mg, 6.40 mmol), followed by (-)-2-norcamphor (706 mg, 6.40 mmol), acetic acid (770 mg, 12.8 mmol) and $NaBH(OAc)_3$ (2.72 g, 12.8 mmol). The reaction was stirred vigorously under nitrogen at room temperature for ~72 h (~77% conversion by LC/MS at 220 nm). The reaction was quenched with methanol (10 mL) and stirred vigorously for 10 min at room temperature. The reaction mixture was then concentrated under reduced pressure and the residue obtained dissolved in a 1:1 mixture of DMSO:CH_3OH (30 mL). The mixture was centrifuged (3,000 rpm, 10 min) and the supernatant filtered and purified by reverse-phase HPLC (10-99% CH_3CN/0.05% TFA, 50 mL/min). The combined pure fractions were concentrated under reduced pressure to afford 2.25 g of the *N*-Boc intermediate **7b** (isolated as the TFA salt) as an off-white solid (69% isolated yield, Purity = 99+%). LC/MS (RP-C_{18}, 10-99% CH_3CN/0.05% TFA gradient over 5 min) *m/z* 397.4 $[M+H]^+$, retention time 2.70 min.

[0231] The *N*-Boc intermediate **7b** (2.25 g, 4.41 mmol) was dissolved in dichloromethane (25 mL) and slowly treated with trifluoroacetic acid (15 mL). The reaction was stirred at room temperature for 30 min, and then concentrated under reduced pressure. The oil obtained was slowly treated with 1 N NaOH (100 mL) and extracted with CH_2Cl_2 (2 × 75 mL). The combined extracts were washed with H_2O, saturated brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford 1.147 g (3.87 mmol) free base as a yellow oil. The free base was dissolved in a minimal volume of anhydrous diethyl ether and treated with 0.95 eq 1 N ethereal HCl. The suspension was cooled in an ice/H_2O bath for 1 h, filtered, rinsed with Et_2O, and dried overnight under reduced pressure to yield 1.213 g (57% yield) of the desired product **7c** as a fine, off-white to very pale yellow powder. LC/MS (RP-C_{18}, 10-99% CH_3CN/0.05% TFA gradient over 5 min) *m/z* 297.2 $[M+H]^+$, retention time 1.72 min.

[0232] The deprotected amine HCl salt **7c** (33 mg, 0.10 mmol) was suspended in anhydrous CH_3CN (1.0 mL) and treated with triethylamine (20 mg, 0.20 mmol), followed by

methanesulfonyl chloride (14 mg, 0.12 mmol). The reaction was stirred at room temperature for 10 min, then quenched with DMSO:CH_3OH (1.0 mL, 1:1 v/v) and centrifuged (4000 rpm, 7 min). The supernatant was filtered and purified by reverse-phase HPLC (2-99% CH_3CN, 50 mL/min, 2.0 mL injected) to yield the desired compound no. 231 as the TFA salt. LC/MS (RP-C_{18}, 10-99% CH_3CN/0.05% TFA gradient over 5 min) *m/z* 375.0 $[M+H]^+$, retention time 2.08 min.

Example 8:



[0233] Boc-protected fluoroindoline **8a** (1.41 g; 4.11 mmol) and benzyl 4-oxotropane-*N*-carboxylate (1.07 g; 4.11 mmol) were dissolved in a mixture of DCE (5 mL) and DME (5 mL) and placed under a nitrogen atmosphere. TEA (0.57 mL; 0.42 g; 4.11 mmol) was added, followed by Ti(O*i*Pr)$_4$ (1.21 mL; 1.17 g; 4.11 mmol) and the reaction was allowed to stir at room temperature for 60 h. The reaction mixture was diluted with 30 mL MeOH and cooled to -40°C to -50°C. $NaBH_4$ (0.6 g; 13.45 mmol) was added portion-wise over 30 min and the reaction was allowed to stir at -40°C to -20°C until bubbling subsided (3 h), then warmed slowly to room temperature and was stirred for 2 h. The sticky suspension was filtered through a pad of Celite, and the filter cake was washed with MeOH (2 x 30mL) and Et_2O (3 x 50mL). The filtrate was separated into the corresponding layers, and the aqueous layer was extracted with Et_2O (2 x 50mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to provide the crude product as a white foam. This material was dissolved in Et_2O (400 mL) and treated with 1 N aq. HCl (500 mL) and the mixture was vigorously stirred for 20 min. The resulting biphasic

suspension was filtered, the precipitate was washed with HCl 1N (2 x 30mL), H_2O (2 x 30mL) and Et_2O (3 x 30mL) and dried. To remove the unreacted starting material by conversion to the corresponding ethyl carbamate, the crude HCl salt was suspended in acetonitrile (10 mL) and treated sequentially with ethyl chloroformate (1 mL) and triethylamine (2 mL). After 10 min, the mixture was diluted with Et_2O (300 mL) and poured onto 1 N aq HCl (300 mL). The biphasic suspension was filtered, and the precipitate was washed with HCl 1N (2 x 30mL), H_2O (2 x 30mL) and Et_2O (3 x 30 mL) and dried to provide the desired product **8b** hydrochloride salt. LC/MS m/z $[M+H]^+$ 550.4 retention time 2.93 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min).

[0234] Cbz-protected starting material **8b** (1.140 g; 1.945 mmol) was dissolved in methanol (20 mL) and treated with 10% wet Pd/C (1.14 g) and NH_4COOH (2.45 g; 38.9 mmol) The mixture was allowed to stir vigorously overnight under an empty balloon (for venting). LC/MS analysis shows complete conversion to the desired product. The reaction mixture was filtered through a pad of Celite under a nitrogen atmosphere, and the filter cake was rinsed with methanol (4 x 30 mL). The filtrate was concentrated to provide the crude product, which was taken up in a mixture of EtOAc (100 mL) and $NaHCO_3$ sat. (100 mL). The layers were separated, the aqueous layer was extracted with EtOAc (2 x 100mL), Et_2O (100 mL), and CH_2Cl_2 (2 x 100mL). The combined organic layers were dried over Na_2SO_4 and concentrated to provide the crude product **8c** as a white foam (707 mg, 87% yield). LC/MS m/z 416.4 $[M+H]^+$, retention time 2.26 (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min)

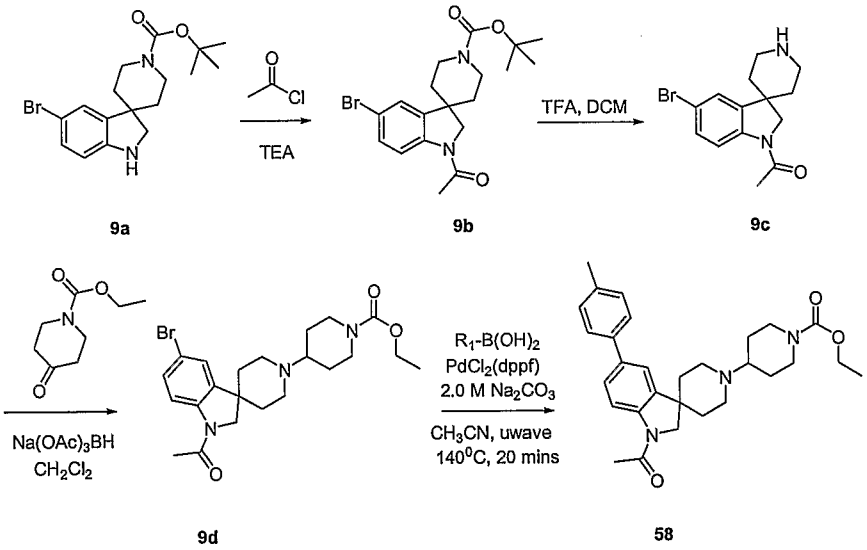
[0235] Compound **8c** (250.0 mg; 0.60 mmol) was dissolved in DCM (15 mL) and treated sequentially with methoxyethyl chloroformate (138.4 uL; 166.1 mg; 1.203 mmol) and TEA (401.7 uL; 291.7 mg; 2.89 mmol). After 10 min, the reaction mixture was diluted with DCM (30 mL) and washed with saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with DCM (30 mL) and the combined organic extracts were dried on Na_2SO_4 and concentrated to provide the desired product **8d** which was taken to the next step without further purification. LC/MS m/z 518.0 $[M+H]^+$, retention time 2.43 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min).

[0236] Intermediate **8d** was dissolved in a mixture of DCM (15 mL) and TFA (20 mL) and allowed to stir at room temperature for 2 h. The reaction mixture was concentrated, dissolved in water (20 mL) and the pH was adjusted to basic by portion-wise addition of solid KOH. The resulting suspension was extracted with DCM (3 x 30mL) and Et_2O (30 mL) and the organic extracts were dried over Na_2SO_4, and then concentrated to provide the free base of the desired product. The material was dissolved in Et_2O (20 mL) and treated with excess 1N HCl in ether (2

mL). The resulting suspension was filtered under nitrogen and the filtrate was washed with Et_2O (3 x 10 mL) and dried under vacuum to provide the desired product **8e** as an off white solid (232 mg, 85% yield over 2 steps). LC/MS m/z 418.2 $[M+H]^+$, retention time 1.16 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min).

[0237] Intermediate **8e** (230.0 mg; 0.51 mmol) was suspended in DCM (15 mL) and treated sequentially with dimethyl carbamoyl chloride (931.3 uL; 1089.7 mg; 10.13 mmol) and TEA (704.8 uL; 511.70 mg; 5.07 mmol). The reaction was allowed to stir overnight at room temperature, and then the mixture was diluted with DCM (30 mL) and washed with saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with DCM (30 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated to provide the free base of the desired product. This material was dissolved in Et_2O (20 mL) and treated with excess 1N HCl in ether (3 mL). The resulting suspension was filtered under nitrogen and the filtrate was washed with Et_2O (3 x 10mL) and dried under vacuum to provide the desired compound no. 119 as an off-white solid. LC/MS m/z 489.4 $[M+H]^+$, retention time 2.20 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min). ^1H NMR (400 MHz, DMSO-d_6) δ 1.66 (d, J = 7.0 Hz, 2H), 1.82 (s, 4H), 1.86 (s, 2H), 1.92 (s, 2H), 2.07 (s, 2H), 2.22 (t, J = 12.1 Hz, 2H), 2.87 (s, 6H), 3.05 (q, J = 11.1 Hz, 2H), 3.28 (s, 3H), 3.53 (m, 4H), 3.73 (m, 1H), 4.15 (d, J = 4.4 Hz, 2H), 4.27 (s, 2H), 6.90 (dd, J = 8.3, 2.4 Hz, 1H), 7.00 (m, 2H), 10.41 (s, 1H).

Example 9:



[0238] Example 9: Bromo-spiroindoline **9a** (1.5g, 4.08 mmol) was dissolved in anhydrous dichloromethane (20 mL) and cooled to 0 °C. To the rapidly stirring solution was added acetyl chloride (0.481g, 6.13 mmol) followed by triethylamine (0.853 mL, 6.13 mmol). The reaction mixture was stirred at room temperature for 1 h. Then mixture was concentrated under reduced

pressure to afford desired product **9b** as viscous pale yellow oil and carried to the next step without further purification. LC/MS (RP-C_{18}, 10-99% CH_3CN/0.05% TFA gradient over 5 min) *m/z* 411.0 $[M+H]^+$, retention time 3.39 min.

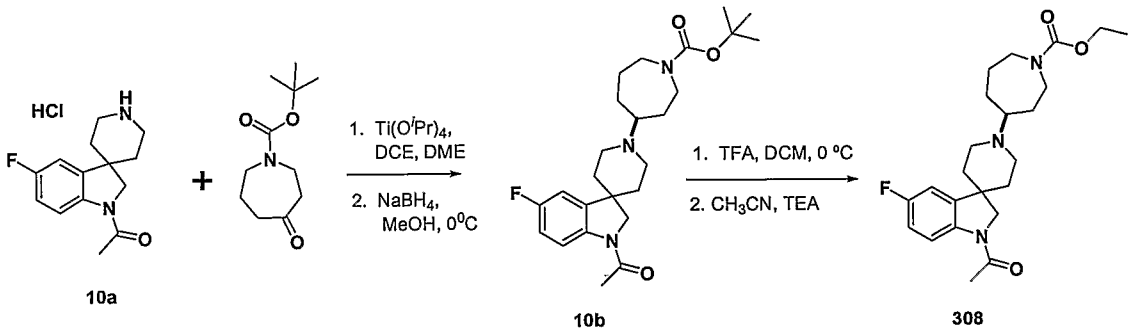
[0239] The intermediate **9b** was dissolved in 10 mL of dichloromethane and treated with trifluoroacetic acid (10 mL). The reaction was stirred at room temperature for 30 min, and then concentrated under reduced pressure. The oil obtained was re-dissolved in acetonitrile, re-concentrated under reduced pressure, treated with 2 N NaOH (25 mL) and extracted with dichloromethane (2 × 50 mL). The combined extracts were washed with saturated $NaHCO_3$, saturated brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford crude free base **9c** as a pale yellow oil. LC/MS (RP-C_{18}, 10-99% CH_3CN/0.05% TFA gradient over 5 min) *m/z* 309.7 $[M+H]^+$, retention time 2.07 min.

[0240] Intermediate **9c** (1.260g, 4.08 mmol) was dissolved in anhydrous 1,2-dichloroethane (10 mL) and treated with 2 eq of 1-carbethoxy-4-piperidone (1.393 g, 8.16 mmol), followed by glacial acetic acid (0.490 g, 8.16 mmol) and sodium triacetoxyborohydride (1.721g, 8.16 mmol). The reaction was stirred at room temperature under nitrogen for 48 h. The reaction was diluted with dichloromethane (50 mL), quenched with 1.0 *N* NaOH (20 mL) and stirred vigorously at room temperature for 30 min. The layers were separated and the aqueous layer extracted with DCM (2 x 20 mL). The pooled organic layers were washed with H_2O (20 mL), brine (20 mL), then dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford 1.8 g crude product **9d** as pale yellow oil (~95% yield). An analytical sample was subjected to reverse-phase HPLC purification (2-50% CH_3CN gradient over 13 min with 0.1% TFA (aq), 35 mL/min, 1.0 mL injected). The remainder of the material was taken to the next step without purification. ^1H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 4.13 (m, 4H), 4.06 (q, J = 7.1 Hz, 2H), 3.54-3.46 (m, 3H), 3.16 (q, J = 11.0 Hz, 2H), 2.83 (bs, 2H), 2.21 (s, 3H), 2.17-2.07 (m, 4H), 1.93 (d, J = 15.6 Hz, 2H), 1.66-1.55 (m, 2H), 1.20 (t, J = 7.0 Hz, 3H). LC/MS (RP-C_{18}, 10-99% CH_3CN/0.05% TFA gradient over 5 min) *m/z* 467.2 $[M+H]^+$, retention time 1.97 min.

[0241] Product **9d** (46.4 mg, 0.1 mmol) was mixed with 4-methylphenyl boronic acid (14 mg, 0.1 mmol) in 1 mL of CH_3CN and 1 mL of 2 M aq. Na_2CO_3. The microwave tube was purged with N_2 and 7 mg (10 mol%) of $PdCl_2$(dppf) was added and tube was again purged with N_2, then sealed and microwaved for 20 min at 150 °C. After reaction was complete, organic layer was separated, filtered trough silica gel plug, concentrated and was subjected to reverse-phase HPLC purification (RP-C_{18}, 2-50% CH_3CN/0.1% aq. TFA gradient over 13 min, 35 mL/min) to yield compound no. 58. ^1H NMR (400 MHz, DMSO-d6) δ 9.79 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.53

(d, J = 1.9 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 1.5 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 4.14 (s, 4H), 4.06 (q, J = 7.1 Hz, 2H), 3.58 (m, 3H), 3.19 (q, J = 11.1 Hz, 2H), 2.85 (bs, 2H), 2.34 (s, 3H), 2.29-2.23 (m, 5H), 2.09 (d, J = 12.9 Hz, 2H), 1.96 (d, J = 13.9 Hz, 2H), 1.67-1.57 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H). LC/MS (RP-C_{18}, 10-99% CH_3CN/0.05% TFA gradient over 5 min): m/z 476.2 $[M+H]^+$, retention time 2.36 min.

Example 10:



10a 10b 308

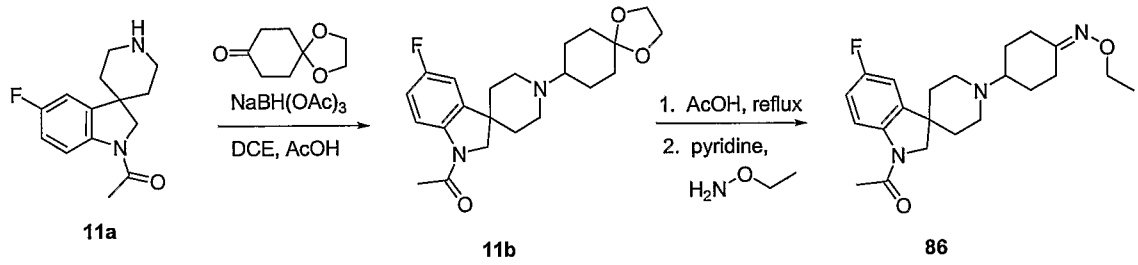
[0242] 1.0 eq of the amine hydrochloride **10a** (416 mg, 1.46 mmol) was suspended in anhydrous 1,2-dichloroethane:1,2-dimethoxyethane (6.0 mL, 1:1 v/v) and treated with 1.0 eq triethylamine (148 mg), followed by 1.5 eq *tert*-butyl 4-oxoazepane-1-carboxylate (467 mg, 2.19 mmol) and 3.0 eq titanium tetraisopropoxide (1.3 mL, 1.26 g, 4.4 mmol). The reaction vial was flushed with nitrogen and stirred at room temperature for 3 days. The reaction was diluted with methanol (6.0 mL), cooled in an ice-H_2O bath and treated with sodium borohydride (110 mg, 2.92 mmol). The reaction was slowly warmed to room temperature and stirred thereafter for 90 min. The reaction was then further diluted with methanol (10 mL), quenched with 1.0 *N* NaOH (5.0 mL) and stirred vigorously at room temperature for 10 min. The suspension obtained was centrifuged (3K rpm, 10 min) and the supernatant concentrated under reduced pressure. The residue obtained was dissolved in dichloromethane (75 mL) and washed successively with H_2O, saturated sodium bicarbonate, and saturated brine, then dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford 704 mg crude product **10b** as a viscous, pale yellow oil. The crude product was used in the next step without further purification. t_R = 2.14 min [10-99% CH_3CN gradient over 5 mins with 0.1% TFA (aq)]; Theoretical $(M+H)^+$ m/z for $C_{25}H_{36}FN_3O_3$ = 446.3; Found 446.4.

[0243] The Boc-protected amine **10b** (573 mg) was dissolved in dichloromethane (5 mL), cooled in an ice-H_2O bath and treated slowly with ice-cold trifluoroacetic acid (5 mL). The reaction was stirred at ~0°C for 1 h, then concentrated under reduced pressure. The oil obtained was dissolved in acetonitrile and re-concentrated under reduced pressure. The crude TFA salt was dissolved in methanol (6.0 mL) and purified by reverse-phase HPLC (2-25% CH_3CN/ 0.1%

TFA gradient over 10 min, 6 x 1.0 mL injected, 35 mL/min). The combined pure fractions were concentrated *in vacuo* to afford 291 mg amine **10c** as the di-TFA salt, as a viscous, colorless oil. Yield (over 2 steps) = 35%. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.83 (br s, 1H), 8.74 (br s, 2H), 8.06 (dd, J = 8.8 Hz, 5.0 Hz, 1H), 7.06 (br m, 1H), 6.97 (br m, 1H), 4.12 (s, 2H), 3.59 (br s, 1H), 3.13 (br m, 6H), 2.36 (m, 1H), 2.20 (s, 3H), 2.13 (m, 5H), 1.89 (m, 5H), 1.71 (m, 1H); t_R = 1.06 min [10-99% CH_3CN gradient over 5 min with 0.1% TFA (aq)]; Theoretical $(M+H)^+$ *m/z* for $C_{20}H_{28}FN_3O$ = 346.2; Found 346.0.

[0244] Deprotected amine **10c** (46 mg, 0.080 mmol, di-TFA salt) was dissolved in anhydrous acetonitrile (750 μL) and treated with 3.0 eq triethylamine (24 mg, 0.24 mmol). The mixture was then treated with ethyl chloroformate (9 μL, 10 mg, 0.096 mmol) and stirred at room temperature for 30 min. The reaction was quenched with methanol (500 μL) and purified by reverse-phase HPLC to provide compound no. 308 (2-40% CH_3CN/0.1% TFA gradient over 10 min, 1.0 mL injected, 35 mL/min). t_R = 1.90 min [10-99% CH_3CN gradient over 5 min with 0.1% TFA (aq)]; Theoretical $(M+H)^+$ *m/z* for $C_{23}H_{32}FN_3O_3$ = 418.2; Found 418.4.

Example 11:



11a **11b** **86**

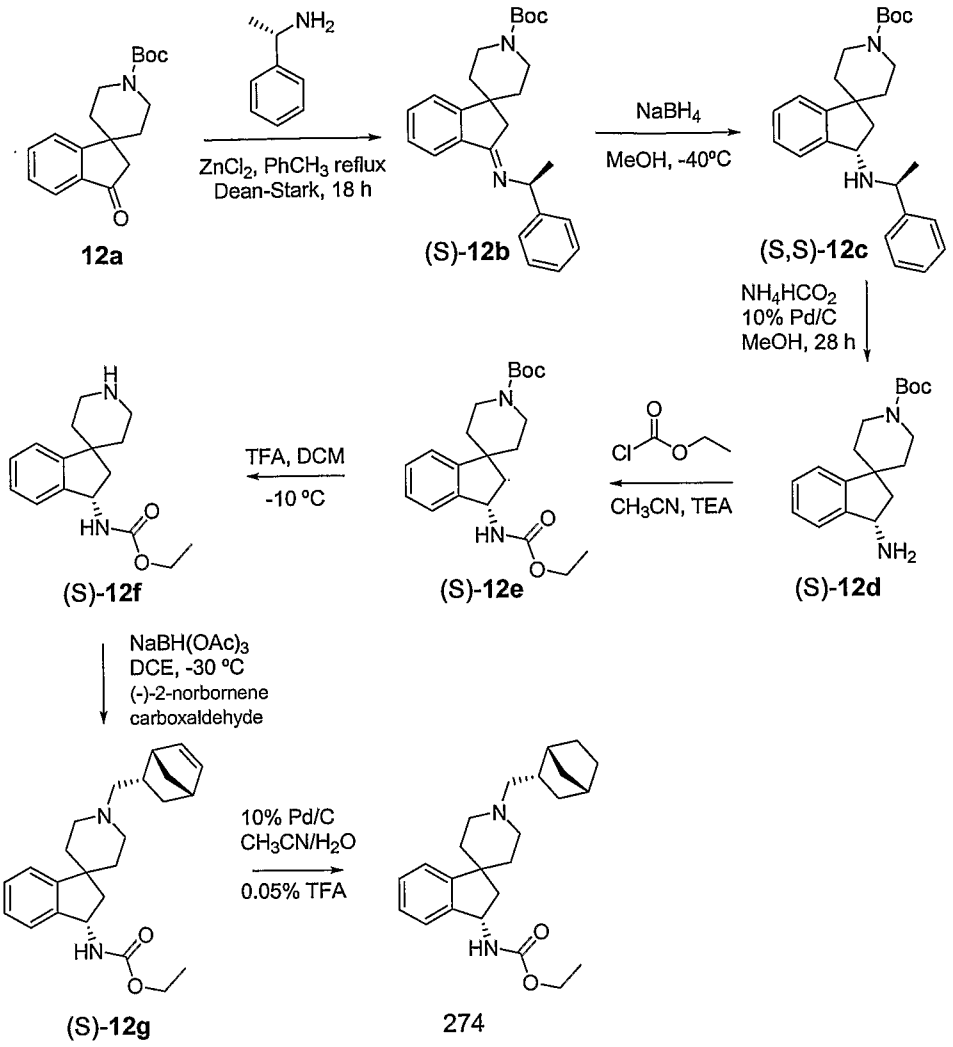
[0245] Spiroindoline **11a** (300.0 mg; 1.21 mmol) and 4-oxocyclohexane spirodioxolane (283.1 mg; 1.81 mmol) were dissolved in DCE (5 mL). After 10 min, $NaBH(OAc)_3$ (512.1 mg; 2.42 mmol) was added, followed by AcOH (69.7 uL; 72.5 mg; 1.208 mmol) and the mixture was allowed to stir at room temperature for 75 h. The reaction was quenched by adding MeOH (10 mL) and was allowed to stir for 24 h. The resulting suspension was diluted with DCM (30 mL) and NaOH 1 N (5mL) was added. The layers were separated, and the aqueous layer was extracted with DCM (3 x 30mL). The combined organic extracts were dried on Na_2SO_4 and concentrated. The white solid residue was suspended in ether, the ethereal suspension was filtered and the precipitate was washed with ether (3 x 20mL) and dried to provide the acetate salt of the desired product **11b** (400 mg, 74% yield). The material was used for the next step without further purification. LC/MS *m/z* 389.2 $[M+H]^+$, retention time 1.73 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.49 (m, 4H), 1.60 (d, J = 13.0 Hz, 2H), 1.72 (d, J = 9.4 Hz, 4H), 1.81 (td, J = 13.4, 2.5 Hz, 2H), 2.19 (s, 3H), 2.28 (t, J = 11.5 Hz, 2H), 2.37 (m, 1H), 2.80 (d, J = 11.5 Hz, 2H), 3.85 (t, J = 2.3 Hz, 4H),

3.95 (s, 2H), 6.97 (td, J = 8.3, 1.8 Hz, 1H), 7.18 (dd, J = 8.8, 2.7 Hz, 1H), 8.02 (dd, J = 8.8, 5.0 Hz, 1H)

[0246] The ketal **11b** (350.0 mg; 0.82 mmol) was dissolved in 80% aq. acetic acid (20 mL) and the solution was refluxed overnight. LC/MS analysis shows complete deprotection of the ketal, along with some deacetylation of the indoline nitrogen. The reaction mixture was diluted with water (20 mL), cooled on an ice bath and neutralized by addition of solid KOH. The resulting suspension was filtered and the precipitate was washed with water (3 x 10mL) and dried to provide the crude product as a tan powder. This material was dissolved in DCM (10 mL) and treated with excess AcCl (1 mL) and triethylamine (1 mL). After stirring at room temperature for 3 h, the mixture was diluted with DCM (30 mL) and washed with saturated $NaHCO_3$. The organic layer was dried on Na_2SO_4 and concentrated to provide the product **11c** as a yellow oil (253 mg, 89% yield), which was used for the next step without further purification. LC/MS m/z 345.0 $[M+H]^+$, retention time 1.43 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min); ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (d, J = 13.3 Hz, 2H), 1.82 (m, 2H), 1.91 (m, 2H), 2.07 (m, 2H), 2.18 (s, 3H), 2.29 (m, 6H), 2.45 (m, 2H), 2.78 (t, J = 9.5 Hz, 1H), 2.97 (d, J = 11.6 Hz, 2H), 3.81 (s, 2H) 6.88 (m, 2H), 8.16 (dd, J = 8.5, 4.8 Hz, 1H).

[0247] The crude ketone **11c** (100.0 mg; 0.29 mmol) was dissolved in pyridine (1 mL) and treated with O-ethyl hydroxylamine hydrochloride (21.3 mg; 0.35 mmol). The vial was sealed and heated to 60 °C for 1 h. The solvent was evaporated under reduced pressure and the residue was dissolved in DMSO (2 mL) and the product oxime compound no. 86 purified by reverse phase HPLC (2-99% CH_3CN-H_2O gradient with 0.03% TFA, 15 min. run). LC/MS m/z 388.4 $[M+H]^+$, retention time 1.87 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min); ^1H NMR (free base, 400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3H), 1.55 (m, 2H), 1.71 (d, J = 13.1 Hz, 2H), 1.94 (m, 5H), 2.14 (m, 1H), 2.25 (s, 3H), 2.30 (td, J = 11.9, 5.6 Hz, 2H), 2.50 (d, J = 14.3 Hz, 1H), 2.62 (t, J = 9.6 Hz, 1H), 2.94 (d, J = 11.8 Hz, 2H), 3.25 (d, J = 14.7 Hz, 1H), 3.86 (s, 2H), 4.07 (q, J = 7.0 Hz, 2H), 6.88 (m, 2H), 8.16 (dd, J = 8.5, 4.8 Hz, 1H).

Example 12:



[0248] The *N*-Boc protected indanone **12a** (6.5 g, 21.6 mmol), (S)-1-phenylethanamine (2.875 g, 23.72 mmol, 1.1 eq), and anhydrous $ZnCl_2$ (88 mg, 0.647 mmol, 0.03 eq) were brought up in 35 mL dry toluene in a 100-mL flask under N_2 atmosphere. The flask was fitted with a Dean-Stark trap and reflux condenser for the removal of water. The reaction mixture was heated at reflux for 18 h. The reaction mixture was cooled, diluted with EtOAc (200 mL), and washed with 0.1 N NaOH (2 × 30 mL), 20% saturated NH_4Cl (1 × 100 mL), and brine (1 × 100 mL). The organic layer was then dried over Na_2SO_4, filtered, and dried down to afford imine (S)-**12b** as a light orange solid. LC/MS analysis of the crude product indicated complete conversion to the desired product. LC/MS (10-99%) *m/z* 405.2 $[M+H]^+$, retention time 2.76 min.

[0249] The crude imine (S)-**12b** (21.6 mmol) was dissolved in anhydrous MeOH (30 mL) and cooled to -40 °C under N_2 atmosphere. $NaBH_4$ (816 mg, 21.6 mmol, 1.0 eq) was added in one portion. The reaction mixture was allowed to warm to -20 °C over 2 h, then warmed to -5 °C for

3 h. The reaction mixture was then diluted with EtOAc (200 mL), then washed with 50% saturated $NaHCO_3$ (100 mL), water (2 × 100 mL), and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered, and dried down to yield (S, S)-**12c** as a colorless oil. The oil was brought up in anhydrous diethyl ether, and 1 eq of ethereal HCl was added to precipitate the product as a fine white solid. The solid was filtered, washed with ether (100 mL), and dried under vacuum to obtain 7.2 of (S, S)-**12c** HCl salt as a white powder (75% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (m, 1H), 9.49 (m, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 7.1 Hz, 2H), 7.29-7.47 (m, 6H), 4.91 (m, 1H), 4.62 (m, 1H), 3.94 (m, 2H), 2.87 (bs, 2H), 2.62 (dd, J = 13.5, 8.0 Hz, 1H), 1.99 (dd, J = 13.5, 7.5 Hz, 1H), 1.92 (dt, J = 12.9, 4.4 Hz, 1H), 1.76 (d, J = 6.7 Hz, 3H), 1.58 (d, J = 12.9 Hz, 1H), 1.42 (s + obscured m, 11H); LC/MS (10-99%) *m/z* 407.4 $[M+H]^+$, retention time 2.70 min.

[0250] (S, S)-**12c** (3.0 g, 6.8 mmol), ammonium formate (8.5 g, 135.4 mmol, 20 eq), and 800 mg 10% Pd/C (wet, 50% by weight) were brought up in MeOH (30 mL) in a 100-mL flask fixed with a N_2 balloon. The mixture was stirred at room temperature for 28 h. The reaction mixture filtered through packed Celite and concentrated in vacuo to ~10 mL. The concentrate was diluted with 50% saturated $NaHCO_3$ (200 mL), and the product extracted into EtOAc (3 × 100 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo to obtain (S)-**12d** as a colorless oil (2.0 g, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (m, 1H), 7.02-7.21 (m, 3H), 4.23 (t, J = 7.7 Hz, 1H), 3.99 (m, 2H), 2.90 (br s, 2H), 2.57 (dd, J = 12.7, 7.3 Hz, 1H), 2.00 (bs, 2H), 1.92 (dt, J = 12.9, 4.5 Hz 1H), 1.42 (s + obscured m, 13H); LC/MS (10-99%) *m/z* 303.2 $[M+H]^+$, 286.2 $[m/z - NH_3]^+$, retention time 2.31 min.

[0251] (S)-**12d** (300 mg, 0.99 mmol) was dissolved in 1.5 mL anhydrous CH_3CN and cooled to 0 °C, followed by ethyl chloroformate (118 mg, 1.09 mmol, 1.1 eq) and triethylamine (200 μL). White precipitate formed upon addition of the triethylamine. The reaction was allowed to warm to room temperature and then stirred for 1 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with 50% saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). The solution was dried over Na_2SO_4, filtered, and dried in vacuo to obtain product (S)-**12e** as a light yellow oil (>90% pure). LC/MS (10-99%) *m/z* 375.2 $[M+H]^+$, retention time 3.43 min.

[0252] The crude (S)-**12e** was dissolved 5 mL CH_2Cl_2 and cooled to 0 °C, followed by the addition of 5 mL TFA. The reaction mixture was stirred at 0 °C for 1 h, diluted with CH_3CN (20 mL), and dried in vacuo to obtain the (S)-**12f** TFA salt. The oil was dissolved in CH_2Cl_2 (30 mL), washed with 0.1 N NaOH (2 × 10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and

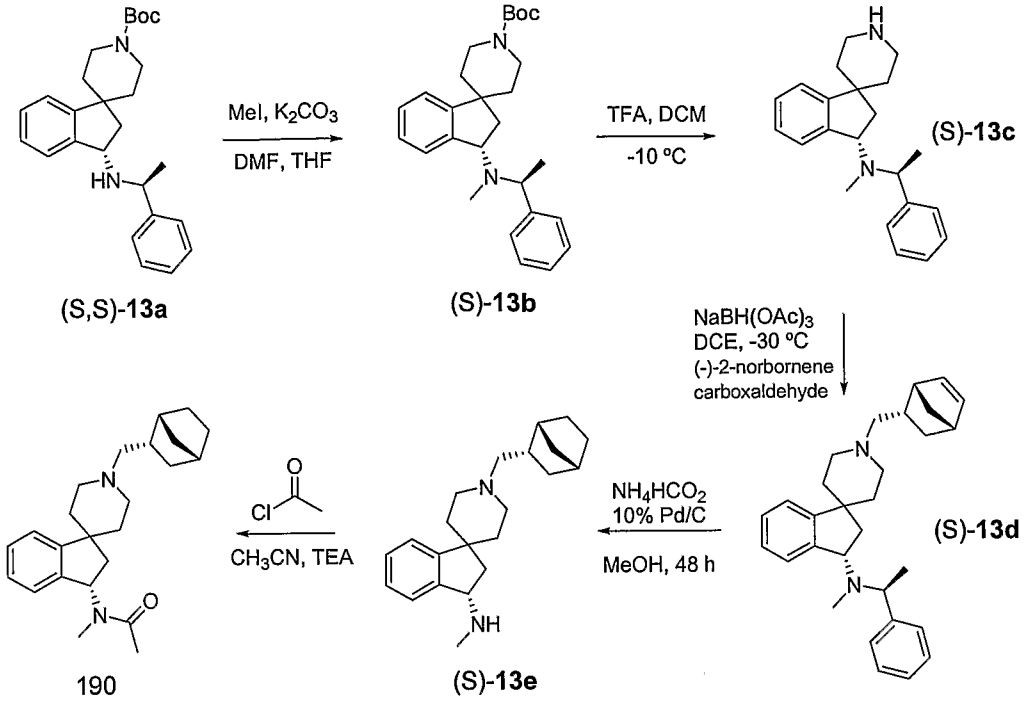
dried in vacuo to obtain the product (S)-**12f** as a light yellow oil (269 mg, 98% yield over 2 steps). LC/MS (10-99%) *m/z* 275.2 $[M+H]^+$, retention time 1.42 min.

[0253] (S)-**12f** (269 mg, 0.98 mmol) was dissolved in cold DCE (1.5 mL) and treated with (1S,2S,4S)-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (119 mg, 0.98 mmol, 1.0 eq), followed by portion-wise addition of $NaBH(OAc)_3$ (300 mg, 1.4 mmol, 1.4 eq). The reaction was allowed to stir at room temperature for 1 h and was then quenched with MeOH (1 mL) and allowed to stir for another 30 min (until gas evolution stopped). The crude reaction mixture was purified by HPLC (10-99 CH_3CN gradient, 0.05% TFA) to provide the desired product (S)-**12g** as the TFA salt. LC/MS (10-99%) *m/z* 381.2 $[M+H]^+$, retention time 2.28 min.

[0254] The combined HPLC fractions (~10 mL) were treated with 10% Pd/C (50 mg, wet, 50% by weight) under H_2 atmosphere with to cleanly provide (S)-**12g** after 2 h of rapid stirring at room temperature. The solution was filtered through a 0.2 micron nylon filter and concentrated to provide 114 mg of compound no. 274 TFA salt (23% over 2 steps). LC/MS (10-99%) *m/z* 383.2 $[M+H]^+$, retention time 2.28 min; ^{1}H-NMR (HCl salt, 400 MHz, DMSO-d_6) δ 10.39 (br s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.25 (m, 4H), 5.11 (m, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.45 (m, 2H), 3.09 (m, 4H), 2.64 (m, 2H), 2.33 (br s, 2H), 2.15 (m, 2H), 1.84 (m, 1H), 1.67 (m, 3H), 1.48 (m, 2H), 1.34 (m, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.14 (m, 1H), 0.88 (m, 1H).

[0255] Spiroindane (R)- compound no. 274 was produced utilizing an analogous synthetic route with the substitution of (R)-1-phenylethanamine for (S)-1-phenylethanamine in the synthesis of intermediate imine **12b** (step 1).

Example 13:



[0256] To a flask containing (S, S)-**13a** (See Example 12, 1.5 g, 3.39 mmol) and K_2CO_3 (1.87 g, 13.54 mmol, 4 eq) was added 2 mL anhydrous DMF followed by 8 mL anhydrous THF. The mixture was treated with MeI (2.40 g, 16.93 mmol, 5 eq) and heated to 45 °C for 6 h, followed by stirring at room temperature for 16 h. The reaction mixture was diluted with EtOAc (200 mL) and washed with 20% saturated NH_4Cl (50 mL), 50% saturated $NaHCO_3$ (50 mL), brine (50 mL). The solution was dried over Na_2SO_4, filtered, and dried in vacuo to yield a reddish oil. The oil was dissolved in diethyl ether and filtered to remove insoluble material, followed by treatment with 1 eq of ethereal HCl. The resulting solution was dried down in vacuo to yield crude (S)-**13b** as a light orange solid. LC/MS (10-99%) *m/z* 421.0 $[M+H]^+$, retention time 2.77 min.

[0257] Crude (S)-**13b** was dissolved in CH_2Cl_2 (50 mL) and cooled to -10 °C, followed by the addition of 10 mL TFA. The reaction mixture was stirred at -10 °C for 1 h, diluted with CH_3CN (20 mL), and dried in vacuo to obtain the (S)-**13c** TFA salt. The oil was dissolved in CH_2Cl_2 (30 mL), washed with 50% saturated $NaHCO_3$ (2 × 10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and dried in vacuo to obtain the product (S)-**13c** as a colorless oil (673 mg, 67% yield over 2 steps). ^1H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.16-7.25 (m, 5H), 4.66 (t, J = 8.0 Hz, 1H), 3.79 (q, J = 6.7 Hz, 1H), 2.99 (app t, J = 12.0 Hz, 2H), 2.79 (dt, J = 12.4, 2.5 Hz, 1H), 2.69 (dt, J = 12.7, 2.3 Hz, 1H), 2.07 (q, J = 8.0 Hz, 1H), 1.97 (dt, J = 13.3, 4.2 Hz, 1H), 1.85 (s, 3H), 1.73 (m, 1H), 1.52 (dt, J = 12.7, 4.2 Hz, 1H), 1.42

(d, J = 6.6 Hz, 3H), 1.36 (app t, J = 12.9 Hz, 3H); LC/MS (10-99%) *m/z* 321.2 $[M+H]^+$, retention time 1.60 min.

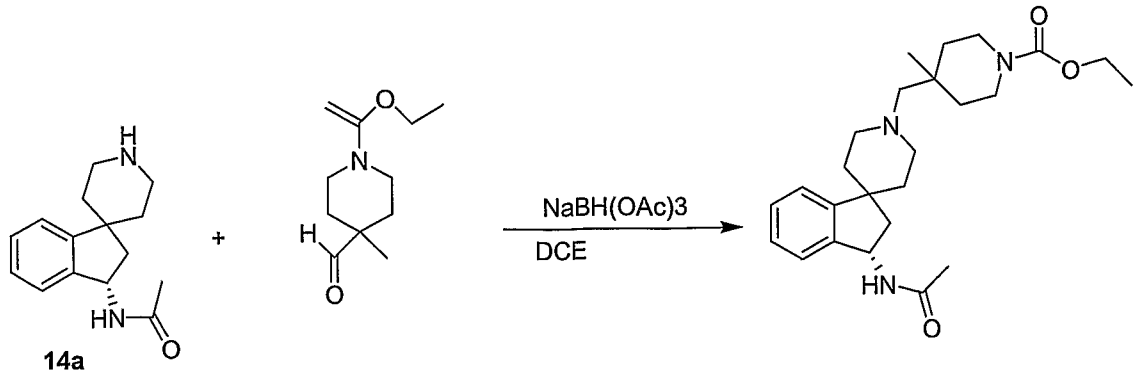
[0258] (S)-**13c** (650 mg, 2.03 mmol) and (1S,2S,4S)-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (262 mg, 2.15 mmol) were dissolved in DCE (13 mL) and the mixture cooled to -30 °C, followed by portion-wise addition of $NaBH(OAc)_3$ (646 mg, 3.05 mmol). The reaction was stirred at -30 °C for 2 h and was the allowed to come to room temperature and stirred for 16 h. The reaction was quenched with MeOH (5 mL) and diluted with EtOAc (200 mL). The crude reaction was washed with 50% saturated $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over Na_2SO4, filtered and dried in vacuo to yield the product (S)-**13d** as a colorless oil (802 mg, 93% yield).

[0259] (S)-**13d** (800 mg, 6.8 mmol), ammonium formate (2.36 g, 37.5 mmol), and 800 mg 10% Pd/C (wet, 50% by weight) were brought up in MeOH (8 mL) in a 25-mL flask fixed with a N_2 balloon. The mixture was stirred at room temperature for 24 h. 1.18 g of ammonium formate were added and the mixture stirred for an additional 24 h. The reaction mixture was filtered through packed Celite, diluted with 50% saturated $NaHCO_3$ (200 mL), and the product (S)-**13e** extracted into EtOAc (5 × 75 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo to obtain (S)-**13e** as a colorless oil (493 mg, 81% yield). LC/MS (10-99%) *m/z* 325.4 $[M+H]^+$, retention time 1.52 min.

[0260] (S)-**13e** (123 mg, 0.38 mmol) was dissolved in 1.5 mL anhydrous CH_3CN and cooled to 0 °C, followed by the additional of acetyl chloride (33 mg, 0.42 mmol) and triethylamine (200 μL). White precipitate formed upon addition of the triethylamine. The reaction was allowed to warm to room temperature and then stirred for 1 h. The crude reaction mixture was purified by HPLC (10-99 CH_3CN gradient, 0.05% TFA) to provide the desired compound no. 190 as the TFA salt (65 mg, 47% yield). LC/MS (10-99%) *m/z* 367.2 $[M+H]^+$, retention time 1.99 min.

[0261] Spiroindane (R) form of compound no. 190 was produced utilizing an analogous synthetic route with the substitution of (R)-1-phenylethanamine for (S)-1-phenylethanamine in the synthesis of intermediate **13a** (See Example 12).

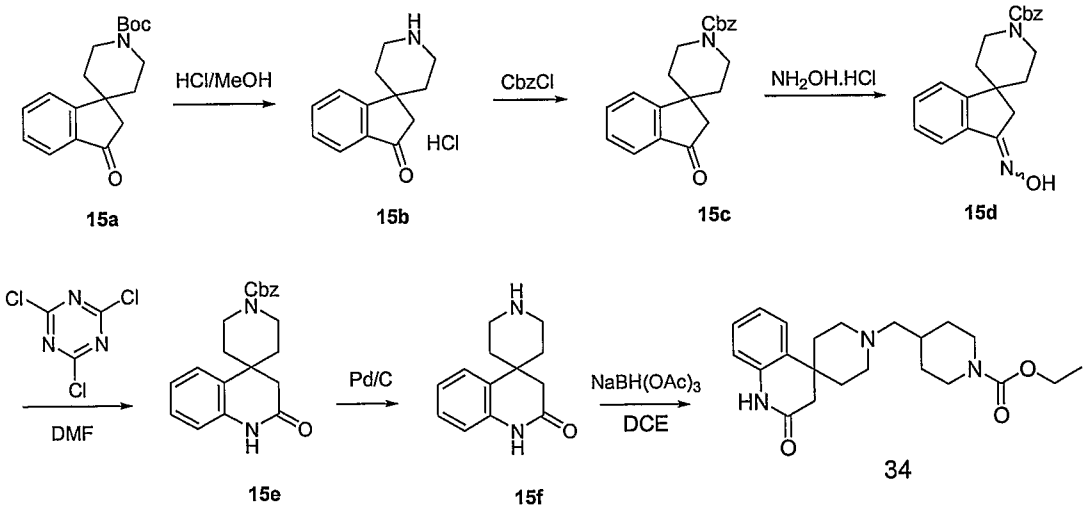
Example 14:



14a 314

[0262] Intermediate **14a** (49 mg; 0.2 mmol) and 4-formyl-4-methylpiperidine-1-carboxylate (40 mg; 0.2 mmol) were dissolved in DCE (2 mL) and $NaBH(OAc)_3$ (85 mg; 0.4 mmol) was added. The reaction was stirred at room temperature for 20 hours. The reaction was diluted with DCM (10 mL) and 1N HCl (20 mL), the layers were separated, and the organic layer was discarded. The aqueous layer was washed with DCM (10 mL) and then was basified with NaOH. The aqueous layer was then washed with EtOAc (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under high vacuum. The crude product compound no. 314 was purified using reversed-phase chromatography (2-99% CH_3CN/H_2O gradient with 0.05% TFA). LC/MS m/z $[M+H]^+$ 428.2, retention time 1.85 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.50 (br s, 1H), 8.26 (d, J = 8.2 Hz, 1H), 7.27 (m, 4H), 5.35 (m, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.69 (m, 2H), 3.53 (m, 2H), 3.31 (m, 2H), 3.18 (m, 5H), 2.69 (m, 1H), 2.07 (m, 1H), 1.89 (s, 3H), 1.66 (m, 3H), 1.50 (m, 4H), 1.19 (overlapping q and s, 6H).

Example 15:



15a 15b 15c 15d 15e 15f 34

[0263] The mixture of *N*-Boc protected spiroindanone **15a** (20 g, 66.4 mmol) and MeOH/HCl (2.5 mol/L, 100 mL) were stirred overnight. After evaporation the residue was washed by petroleum ether to gave the corresponding amine hydrochloride **15b** (15.4 g, 97.6%).

[0264] To a solution of compound **15b** (5.0 g, 24.84 mmol) and Et_3N (7.54 g, 74.53 mol) in CH_2Cl_2 (50 mL) was added drop-wise Cbz-Cl (4.66 g, 27.33 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. The precipitate was filtered, washed with Et_2O and dried to furnish compound **15c** (6.1 g, yield 99%).

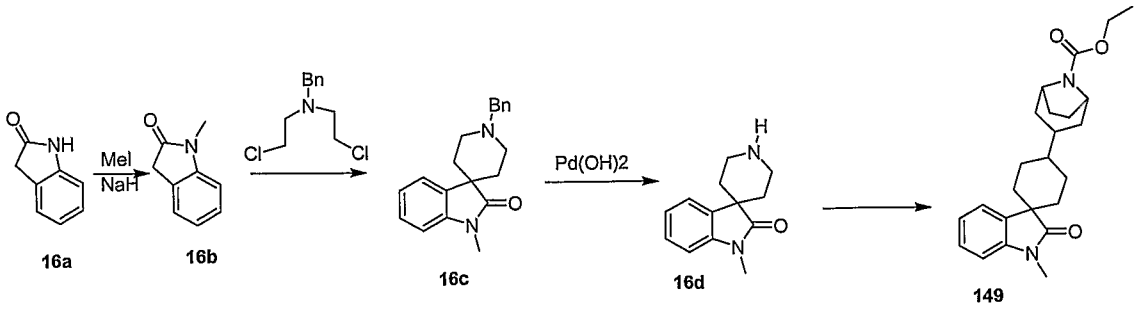
[0265] A solution of compound **15c** (3 g, 10.3 mmol) in EtOH (30 mL) containing $NH_2OH.HCl$ (1.43 g, 20.6 mmol) and NaOAc (1.52 g, 18.53 mmol) was heated under reflux for 1.5 h. The solvent was removed by evaporation and the residue was partitioned between CH_2Cl_2 and water. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated to give compound **15d** (3.14 g, yield 99%), which could be used directly in the next step.

[0266] 2,4,6-trichloro-[1,3,5]-triazine (1.32 g, 7.16 mmol) was added to DMF (9.6 mL) maintained at 25 °C. The reaction was monitored by TLC until TCT was consumed. Then compound **15d** (1.6 g, 4.77 mmol) in DMF (17 mL) was added. After the addition, the mixture was stirred at room temperature overnight. Water was added. The mixture was extracted with EtOAc. The combined organic layers were washed with sat. Na_2CO_3, followed by 1N HCl and brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep HPLC to obtain compound **15e** (260 mg, yield 16%).

[0267] The mixture of compound **15e** (1.2 g, 3.4 mmol) and Pd/C (200 mg) in MeOH (20 mL) was hydrogenated under atmosphere pressure at room temperature for 3 h. The catalyst was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC twice to give **15f** (110 mg, 11 %) as a TFA salt. ^1H NMR ($CDCl_3$) δ 7.65 (d, J=7.5 Hz,1 H), 7.29-7.45 (m, 3 H), 3.45 (d, J= 12.3 Hz, 2 H), 3.20 (t, J= 12.3 Hz, 2 H), 2.96 (s, 2 H), 2.10-2.21 (m, 2 H), 1.70 (d, J= 14.1 Hz, 2 H). MS (ESI) *m/z* 217.06 $[M+H]^+$.

[0268] Amine **15f** (22 mg, 0.1 mmol) and ethyl 4-formylpiperidine-1-carboxylate (28 mg, 0.15 mmol) were dissolved in DCE (1 mL) and $NaBH(OAc)_3$ (42 mg; 0.2 mmol) was added. The reaction was stirred at room temperature for 16 h. The reaction was diluted methanol (0.5 mL), filtered, and compound no. 34 was purified using reversed-phase chromatography (10-99% CH_3CN/H_2O gradient with 0.05% TFA). LC/MS m/z 386.2 $[M+H]^+$, retention time 2.05 min (10-99% CH_3CN-H_2O gradient with 0.03% TFA, 5 min); ^1H NMR (free base, 400 MHz, DMSO-d_6) δ 7.71 (d, J= 3.9 Hz, 2H), 7.61 (d, J= 7.6 Hz, 1H), 7.47-7.41 (m, 1H), 4.05-3.96 (m, 4H), 2.86-2.67 (m, 4H), 2.56 (d, J= 9.7 Hz, 2H), 2.18 (s, 2H), 2.01 (d, J= 7.7 Hz, 4H), 1.73 (d, J= 11.1 Hz, 4H), 1.45 (d, J= 8.7 Hz, 2H), 1.18 (t, J= 7.1 Hz, 3H), 1.03-0.96 (m, 2H).

Example 16:



[0269] A stirred mixture of sodium hydride (60%, 31g, 0.79 mol) in dry xylene (500 mL), under a nitrogen atmosphere, was heated to reflux for 30 min. 1,3-Dihydro-indol-2-one **16a** (100 g, 0.75 mol) was then slowly added via an addition funnel and stirred at reflux for 1.5 hrs. Dimethyl sulfate (104 g, 0.83 mol) was added drop-wise, whereupon the resulting homogeneous solution was refluxed for an additional 2 hrs. After cooling to room temperature, the reaction mixture was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford 1-methyl-1,3-dihydro-indol-2-one **16b** (74 g, 67.3%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.31 (m, 2 H), 7.04 (t, J = 7.5 Hz, 1 H), 6.82 (d, J = 7.8 Hz, 1 H), 3.52 (s, 2 H), 3.21 (s, 3 H).

[0270] A suspension of NaH (60%, 70 g, 0.48 mol) in THF (300 mL) was stirred for 10 min at 0 °C. Then a solution of 1-methyl-1,3-dihydro-indol-2-one **16b** (70 g, 2.88 mol) in THF (200 mL) was added at 0 °C, and the mixture was stirred for 1 h at room temperature. Benzyl-bis-(2-chloro-ethyl)-amine (129 g, 0.48 mol) was added in portions at 0 °C. The mixture was stirred overnight at room temperature, and then was poured into ice-water, extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column on silica gel (P.E./E.A. 2:1) to give compound **16c** (24 g, 16.3%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.42 (m, 7 H), 7.02-7.07 (m, 1 H), 6.83 (d, J = 7.5, 1 H), 3.68 (s, 2 H), 3.19 (s, 3 H), 2.74-2.99 (m, 2 H), 2.66-2.72 (m, 2 H), 1.93-2.01 (m, 2 H), 1.79-1.85 (m, 2 H).

[0271] To a solution of compound **16c** (12 g, 39.2 mmol) in MeOH (100 mL) was added $Pd(OH)_2/C$ (1.5 g, 20%) under N_2. The suspension was hydrogenated under H_2 (50 psi) at room temperature for 4.5 hrs. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the deprotected spiroindolone product **16d** (8 g, 94.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 7.2, 1 H), 7.23-7.27 (m, 1 H), 6.96-7.03 (m, 2 H), 3.04-3.14 (m, 5 H), 2.83-2.89 (m, 2 H), 1.61-1.67 (m, 2 H), 1.45-1.51 (m, 2 H). MS (ESI) *m/z* 217.1 $[M+H]^+$.

[0272] 1.0 eq of deprotected spiroindolone **16d** (22 mg, 0.10 mmol) was dissolved in anhydrous 1,2-dichloroethane:1,2-dimethoxyethane (1.0 mL, 1:1 v/v) and treated with 1.5 *N*-Carbethoxy-4-

tropinone (30 mg, 0.15 mmol), followed by titanium tetraisopropoxide (88 μL, 85 mg, 0.30 mmol). The vial was flushed with nitrogen and stirred at room temperature ~70 h. The reaction was then diluted with methanol (1.0 mL), cooled in an ice-H_2O bath and treated with sodium borohydride (8 mg, 0.20 mmol). After warming to room temperature and stirring for 90 min, the reaction was further diluted with methanol (2.0 mL), quenched with 1.0 N NaOH (500 μL) and stirred vigorously at room temperature for 10 min. The suspension obtained was centrifuged (3K rpm, 10 min) and the supernatant concentrated under reduced pressure. The residue obtained was dissolved in MeOH:acetonitrile (1250 μL, 1:1 v/v), filtered, and purified by reverse-phase HPLC (2-40% CH_3CN/0.1% TFA gradient over 10 min) to yield product compound no. 149. LC/MS (10-99%) *m/z* $[M+H]^+$ 398.2, retention time 1.93 min.

Example 17:

Compound no. 364 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 6.3 Hz, 3H), 1.56 (d, *J* = 11.5 Hz, 2H), 1.67 (q, *J* = 7.0 Hz, 4H), 1.82 (m, 2H), 1.97 (m, 6H), 2.29 (t, *J* = 11.5 Hz, 2H), 2.82 (m, 1H), 2.89 (dd, *J* = 13.7, 6.5 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.35 (d, *J* = 24.4 Hz, 2H), 7.17 (m, 4H).

Example 18:

Compound no. 413 was synthesized using known methods and those described above.

^{1}H NMR (free base, 400 MHz, DMSO-d6) δ 7.20-7.10 (m, 4H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.99-3.96 (m, 2H), 2.84 (t, *J* = 7.3 Hz, 2H), 2.81-2.77 (m, 4H), 2.16 (d, *J* = 4.9 Hz, 2H), 2.06 (t, *J* = 12.2 Hz, 2H), 1.94 (t, *J* = 7.3 Hz, 2H), 1.80 (t, *J* = 11.3 Hz, 2H), 1.74-1.70 (m, 3H), 1.43 (d, *J* = 12.5 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.02-0.93 (m, 2H).

Example 19:

Compound no. 375 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 6.99 (dt, *J* = 12.8, 4.5 Hz, 1H), 6.91 (dd, *J* = 8.0, 2.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 4.1 Hz, 1H), 6.25 (q, *J* = 2.9 Hz, 1H), 6.07 (q, *J* = 2.7 Hz, 1H), 4.50 (s, 2H), 3.51 (t, *J* = 13.2 Hz, 2H), 3.04-2.96 (m, 3H), 2.91-2.84 (m, 2H), 2.74-2.68 (m, 1H), 2.40-2.30 (m, 2H), 2.03-1.97 (m, 2H), 1.88 (d, *J* = 14.2 Hz, 2H), 1.32 (dd, *J* = 33.8, 7.1 Hz, 2H), 0.69 (d, *J* = 11.4 Hz, 1H).

Example 20:

Compound no. 181 was synthesized using known methods and those described above.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.03 (br s, 1H), 7.21 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 4.52 (s, 2H), 3.41 (m, 2H), 3.25 (m, 1H), 3.01 (m, 2H), 2.63 (m, 2H), 2.44 (m, 1H), 2.27 (m, 1H), 1.86 (m, 4H), 1.51 (m, 3H), 1.39 (m, 2H), 1.24 (m, 1H).

Example 21:

Compound no. 23 was synthesized using known methods and those described above.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.27 (br s, 1H), 8.53 (br s, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.88 (s, 1H), 6.72 (d, J = 7.9 Hz, 1H), 3.48 (s, 2H), 3.40 (m, 3H), 3.04 (m, 2H), 2.64 (m, 1H), 2.57 (br s, 1H), 2.38 (m, 1H), 2.26 (m, 1H), 2.24 (s, 3H), 1.94 (m, 2H), 1.78 (m, 2H), 1.55 (m, 3H), 1.39 (m, 3H).

Example 22:

Compound no. 367 was synthesized using known methods and those described above.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.08 (m, 1H), 6.95 (m, 2H), 4.28 (br s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.80 (s, 2H), 3.62 (m, 2H), 3.00 (m, 2H), 2.91 (m, 2H), 2.49 (m, 3H), 1.95-2.02 (m, 6H), 1.69 (m, 2H), 1.48 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H).

Example 23:

Compound no. 370 was synthesized using known methods and those described above.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.65 (br s, 1H), 8.05 (dd, J = 8.9, 4.9 Hz, 1H), 7.06 (td, J = 9.0, 2.7 Hz, 1H), 6.92 (dd, J = 8.3, 2.7 Hz, 1H), 4.27 (br s, 2H), 4.08 (m, 4H), 3.74 (m, 1H), 3.55 (br s, 2H), 3.06 (m, 2H), 2.30 (m, 2H), 2.20 (s, 3H), 2.07 (m, 2H), 1.86 (m, 6H), 1.67 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H).

Example 24:

Compound no. 422 was synthesized using known methods and those described above.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.61 (br s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.96 (s, 1H), 4.06 (s, 2H), 3.96 (m, 3H), 3.59 (s, 3H), 3.51 (m, 2H), 3.11 (m, 2H), 3.00 (t, J = 6.0 Hz, 2H), 2.83 (br s, 2H), 2.47 (m, 1H), 2.28 (s, 3H), 2.18 (s, 3H), 2.11 (m, 1H), 1.88 (m, 2H), 1.77 (m, 2H), 1.13 (m, 2H).

Example 25:

Compound no. 92 was synthesized using known methods and those described above.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.97 (br s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.95 (s, 1H), 4.13 (m, 2H), 4.06 (m, 4H), 3.45 (m, 3H), 3.12 (m, 2H), 2.83 (br s, 2H), 2.43 (m, 2H), 2.28 (s, 3H), 2.19 (s, 3H), 2.17 (m, 2H), 1.82 (m, 2H), 1.64 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H).

Example 26:

Compound no. 412 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 8.05 (q, J = 4.6 Hz, 1H), 7.06 (dt, J = 12.9, 4.5 Hz, 1H), 6.94 (dd, J = 8.3, 2.6 Hz, 1H), 4.13-4.09 (m, 4H), 4.05 (q, J = 7.1 Hz, 2H), 3.50-3.39

(m, 3H), 3.13 (q, J = 11.4 Hz, 2H), 2.83 (bs, 2H), 2.46 (t, J = 13.5 Hz, 2H), 2.20 (s, 3H), 2.16 (d, J = 11.6 Hz, 2H), 1.88 (d, J = 13.8 Hz, 2H), 1.67-1.59 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H).

Example 27:

Compound no. 361 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (t, J = 7.2 Hz, 3H), 1.66 (d, J = 6.5 Hz, 2H), 1.87 (m, 6H), 2.05 (s, 2H), 2.21 (t, J = 12.3 Hz, 2H), 2.87 (s, 6H), 3.05 (m, 2H), 3.52 (d, J = 11.6 Hz, 2H), 3.73 (m, 1H), 3.84 (s, 2H), 4.08 (q, J = 7.1 Hz, 2H), 4.26 (s, 2H), 6.90 (dd, J = 8.3, 2.4 Hz, 1H), 7.00 (m, 2H), 10.38 (br s, 1H).

Example 28:

Compound no. 39 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.25 (t, J = 7.1 Hz, 3H), , 1.66 (qd, J = 12.3, 4.5 Hz, 2H), 1.98 (s, 2H), 2.10 (d, J = 11.8 Hz, 2H), 2.28 (td, J = 14.2, 3.7 Hz, 2H), 2.81 (t, J = 15.9 Hz, 2H), 2.92 (s, 6H), 3.08 (q, J = 11.3 Hz, 2H), 3.38 (dd, J = 13.4, 10.5 Hz, 1H), 3.52 (d, J = 12.3 Hz, 2H), 3.87 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 4.26 (d, J = 12.1 Hz, 2H), 6.97 (m, 3H).

Example 29:

Compound no. 91 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 0.96 (t, J = 7.4 Hz, 3H), 1.66 (m, 4H), 1.98 (s, 2H), 2.10 (d, J = 11.3 Hz, 2H), 2.28 (dt, J = 19.9, 7.2 Hz, 2H), 2.87 (br s, 2H), 2.92 (s, 6H), 3.08 (q, J = 11.2 Hz, 2H), 3.38 (t, J = 12.2 Hz, 1H), 3.52 (d, J = 11.9 Hz, 2H), 3.87 (s, 2H), 4.02 (t, J = 6.6 Hz, 2H), 4.27 (d, J = 12.8 Hz, 2H), 6.97 (m, 3H).

Example 30:

Compound no. 54 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.24 (d, J = 6.2 Hz, 6H), 1.65 (dq, J = 12.3, 4.5 Hz, 2H), 1.99 (s, 2H), 2.09 (d, J = 11.9 Hz, 2H), 2.25 (td, J = 14.2, 3.7 Hz, 2H), 2.81 (t, J = 11.4 Hz, 2H), 2.93 (s, 6H), 3.09 (q, J = 11.3 Hz, 2H), 3.39 (m, 1H), 3.52 (d, J = 12.3 Hz, 2H), 3.87 (s, 2H), 4.26 (d, J = 12.8 Hz, 2H), , 4.86 (heptet, J = 6.2 Hz, 1H), 6.98 (m, 3H).

Example 31:

Compound no. 208 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.67 (dq, J = 12.2, 4.2 Hz, 2H), 2.15 (m, 4H), 2.27 (t, J = 14.2 Hz, 2H), 2.87 (br s, 2H), 2.92 (s, 6H), 3.09 (q, J = 11.3 Hz, 2H), 3.39 (t, J = 12.0 Hz, 1H), 3.52 (d, J = 12.0 Hz, 2H), 3.82 (m, 6H), 3.87 (s, 2H), 4.25 (d, J = 11.2 Hz, 2H), 5.19 (s, 1H), 6.96 (m, 3H).

Example 32:

Compound no. 120 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.67 (dq, J = 12.2, 4.2 Hz, 2H), 2.15 (m, 4H), 2.27 (t, J = 14.2 Hz, 2H), 2.87 (br s, 2H), 2.92 (s, 6H), 3.09 (q, J = 11.3 Hz, 2H), 3.39 (t, J = 12.0 Hz, 1H), 3.52 (d, J = 12.0 Hz, 2H), 3.82 (m, 6H), 3.87 (s, 2H), 4.25 (d, J = 11.2 Hz, 2H), 5.19 (s, 1H), 6.96 (m, 3H).

Example 33:

Compound no. 48 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.69 (dq, J = 12.3, 4.1 Hz, 2H), 1.99 (s, 2H), 2.12 (d, J = 11.5 Hz, 2H), 2.28 (t, J = 14.1 Hz, 2H), 2.87 (brs, 2H), 2.92 (s, 6H), 3.09 (q, J = 11.3 Hz, 2H), 3.40 (t, J = 11.9 Hz, 1H), 3.52 (d, J = 12.3 Hz, 2H), 3.87 (s, 2H), 4.27 (m, 3H), 4.34 (m, 1H), 4.56 (t, J = 3.9 Hz, 1H), 4.68 (t, J = 3.9 Hz, 1H), 6.97 (m, 3H).

Example 34:

Compound no. 352 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.68 (qd, J = 12.3, 4.5 Hz, 2H), 1.85 (t, J = 2.3 Hz, 3H), 1.98 (s, 2H), 2.12 (d, J = 12.1 Hz, 2H), 2.30 (td, J = 14.1, 3.7 Hz, 2H), 2.87 (br s, 2H), 2.92 (s, 6H), 3.08 (q, J = 11.0 Hz, 2H), 3.39 (t, J = 12.1 Hz, 1H), , 3.51 (d, J = 11.8 Hz, 2H), 3.87 (s, 2H), 4.25 (br s, 2H), 4.65 (d, J = 2.1 Hz, 2H), 6.98 (m, 3H).

Example 35:

Compound no. 127 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.68 (qd, J = 12.3, 4.4 Hz, 2H), 1.99 (s, 2H), 2.11 (d, J = 12.3 Hz, 2H), 2.27 (m, 2H), 2.55 (td, J = 6.6, 2.7 Hz, 2H), 2.85 (br s, 2H), 2.92 (s, 6H), 3.08 (q, J = 11.1 Hz, 2H), 3.39 (t, J = 11.9 Hz, 1H), 3.51 (d, J = 12.4 Hz, 2H), 3.87 (s, 2H), 4.15 (t, J = 6.6 Hz, 2H), 4.26 (d, J = 13.2 Hz, 2H), 6.97 (m, 3H).

Example 36:

Compound no. 264 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.67 (qd, J = 12.3, 4.3 Hz, 2H), 1.99 (s, 2H), 2.11 (d, J = 10.6 Hz, 2H), 2.29 (t, J = 14.1 Hz, 2H), 2.87 (br s, 2H), 2.92 (s, 6H), 3.08 (q, J = 10.9 Hz, 2H), 3.34 (s, 3H), 3.40 (t, J = 6.6 Hz, 1H), 3.52 (d, J = 6.3 Hz, 2H), 3.57 (t, J = 4.6 Hz, 2H), 3.86 (s, 2H), 4.18 (dd, J = 5.1, 4.0 Hz, 2H), 4.26 (d, J = 12.7 Hz, 2H), 6.96 (m, 3H).

Example 37:

Compound no. 172 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.71 (qd, J = 12.3, 4.4 Hz, 2H), 1.99 (s, 2H), 2.14 (d, J = 14.4 Hz, 2H), 2.22 (s, 3H), 2.35 (td, J = 14.2, 3.4 Hz, 2H), 2.89 (br s, 2H), 3.10 (q, J = 10.6 Hz, 2H), 3.41 (t, J = 11.4 Hz, 1H), 3.53 (d, J = 12.6 Hz, 2H), 4.06 (s, 2H), 4.28 (m, 2H), 4.35 (t, J = 4.0 Hz, 1H), 4.57 (t, J = 4.0 Hz, 1H), 4.69 (t, J = 4.0 Hz, 1H), 7.01 (m, 2H), 8.14 (dd, J = 8.8, 4.9

Hz, 1H).

Example 38:

Compound no. 102 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.71 (qd, J = 12.3, 4.4 Hz, 2H), 1.85 (t, J = 2.4 Hz, 3H), 1.99 (s, 2H), 2.13 (d, J = 12.2 Hz, 2H), 2.22 (s, 3H), 2.35 (td, J = 14.1, 3.6 Hz, 2H), 2.88 (br s, 2H), 3.09 (q, J = 11.2 Hz, 2H), 3.40 (t, J = 12.0 Hz, 1H), 3.53 (d, J = 12.7 Hz, 2H), 4.06 (s, 2H), 4.26 (br s, 2H), 4.66 (d, J = 2.2 Hz, 2H), 6.99 (td, J = 9.0, 2.7 Hz, 1H), 7.05 (dd, J = 8.6, 2.6 Hz, 1H), 8.14 (dd, 8.7, 4.8, 1H).

Example 39:

Compound no. 62 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.70 (qd, J = 12.2, 4.3 Hz, 2H), 1.99 (s, 2H), 2.13 (d, J = 11.1 Hz, 2H), 2.22 (s, 3H), 2.27 (t, J = 2.6 Hz, 1H), 2.36 (td, J = 14.0, 3.5 Hz, 2H), 2.55 (td, J = 6.6, 2.7 Hz, 2H), 2.87 (br s, 2H), 3.09 (q, J = 10.4 Hz, 2H), 3.40 (t, J = 12.1 Hz, 1H), 3.53 (d, J = 12.3 Hz, 2H), 4.06 (s, 2H), 4.16 (t, J = 6.6 Hz, 2H), 4.28 (d, J = 12.6 Hz, 2H), 6.99 (td, J = 9.0, 2.6 Hz, 1H), 7.05 (dd, J = 8.6, 2.6 Hz, 1H), 8.13 (dd, J = 8.8, 4.9 Hz, 1H).

Example 40:

Compound no. 32 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.72 (d, J = 7.3 Hz, 2H), 1.91 (d, J = 2.5 Hz, 2H), 1.99 (s, 2H), 2.10 (m, 2H), 2.31 (td, J = 14.0, 3.7 Hz, 2H), 2.91 (s, 6H), 2.96 (m, 2H), 3.36 (m, 2H), 3.57 (d, J = 12.4 Hz, 2H), 3.63 (br s, 1H), 3.84 (s, 2H), 4.29 (t, J = 4.0 Hz, 1H), 4.37 (m, 3H), 4.58 (t, J = 3.9 Hz, 1H), 4.70 (t, J = 3.9 Hz, 1H), 6.96 (m, 3H).

Example 41:

Compound no. 200 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.72 (d, J = 7.2 Hz, 2H), 1.85 (t, J = 2.4 Hz, 3H), 1.98 (m, 4H), 2.11 (m, 2H), 2.30 (td, J = 14.0, 3.6 Hz, 2H), 2.91 (s, 6H), 2.96 (br s, 2H), 3.08-3.72 (m, 5H), 3.84 (s, 2H), 4.37 (s, 2H), 4.67 (d, J = 16.6 Hz, 2H), 6.96 (m, 3H).

Example 42:

Compound no. 229 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, CD_3CN) δ 1.66 (br s, 2H), 1.84 (br s, 2H), 1.92 (br s, 2H), 1.98 (br s, 2H), 2.23 (m, 3H), 2.50 (dd, J = 6.4, 2.5 Hz, 2H), 2.84 (s, 6H), 2.93 (m, 2H), 3.08 (m, 2H), 3.50 (d, J = 10.9 Hz, 2H), 3.65 (br s, 1H), 3.77 (s, 2H), 4.11 (s, 2H), 4.30 (s, 2H), 6.90 (m, 3H).

Example 43:

Compound no. 165 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) d 9.73 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.74 (q, J = 1.3 Hz, 1H), 7.65 (q, J = 2.6 Hz, 1H), 7.60 (dd, J = 8.4, 1.7 Hz, 1H), 7.49 (dd, J = 5.0, 1.2 Hz, 1H), 7.45 (d, J = 1.5 Hz, 1H), 4.16-4.10 (m, 4H), 4.06 (q, J = 7.1 Hz, 2H), 3.56-3.49 (m, 3H), 3.19 (q, J = 11.3 Hz, 2H), 2.85 (br s, 2H), 2.28-2.23 (m, 5H), 2.10 (d, J = 12.9 Hz, 2H), 1.96 (d, J = 13.9 Hz, 2H), 1.66-1.57 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H).

Example 44:

Compound no. 406 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.10 (s, 1H), 6.39 (d, J = 10.3 Hz, 1H), 5.78-5.69 (m, 1H), 4.15-4.10 (m, 4H), 4.06 (q, J = 7.1 Hz, 2H), 3.58-3.49 (m, 3H), 3.16 (q, J = 10.8 Hz, 2H), 2.84 (br s, 2H), 2.21 (s, 3H), 2.16-2.07 (m, 4H), 1.93 (d, J = 13.9 Hz, 2H), 1.87 (d, J = 7.2 Hz, 3H), 1.63-1.55 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H

Example 45:

Compound no. 158 was synthesized using known methods and those described above.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.40 (br s, 1H), 8.31 (d, J = 8.2 Hz, 1H), 7.27 (m, 4H), 5.34 (m, 1H), 3.40 (m, 3H), 3.13 (m, 1H), 2.97 (m, 2H), 2.65 (m, 1H), 2.57 (br s, 1H), 2.30 (m, 2H), 1.97 (m, 2H), 1.88 (s, 3H), 1.65 (m, 4H), 1.46 (m, 5H).

Example 46:

Compound no. 182 was synthesized using known methods and those described above.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.43 (br s, 1H), 8.31 (d, J = 8.2 Hz, 1H), 7.28 (m, 4H), 5.34 (m, 1H), 3.96 (br m, 2H), 3.59 (s, 3H), 3.50 (m, 2H), 3.07 (m, 4H), 2.72 (m, 4H), 2.28 (m, 1H), 2.08 (m, 1H), 1.88 (s, 3H), 1.85 (m, 2H), 1.66 (m, 3H), 1.12 (m, 2H).

Example 47:

Compound no. 358 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.34-7.31 (m, 1H), 7.27 (dt, J = 10.1, 3.7 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 7.17 (d, J = 7.3 Hz, 1H), 5.33 (q, J = 7.8 Hz, 1H), 4.26 (m, 2H), 4.08 (q, J = 7.0 Hz, 2H), 3.77-3.70 (m, 1H), 3.52 (t, J = 13.0 Hz, 2H), 3.06 (q, J = 11.5 Hz, 1H), 2.97 (q, J = 11.8 Hz, 1H), 2.61 (dd, J = 13.2, 8.0 Hz, 1H), 2.54-2.47 (m, 1H), 2.15-2.04 (m, 3H), 1.91-1.81 (m, 7H), 1.71-1.66 (m, 5H), 1.22 (t, J = 7.1 Hz, 3H).

Example 48:

Compound no. 191 was synthesized using known methods and those described above.

^{1}H NMR (free base, 400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.18 (dt, J = 10.6, 3.8 Hz, 1H), 6.94 (dt, J = 10.4, 3.8 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 4.03 (q, J = 7.1 Hz,

4H), 2.94-2.88 (m, 2H), 2.79 (s, 2H), 2.72-2.66 (m, 2H), 2.58-2.51 (m, 1H), 1.82-1.75 (m, 4H), 1.64-1.59 (m, 2H), 1.43-1.33 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H).

Example 49:

Compound no. 199 was synthesized using known methods and those described above.

^{1}H NMR ((free base, 400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.17 (dt, J = 10.5, 3.8 Hz, 1H), 6.94 (t, J = 7.1 Hz, 1H), 6.83 (d, J = 7.4 Hz, 1H), 4.18 (m, 2H), 4.05 (q, J = 6.5 Hz, 2H), 2.94-2.84 (m, 3H), 2.63 (t, J = 8.1 Hz, 2H), 1.97-1.83 (m, 3H), 1.78-1.70 (m, 5H), 1.62-1.58 (m, 4H), 1.19 (t, J = 7.1 Hz, 3H).

Example 50:

Compound no. 318 was synthesized using known methods and those described above.

Compound was prepared using reductive amination conditions described above. ^{1}H NMR ((free base, 400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.18 (dt, J = 10.6, 3.8 Hz, 1H), 6.94 (dt, J = 10.4, 3.8 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 3.97 (m, 2H), 2.82-2.77 (m, 4H), 2.56-2.52 (m, 1H), 2.27 (d, J = 6.8 Hz, 2H), 1.84-1.72 (m, 5H), 1.63-1.59 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H), 1.04-0.94 (m, 2H).

Example 51:

Compound no. 104 was synthesized using known methods and those described above.

^{1}H NMR (free base, 400 MHz, DMSO-d6) δ 7.74-7.68 (m, 2H), 7.61 (d, J = 7.6 Hz, 1H), 7.46-7.42 (m, 1H), 6.17-6.15 (m, 1H), 5.97-5.95 (m, 1H), 2.95-2.76 (m, 4H), 2.55 (s, 2H), 2.36-2.28 (m, 1H), 2.09-1.99 (m, 6H), 1.87-1.81 (m, 1H), 1.45 (d, J = 3.9 Hz, 2H), 1.34-1.20 (m, 2H), 0.55-0.51 (m, 1H)

Example 52:

Compound no. 186 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.44 (br s, 1H), 7.07-6.95 (m, 2H), 6.85-6.82 (m, 1H), (tt, J = 28.8, 18.1 Hz, 1H), 4.51 (s, 2H), 4.40-4.31 (m, 4H), 3.74 (q, J = 5.5 Hz, 1H), 3.59-3.40 (m, 4H), 2.98 (q, J = 10.8 Hz, 2H), 2.07-1.93 (m, 8H),1.68 (d, J = 5.5 Hz, 4H).

Example 53:

Compound no. 275 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (br s, 1H), 7.32 (d, J = 2.6 Hz, 1H), 7.16 (dd, J = 8.7, 2.5 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 4.11 (t, J = 5.1 Hz, 2H), 3.38-3.34 (m, 2H), 3.25-3.13 (m, 3H), 2.31-2.23 (m, 2H), 2.08-2.04 (m, 4H), 1.85 (d, J = 13.7 Hz, 4H), 1.63 (d, J = 12.6 Hz, 1H), 1.49-1.39 (m, 2H), 1.34-1.29 (m, 2H), 1.21 (m, 1H)

Example 54:

Compound no. 258 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 9.20 (bs, 1H), 7.30-7.15 (m, 2H), 7.07-6.87 (m, 2H), 3.65-3.35 (m, 5H), 2.66-2.64 (m, 1H), 2.40-2.30 (m, 3H), 2.07-1.98 (m, 1H), 1.92 (d, J = 14.7 Hz, 1H), 1.79 (d, J = 14.3 Hz, 1H), 1.68-1.51 (m, 3H), 1.47-1.38 (m, 3H), 1.27-1.20 (m, 1H).

Example 55:

Compound no. 152 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (br s, 1H), 7.04-6.93 (m, 2H), 6.84-6.80 (m, 1H), 4.53 (s, 2H), 3.47 (d, J = 12.1 Hz, 1H), 3.40-3.38 (m, 1H), 3.24-3.17 (m, 1H), 3.06 (q, J = 11.3 Hz, 2H), 2.19-2.11 (m, 2H), 2.05 (d, J = 10.2 Hz, 2H), 1.94 (d, J = 14.1 Hz, 2H), 1.84 (d, J = 12.9 Hz, 2H), 1.63 (d, J = 12.5 Hz, 1H), 1.46-1.23 (m, 4H), 1.17-1.07 (m, 1H).

Example 56:

Compound no. 288 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (br s, 1H), 7.05-6.92 (m, 2H), 6.85-6.80 (m, 1H), 6.34-6.31 (m, 1H), 4.50 (s, 2H), 4.33 (d, J = 13.4 Hz, 2H), 3.83-3.74 (m, 1H), 3.67-3.51 (m, 3H), 2.95 (q, J = 11.0 Hz, 2H), 2.07-1.85 (m, 8H), 1.74-1.58 (m, 4H), 1.08 (d, J = 6.6 Hz, 6H).

Example 57:

Compound no. 211 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (br s, 1H), 7.06-6.95 (m, 2H), 6.85-6.80 (m, 1H), 5.18 (s, 1H), 4.51 (s, 2H), 4.25 (s, 2H), 3.81-3.71 (m, 5H), 3.58 (d, J = 12.1 Hz, 2H) , 2.98-2.93 (m, 2H), 2.13-1.94 (m, 10H), 1.65 (d, J = 7.4 Hz, 4H).

Example 58:

Compound no. 156 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.56 (br s, 1H), 7.06-6.95 (m, 2H), 6.86-6.80 (m, 1H), 4.51 (s, 2H), 4.26 (s, 2H), 3.57-3.44 (m, 6H), 2.97 (q, J = 11.1 Hz, 2H), 2.08-2.02 (m, 4H), 1.94 (d, J = 13.5 Hz, 4H), 1.70-1.65 (m, 4H).

Example 59:

Compound no. 181 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (br s, 1H), 7.21 (dd, J = 8.5, 2.2 Hz, 1H), 7.08 (d, J = 2.2 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.52 (s, 2H), 3.47-3.21 (m, 3H), 3.10-2.94 (m, 2H), 2.66-2.40 (m, 3H), 2.27 (s, 1H), 1.96-1.83 (m, 4H), 1.56-1.53 (m, 3H), 1.42-1.33 (m, 3H).

Example 60:

Compound no. 178 was synthesized using known methods and those described above.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (br s, 1H), 7.30 (d, J = 2.6 Hz, 1H), 7.18-7.16 (m, 1H), 6.84-6.81 (m, 1H), 4.14-3.99 (m, 2H), 3.46 (d, J = 12.1 Hz, 4H), 3.36-3.31 (m, 2H), 3.20-3.11

(m, 3H), 2.28-2.20 (m, 2H), 2.07-2.00 (m, 4H), 1.88 (d, J = 14.4 Hz, 2H), 1.75-1.64 (m, 2H).

Example 61: Physical Characteristics of Compounds of Formulae (I and II)

Additional compounds having the structures shown in Table 1 were synthesized using known methods and those described above.

Table 2. Physical Characteristics of Compounds in Table 1

Cmd No.	LCMS Plus	LCMS RT
2	327.3	2.8
3	309	1.88
4	379.2	1.99
5	306.2	2.32
6	476.2	2.34
7	309.4	1.93
8	353.3	2.16
9	426.2	1.94
10	519.4	1.92
11	412.2	1.98
12	397.5	2.48
13	328.2	2.05
14	460.5	2.13
15	369.2	2.19
16	508.5	2.2
17	458.4	2.35
18	286	2.13
19	378.2	1.94
20	336.4	2.23
21	484.2	2.2
22	459.4	2.04
23	297.4	1.26
24	524.5	2.44
25	496.5	2.35
26	448.5	2.18
27	359.2	2.09
28	502.2	2.15
29	367.2	2.31
30	462.4	2.53
31	372.2	1.83
32	477.2	2.2
33	476.5	2.29
35	357.2	1.99
36	428.2	2.08
37	307.2	1.01
38	464.2	2.1
39	433.2	2.14
40	546.4	2.53
41	496.4	2.28
42	389.2	2.22
43	411.4	2.31
44	496.5	2.31

Cmd No.	LCMS Plus	LCMS RT
45	496.4	2.29
46	414.5	2.26
47	472.3	2.08
48	451.2	2.1
49	476.2	2.08
50	510.5	2.12
51	365.2	2.11
52	345.2	1.91
53	480.2	2.35
54	447.2	2.22
55	381.2	2.21
56	398.2	2.07
57	498.5	2.28
59	514.4	2.2
60	418.3	2.22
61	400.5	1.89
62	428.2	2.12
63	476.4	2.63
65	448.2	1.77
66	550.4	2.6
67	472.3	2.06
68	395	2.6
69	512.5	2.41
70	387.2	2.02
71	414.2	1.98
72	325.5	1.94
73	510.3	2.4
74	428.2	2.19
75	347	1.57
76	460.5	2.11
77	484.2	2.3
78	476	2.34
79	418.3	2.24
80	532.5	2.33
81	410.3	2.27
82	460.5	2.12
83	526.6	2.09
84	480.2	2.28
85	331.3	1.98
87	498.5	2.29
88	483.3	2.15
89	547.4	2.49

Cmd No.	LCMS Plus	LCMS RT
90	490.4	2.16
91	447.2	2.23
92	400.3	2.16
93	544.5	2.29
94	444.5	2.29
95	399.2	2.31
96	488.7	2.25
97	460.5	2.95
98	432.5	2.33
99	405.2	2.36
100	467.4	2.41
101	351.2	2.11
102	428.2	2.18
103	466.4	2.09
104	308.2	2.08
105	463.4	1.45
106	516.5	2.61
107	377.4	2.29
108	473.4	2.35
109	384.3	1.72
110	297.5	1.7
111	315.3	1.65
112	544.5	2.3
113	390.2	1.76
114	448.4	2.37
115	516.5	2.51
116	397.3	2.59
117	520.5	2.33
118	353.4	2.62
120	475.2	2.05
122	492.5	2.53
123	415.2	2.29
124	443	2.33
125	528.3	2.6
126	462.4	2.23
127	457.4	2.19
128	452.2	2.06
129	404.5	2.09
130	501.3	2.21
131	373.2	2.31
132	404.4	1.76
133	429	2.39

Cmd No.	LCMS Plus	LCMS RT
134	399.2	2.02
135	333.2	1.47
136	430.2	2.07
137	414.4	1.99
138	339.3	1.97
139	398.2	2.21
140	430.5	2.29
141	420.2	1.95
142	432.4	2.08
143	341.2	1.78
144	467.4	1.78
145	448.2	2.36
146	480.2	2.24
148	494.5	2.56
150	492.4	2.25
151	426.3	2.32
152	290	2.16
153	370.3	1.6
154	419.2	2.03
155	305.2	1.88
156	375	1.92
157	319.2	2
158	339.3	1.92
159	341.3	2.96
160	417.5	2.35
161	353.3	2.25
162	532.5	2.33
163	343	2.03
164	344	2.56
165	468.2	1.16
166	500.5	2.78
167	446.4	2.12
168	436.2	1.84
169	495.4	2.27
170	480.3	2.93
171	339.3	1.92
172	422.2	2
173	420.2	2.07
174	456.5	2.4
175	302.3	2.16
176	393.2	2.42
177	540.4	2
178	322.4	2.17
179	470.5	2.51
180	351.3	2.22
181	318	2.38
182	400.2	1.86
183	313	1.46
184	341.2	1.87

Cmd No.	LCMS Plus	LCMS RT
185	351.4	1.86
186	425	2.15
187	331	1.89
188	501.3	2.19
189	552.6	2.52
191	358	1.68
192	488.3	2.25
193	492.4	2.25
194	460.4	2.49
195	516.5	2.56
196	327.2	1.62
197	525.6	2.44
198	544.5	2.3
199	384.2	2.06
200	483.4	2.35
202	432.5	2.31
203	388.2	2.12
204	302.3	2.14
205	412	1.86
206	329.5	0.92
207	316.2	2.45
208	406.4	2.29
209	475.2	2.04
210	345.2	1.94
211	419.4	2.12
212	431.4	1.96
213	351.2	2.11
214	456.5	2.38
215	491.2	2.25
216	532.5	2.33
217	410.2	2.26
218	351.2	2.11
219	388.2	2.04
220	462.4	2.54
221	504.4	2.14
222	510.4	2.35
223	461.4	2.24
224	317	1.8
225	470.5	2.43
226	373	2.23
227	389.2	2.28
228	403.2	1.93
229	446.2	2.21
230	483.4	2.3
232	375	2.08
233	552.5	2.25
234	463.2	1.49
235	432.5	2.24
236	399.2	2.03

Cmd No.	LCMS Plus	LCMS RT
238	308.2	2.09
239	303.3	1.73
240	345.2	2.28
241	NA	NA
242	313.2	1.88
243	544.5	2.31
244	297.5	1.59
245	426.2	2.05
246	395.2	2.28
247	431.5	2.46
248	359.2	2.08
249	418.4	1.98
250	414.4	1.91
251	357.2	1.99
252	414.5	2.35
253	487.4	2.18
254	444.4	2.23
255	459.4	2.02
256	434.4	2.05
257	308.2	2.09
258	409.2	2.68
259	297.2	1.78
260	467.4	1.74
261	355.4	1.94
262	496.4	2.25
263	294.4	2.33
264	297.4	1.24
265	463.2	2.04
266	432.4	2.04
267	484.2	2.27
268	333.5	1.84
269	418.3	2.23
270	446.4	2.29
271	424.2	2.38
272	283.3	1.34
273	403.4	2.17
275	383	2.47
276	320.2	2.37
278	411.2	2.12
279	442.5	2.08
280	341.2	1.85
281	472.4	2.44
282	446.4	2.24
283	403.5	2.21
284	434.5	2.05
285	383.2	2.53
286	417.5	2.36
287	474.3	2.58
288	336.4	2.17

Cmd No.	LCMS Plus	LCMS RT
289	402.4	2.16
290	475.2	1.89
291	339.5	0.51
292	392.2	2.13
293	430.5	2.14
294	480.5	2.48
295	530.2	2.55
296	473.4	2.11
297	516.5	2.65
298	526.6	2.57
299	291	0.45
300	316.2	1.44
301	426.2	1.98
302	484.5	2.61
303	432.5	2.13
304	532.3	2.31
305	351.3	2.22
306	428.5	2.38
307	418.4	1.84
309	418.4	1.9
310	388.5	1.66
311	486.5	2.3
313	294	2.33
315	428	1.85
316	428.2	1.95
317	418.6	1.97
318	426.3	2.1
319	372.2	1.79
320	403.2	2.23
321	457.2	2.07
322	430.2	1.94
323	339.1	1.92
324	432.4	2.14
325	289.2	0.77
326	383.2	2.3
327	386	1.92
328	331.2	2.11
329	500.3	2.86
330	480.2	2.38
331	467.4	2.01
332	397.27	1.79
333	319.2	1.86
334	313	2.01
335	484.2	2.34
336	426	1.96
337	353.2	1.84
338	431.4	1.97

Cmd No.	LCMS Plus	LCMS RT
339	367.3	2.3
340	416.2	1.76
341	347	2.41
342	285.3	1.65
343	316.8	1.64
344	502.4	2.17
345	470.5	2.48
346	458.4	2.35
347	397.2	2.47
348	331.3	1.96
349	494.3	2.3
350	297.3	1.04
351	404.5	1.9
352	344	0.7
353	457.4	2.22
354	437.2	2.48
355	411.4	2.31
356	417.4	1.94
357	403	2.19
358	341.2	1.77
359	426	1.79
360	473.4	2.35
361	516.5	2.5
362	459.2	1.96
363	445.3	2.08
364	424	1.8
365	369.2	2.41
366	369.2	2.14
367	355.2	2.02
368	401.25	1.75
369	332.2	2.4
370	452.2	2.19
371	430.2	1.94
372	313.1	1.55
373	487.4	2.19
374	390.3	1.98
375	271.2	0.59
376	314	2.39
377	315.3	1.66
378	419.2	1.97
379	482.5	2.55
380	414.5	2.28
381	404.4	1.75
382	411.4	2.75
383	452.3	2.17
384	466.4	2.23
385	369	2.19

Cmd No.	LCMS Plus	LCMS RT
386	460.5	2.51
387	331	1.78
388	508.5	2.21
389	470.5	2.5
390	458.5	2.12
391	420.3	2.08
392	351.2	2.11
393	345.2	2.03
394	408.2	1.72
395	432.4	2.01
396	502.2	2.34
397	311.3	1.72
398	442.5	2.08
399	428.2	2.06
400	368	1.97
401	510.4	2.27
402	516.5	2.51
403	456.5	2.17
404	428.3	2.36
405	504.5	2.53
406	505.4	1.81
407	426	2.1
408	351.2	2.11
409	486.5	2.7
410	484.2	2.3
411	552.5	2.25
412	444.4	1.81
413	404.5	2.11
414	357.2	2.39
415	322.4	2.15
416	301.2	1.23
417	446.2	2.04
418	446.3	2.02
419	444.5	2.18
420	297.5	1.61
421	351.2	2.11
422	504.5	2.51
423	400.5	2.16
424	446.3	2.01
425	399.2	2.31
426	452.4	2.28
427	434.4	2.21
428	476.2	2.09
429	316.2	1.4
430	400.3	1.88

Example 62: ASSAYS

Functional mobilization of intracellular calcium to determine muscarinic receptor activity:

[0273] CHO cells expressing muscarinic receptors (M_1 to M_5) are grown as monolayers in tissue culture flasks at 37° C in a humidified atmosphere containing 5% CO_2 and passaged every 3-5 days. The growth media is Dulbecco's modified eagles medium (DMEM, Gibco Cat# 12430-054), containing 25 mM Hepes and supplemented with Fetal Bovine Serum (Hyclone, cat# SH30071.03), 0.1 mM of MEM non-essential amino acids (GIBCO, Cat# 11140-050), 1 mM MEM Sodium Pyruvate (GIBCO Cat# 11360-070) and 100 units/ml of Penicillin G and 100 μg/ml of Streptomycin (GIBCO Cat# 15140-122). The recombinant muscarinic receptor cell lines are grown under antibiotic pressure with media containing 25 μg/ml zeocin and 500 μg/ml G418 (M1-CHO), 4 μg/ml puromycin, 50 μg/ml zeocin and 2.5 μg/ml blasticidin (M2 and M4-CHO) or 50 μg/ml zeocin and 4 μg/ml puromycin (M3 and M5-CHO).

[0274] Cells are harvested at 80-90% confluence using Versene (GIBCO Cat# 15040-066), collected by centrifugation and seeded 18-24 hrs prior to running the calcium assay at a density of 5,000-10,000 cells/well in back-walled, clear-bottomed 384-well plates (BD Biocoat, poly-D-lysine, Cat#356663). The day of the experiment, the cells are washed with a plate washer (Bioteck Instruments, ELX 405) using bath1 buffer (140-mM NaCl, 4.5-mM KCl, 2-mM $CaCl_2$, 1-mM $MgCl_2$, 10-mM Hepes-Na, 10-mM Glucose, pH 7.4, with NaOH) containing 1 mM Probenecid. Next, the calcium dye Fluo-3 (25 μl/well of Fluo-3 AM at 4 μM, Molecular Probes F-1241, in Bath 1 buffer containing 1 mM Probenecid) is added to the 25 μl of Bath 1 remaining in each well after the plate wash and the dye is loaded at 37°C in the tissue culture incubator for 60-90 min. The fluorescent dye is removed using the plate washer with Bath 1 containing 1 mM Probenecid, leaving 25 μl/well of this solution after the wash. Alternatively, cells can be loaded with the calcium indicator from Molecular Devices (Calcium 3 Assay Reagents, Cat # R7181) adding 5 μl of a 5X solution dye in Bath 1 containing 1 mM Probenecid (10 ml per dye flask cat# R7182 to generate a solution 20X) to 20 μl of the same buffer. After loading for 60 min, the experiment can be run without having to remove the dye.

[0275] Compounds are prepared at a 2x fold concentration in a 96-well plate (round bottom, Costar Corning cat# 3656), by reconstituting the pre-spotted compounds in bath 1 containing 1 mM probenecid. The final concentration DMSO is 0.5 %, and the amount of DMSO is normalized across the assay plate. To determine an agonist action of the compounds on muscarinic receptors, the reconstituted compounds are added (25 μl compound/well) to the cell assay plate (containing 25 μl/well) using the multi-channel robotic system of the FLIPR 3 Instrument (Molecular Devices, Sunnyvale, CA). To determine a functional inhibitory action of the compounds on muscarinic receptors, the reconstituted compounds are added (25 μl

compound/well) to the assay plate and pre-incubated for 15 min prior to adding 25 μl of Carbachol at 3X the EC80 for each muscarinic subtype. Alternatively, the compounds can be co-applied simultaneously with the agonist. In both assay modes, the fluorescence is recorded for 60 sec (excitation wavelength is 488 nM and emission wavelength 540 nm) using the FLIPR 3 instrument.

[0276] The potency, efficacy and selectivity of the muscarinic compounds were evaluated by screening the compound activity across the whole family (M_1 to M_5 cells). Compounds were also screened for activity on other proteins such as other GPCRs and ion channels to determine selectivity on M4 receptors.

[0277] The compounds of the present invention were found to modulate the M_1 and/or M_4 muscarinic receptors selectively over the other receptor types.

[0278] Examples of activities and efficacies of the muscarinic compounds of formulae (I and II) on modulating M_1 and M_4 receptors are shown below in Table 2. The compound activity for the M_1 and M_4 receptor is illustrated with "xxx" if activity was measured to be less than 0.1 μM, "xx" if activity was measured to be between 0.1 μM and 1.0 μM, and "x" if activity was measured to be greater than 1.0 μM. The efficacy for M_1 and M_4 modulation is illustrated with "xxx" if efficacy was calculated to be greater than 85 %, "xx" if efficacy was calculated to be between 85% and 65%, and "x" if efficacy was calculated to be less than 65 %.

Table 2. Compound activities and efficacies for modulating M_1 and M_4 receptors

Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
1	+	++	++	+++
2	+	+	++	+
3	+	++	++	++
4	+	++	++	+
5	++	++	++	++
6	+	+	+	+
7	+	+	++	++
8	+	++	++	+
9	+++	++	+++	++
10	+	+	++	+
11	+++	+++	++	++
12	+	+	++	++
13	++	++	+	+
14	+	+	+	+
15	++	++	++	+
16	++	++	++	+
17	+	+	+++	+
18	+	+	+	+
19	+++	+++	+++	++
20	+	+	+	+
21	++	++	++	++
22	++	++	++	++

Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
23	+	++	++	++
24	++	++	++	++
25	++	++	++	++
26	+	+	++	++
27	+	+	++	+
28	++	+++	+++	++
29	+	++	+	+
30	+	+	++	++
31	++	++	+++	+++
32	++	++	++	++
33	++	++	++	++
34	+++	+++	++	++
35	+	++	++	++
36	+	+	+	+
37	+	+	++	++
38	++	++	+++	+++
39	+++	+++	++	++
40	++	++	++	++
41	+	+	++	+
42	+++	+++	+++	++
43	++	++	++	+
44	++	++	++	++

Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
45	+	++	++	++
46	++	+++	++	+++
47	++	++	++	+
48	++	++	++	+++
49	++	++	++	++
50	+++	+++	+++	++
51	+	+	+	+
52	+	+	++	++
53	+	+	++	+
54	++	++	++	++
55	+	+	+	+
56	+++	+++	+++	++
57	+	+	++	+
58	+	+	++	++
59	+	+	+	+
60	+++	+++	+++	+++
61	+++	++	+++	+
62	++	+	++	+
63	+	+	++	+
64	++	+	++	+
65	+	+	++	+
66	+	+	++	+
67	++	++	++	+
68	++	++	+	+
69	++	++	++	+
70	++	+++	++	++
71	+	++	++	++
72	+	+	+	+
73	++	++	+	+
74	+++	++	+++	++
75	+	+	+	+
76	++	++	++	+
77	+	+	++	+
78	+	+	++	+
79	++	++	++	+
80	++	++	++	++
81	++	+++	++	++
82	+	+	+	+
83	+	++	++	++
84	+	+	++	+
85	++	++	++	++
86	+++	++	+++	++
87	++	++	++	+
88	++	++	+++	++
89	++	++	++	++
90	++	+++	++	++
91	++	++	++	++
92	+++	++	++	++
93	++	++	++	++
94	++	++	++	+
95	++	++	++	+
96	++	++	++	+
97	++	++	++	+
98	+	+	+	+
99	+++	+++	+++	++
100	+	+	+	+

Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
101	+	++	++	+
102	++	++	+++	+++
103	+++	+++	++	++
104	++	++	++	++
105	+	+	++	++
106	+	++	++	+
107	+++	+++	+++	+++
108	++	++	++	++
109	+++	+++	+++	++
110	+	++	++	++
111	+	++	++	++
112	++	++	++	+
113	+	+	+	+
114	+	+	+++	++
115	++	++	++	++
116	+	+	+++	+
117	++	++	++	++
118	++	++	++	++
119	++	++	++	++
120	+	+	++	+
122	++	++	++	+
123	+++	+	+	+
124	+++	++	++	+
125	+	++	++	+
126	+	+	++	++
127	++	++	++	++
128	++	+	++	+++
129	++	++	++	++
130	++	++	++	++
131	++	+	+++	+
132	++	+	+++	++
133	++	+	+	+
134	+	+	+	+
135	+	+	+	+
136	++	+	++	+
137	+++	++	++	++
138	+	+	++	+
139	++	++	++	++
140	++	+	+	+
141	+++	+++	++	++
142	++	++	++	++
143	+	++	++	+
144	+	+	+++	++
145	++	+	++	++
146	+	+	++	++
147	++	++	++	++
148	+	+	+	+
149	+++	+++	+++	++
150	+	+	++	+
151	++	+	+	+
152	++	++	++	++
153	+++	++	+++	++
154	++	++	+++	+++
155	++	++	++	++
156	++	++	++	++
157	+	++	+	++

Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
158	+	++	++	+++
159	+	++	+	+
160	+	+	+	+
161	++	+++	++	++
162	++	++	++	++
163	+	+	+	+
164	+	+	++	+
165	+	+	++	++
166	+	++	++	+
167	+++	+++	+++	++
168	++	++	++	++
169	++	+	+++	+
170	++	++	++	+
171	+	+	+	+
172	++	+	+++	++
173	++	++	+++	++
174	++	+	++	+
175	+	+	++	++
176	++	+++	+++	+++
177	+	+	++	++
178	++	+	++	++
179	++	++	++	++
180	+	++	+	++
181	++	+	++	++
182	++	+++	++	+++
183	++	++	++	++
184	+	++	++	++
185	++	+++	++	++
186	+++	+++	++	+
187	+	+	+	+
188	++	++	++	++
189	++	++	++	++
190	++	+++	++	++
191	++	++	++	++
192	++	++	++	+
193	+	+	+++	++
194	+	+	++	+
195	++	++	++	+
196	+	+	++	+
197	++	++	+++	++
198	++	++	++	++
199	+++	++	+++	++
200	+++	+++	+++	+++
202	++	++	++	+
203	+	+	+	+
204	+	++	++	++
205	++	++	++	++
206	+	+	++	+
207	++	++	++	++
208	+	+	++	++
209	+	+	++	+
210	+	++	++	++
211	+	+	++	+
212	++	++	++	+
213	++	+++	++	++
214	++	++	++	++

Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
215	+	+	++	++
216	++	++	++	++
217	++	++	++	+
218	++	+++	++	++
219	++	++	++	++
220	+	+	++	++
221	+	+	+++	++
222	+	++	++	++
223	++	++	++	++
224	+	++	++	+++
225	+++	++	++	++
226	+	+	+	+
227	++	+++	++	++
228	++	+	+++	+
229	+++	+++	+++	+++
230	++	++	++	++
231	+	+	+	+
232	+	+	++	++
233	++	+	++	+
234	+	+	+	+
235	++	++	++	+
236	+	+	+	+
237	++	++	++	+++
238	++	+	++	+
239	+	+	+	+
240	+	+	++	+
241	+	++	+	+
242	+	+	++	++
243	++	++	++	+
244	+	+	++	++
245	++	++	++	+++
246	+	++	+	+
247	+	+	+	+
248	+	+	+	+
249	+++	+++	+++	+++
250	+++	+++	+++	+++
251	+	++	++	+
252	++	+	++	+
253	+	+	++	++
254	++	++	++	++
255	++	++	+++	++
256	++	++	++	++
257	+	+	++	++
258	++	+	+	+
259	+	+	++	++
260	+	+	+++	++
261	+	++	+	+
262	+	+	++	++
263	++	++	++	++
264	+	+	++	++
265	++	++	++	++
266	++	+	++	+
267	+	+	++	++
268	+	+	+	+
269	++	++	++	+
270	++	++	+++	++

Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
271	++	++	++	+
272	+	+	++	++
273	+	+	+	+
274	+	+	++	++
275	++	++	++	+
276	++	++	++	++
277	+	+	+	+
278	+++	++	++	+
279	+	+	+	+
280	+	+	++	+
281	+	+	++	+
282	+	+	++	+
283	++	++	++	+
284	++	++	++	+
285	+	++	++	+
286	++	++	++	+
287	+	+	+	+
288	+	+	+	+
289	++	++	++	+
290	++	+	+++	++
291	+	++	++	++
292	+	+	+	+
293	++	++	++	+
294	++	++	++	++
295	+	+	++	++
296	++	++	++	+++
297	++	++	++	++
298	+	++	++	+
299	+	+	++	++
300	+	+	++	+
301	++	++	++	++
302	+	++	++	+
303	+++	+++	+++	+++
304	++	++	++	+
305	++	+++	++	++
306	+	+	+	+
307	++	++	+++	+++
308	++	++	++	++
309	++	++	+++	+++
310	+++	+++	+++	++
311	+	++	++	+
312	++	++	++	++
313	+	+	+	+
314	+	++	+++	+++
315	+++	+++	++	+++
316	+++	+++	++	++
317	++	++	+++	++
318	+++	++	+++	++
319	++	+++	+++	+++
320	++	+	++	+
321	++	+	+++	++
322	+	+	++	++
323	+	+	+	+
324	++	++	++	+
325	++	+++	++	++
326	++	++	++	++

Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
327	++	++	+++	+++
328	++	++	++	+
329	+	+	++	++
330	+	+	++	+
331	++	++	+++	++
332	++	++	++	++
333	++	+++	++	++
334	++	+	++	+
335	++	+	++	+
336	++	++	++	+
337	++	++	++	++
338	++	+	++	+
339	++	+++	+	+
340	++	++	++	++
341	++	+	+++	+
342	+	+	++	+
343	+	+	+	+
344	++	++	++	++
345	++	++	++	+
346	++	++	++	++
347	+	++	++	+
348	+	++	++	++
349	++	++	++	++
350	+	++	++	++
351	+++	+++	+++	++
352	++	++	+++	++
353	++	+++	++	+++
354	+	+	++	+
355	++	++	++	+
356	+++	+++	+++	+++
357	++	+++	++	+++
358	+	+	+	+
359	+++	+++	++	++
360	++	++	++	++
361	++	++	++	++
362	+++	+++	+++	++
363	++	++	+	+
364	+++	+++	++	+++
365	+++	+++	++	++
366	+	+	+	+
367	++	++	+	+
368	+++	+++	+++	++
369	++	+	++	++
370	++	++	++	+
371	+++	+++	+++	++
372	+	+	+	+
373	+	+	++	+
374	++	++	++	++
375	+	+	++	++
376	++	+++	++	++
377	++	++	++	++
378	++	++	++	+
379	++	++	++	+
380	++	++	++	+
381	+	+	++	++
382	+	+	++	+

Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
383	++	++	++	+
384	+	+	++	+
385	++	++	++	++
386	++	++	++	+
387	+	+	++	++
388	++	++	++	+
389	++	++	++	+
390	++	++	++	++
391	+++	+++	+++	++
392	+	++	++	++
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395	++	+	++	+
396	+	+	+++	++
397	+	++	++	++

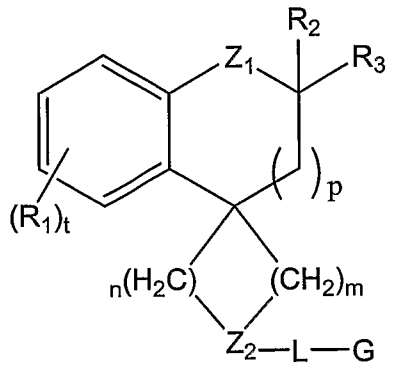
Cmd No.	M_1 Activity	M_4 Activity	M_1 Efficacy	M_4 Efficacy
398	++	+	+	+
399	++	++	+	+
400	+	+	+	+
401	+	+	+++	++
402	++	++	++	+
403	+	+	+	+
404	+	+	+	+
405	++	++	++	++
406	+	+	++	+
407	++	++	+++	+++
408	+	+	+	+
409	++	++	+++	++
410	+	+	++	+
411	++	++	++	+

OTHER EMBODIMENTS

[0279] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method of modulating activity of a muscarinic receptor, comprising the step of contacting said receptor with a compound of formula (I)



(I)

or pharmaceutically acceptable salts thereof, wherein

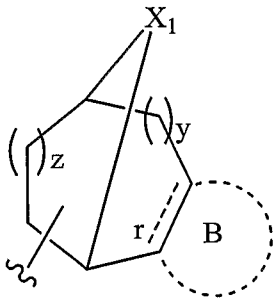
Each of R_1, R_2, R_3 is independently Q_1 or Q_2, or R_2 and R_3 together form oxo;

Z_1 is $-C(Q_1)_2-$, $-C(H)(Q_1)-$, $-C(H)(Q_5)-$, $-C(O)-$, $-CH_2-$, $-N(Q_1)-$, $-N(Q_2)-$, or O;

Z_2 is N;

L is a bond, an aliphatic group, C_3-C_6 cycloaliphatic, $-O-$, $-S(O)_z-$, $-S(O)_z-(C_1-C_4)$alkyl-, $-C(O)N(Q_2)-$, or $-S(O)_z N(Q_2)-$, in which the aliphatic group is optionally substituted with 1-3 of oxo, Q_1, or Q_2;

G is a monocycloaliphatic group, a monocycloheteroaliphatic group, adamantyl, or a bicyclic or a tricyclic group of the formula (III)



(III)

in which the monocycloaliphatic group, the monocycloheteroalipahtic group, the adamantyl, and the bicyclic or tricyclic group are connected to L via any ring atom including those in X_1 and ring B, and the monocycloaliphatic, the monocycloheteroaliphatic, the bicyclic, and the tricyclic groups are optionally substituted with 1-3 of oxo, $=N-OQ_4$, fluorine, Q_2, $-C(O)-X_2$-aliphatic in which X_2 is absent, $-O-$, $-NH-$, $-NQ_2-$, or $-S(O)_z-$ and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3;

Bond r is a single or double bond and when ring B is present, bond r is fused with B;

Ring B, when present, is a 5-6 membered cycloaliphatic or heterocycloaliphatic ring, and is optionally substituted with 1-3 of oxo, Q_1, or Q_2;

X_1 is $-(CH_2)_i-$, -O-, -S-, $-N(Q_2)-$, or $-N(-C(O)-X_2-\text{aliphatic})$ in which X_2 is absent, –O-, -NH-, $-NQ_2-$, or $-S(O)_z-$ and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3;

Each Q_1 is independently halo, -CN, $-NO_2$, $-OQ_2$, $-S(O)_zQ_2$, $-S(O)_zN(Q_2)_2$, $-N(Q_2)_2$, $-C(O)OQ_2$, $-C(O)-Q_2$, $-C(O)N(Q_2)_2$, $-C(O)N(Q_2)(OQ_2)$, $-N(Q_2)C(O)-Q_2$, $-N(Q_2)C(O)N(Q_2)_2$, $-N(Q_2)C(O)O-Q_2$, $-N(Q_2)S(O)_z-Q_2$ or aliphatic optionally including 1-3 substituents independently selected from Q_2 or Q_3;

Each Q_2 is independently H, aliphatic, cycloaliphatic, aryl, arylalkyl, heterocyclic, or heteroaryl ring, each optionally including 1-3 substituents independently selected from Q_3;

Each Q_3 is halo, oxo, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, -OH, $-S(O)_zQ_4$, $-N(Q_4)_2$, $-COOQ_4$, $-C(O)Q_4$, $-OQ_4$, or C_1-C_4 alkyl optionally substituted with halo, oxo, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, -OH, -SH, $-S(O)_zH$, $-NH_2$, or -COOH;

Each Q_4 is aliphatic, cycloaliphatic, aryl, aralkyl, heterocycloaliphatic, heteroaralky, or heteroaryl, each optionally including 1-3 substituents selected from halo, oxo, CN, NO_2, CF_3, OCF_3, OH, SH, $-S(O)_zH$, $-NH_2$, or COOH;

Each Q_5 is a heterocyclic ring optionally including 1-3 substituents selected from halo, C_1-C_4alkyl, oxo, CN, NO_2, CF_3, OCF_3, OH, SH, $-S(O)_zH$, $-NH_2$, COOH;

Each i is independently 1, 2, or 3;

Each m and n is independently 1, 2, 3, or 4 provided that m + n is at least 4;

Each p is 0 or 1;

Each y is independently 0 or 1;

Each t is 1 to 4; and

Each z is independently 0, 1, or 2;

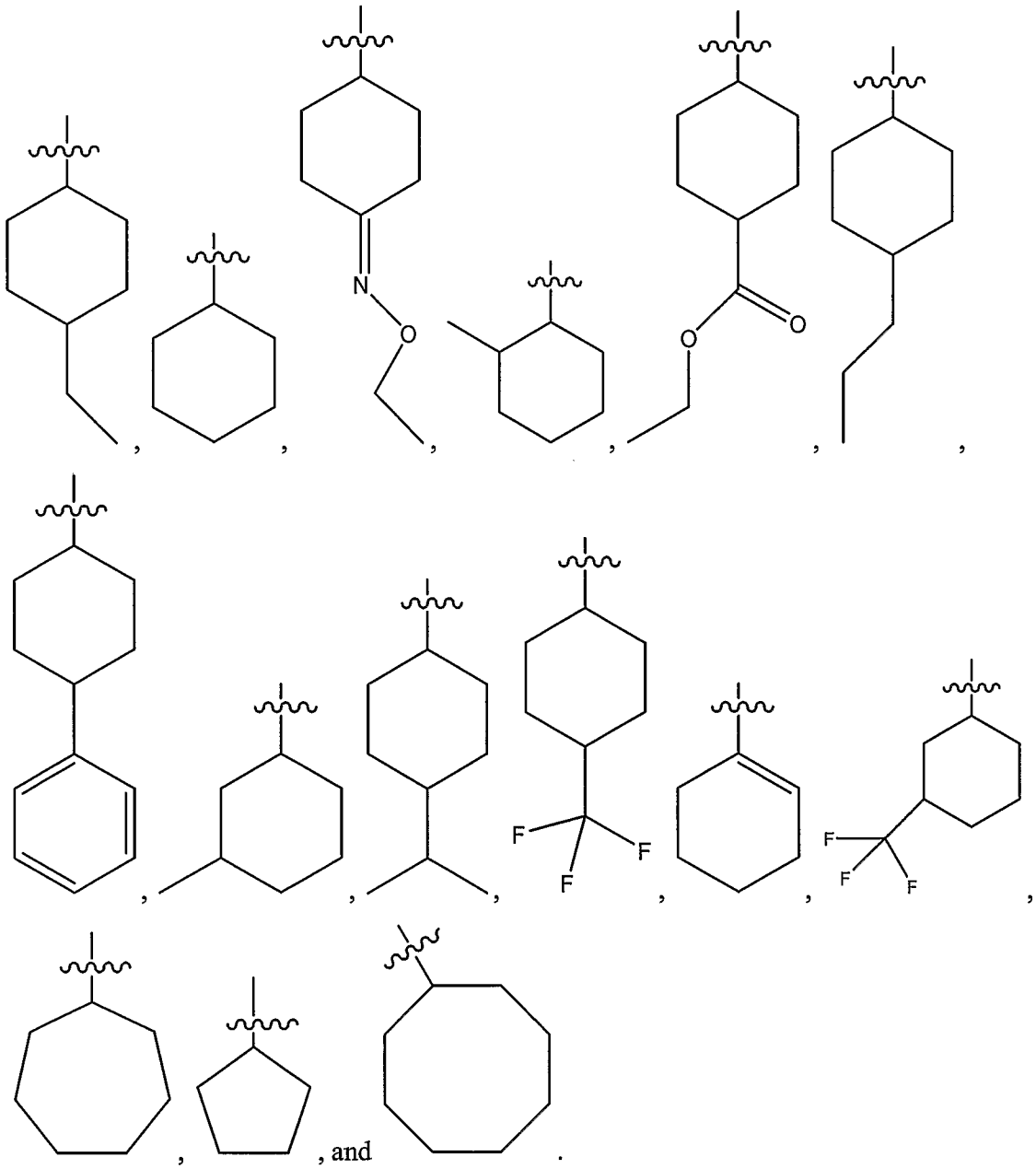
2. The method of claim 1, wherein G is an optionally substituted 5 to 8 membered monocycloaliphatic group.

3. The method of claim 2, wherein G is optionally substituted cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, or cyclooctyl.

4. The method of claim 3, wherein G is optionally substituted with Q_2, or -C(O)-X_2-aliphatic, where X_2 is absent, -O-, -NH-, or -NQ_2-, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

5. The method of claim 1, wherein G is substituted with alkyl, aryl, haloalkyl, alkoxycarbonyl, or alkoxyamino.

6. The method of claim 1, wherein G is selected from



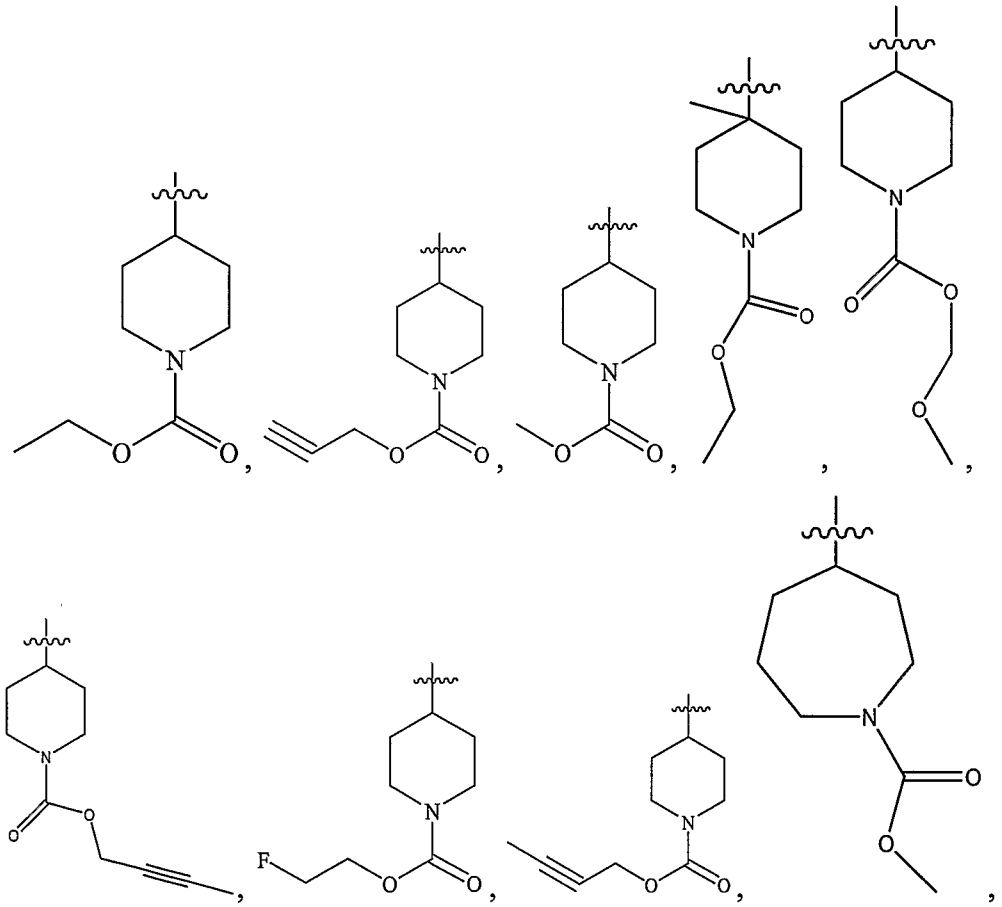
7. The method of claim 1, wherein G is an optionally substituted 5 to 7 membered monoheterocycloaliphatic group.

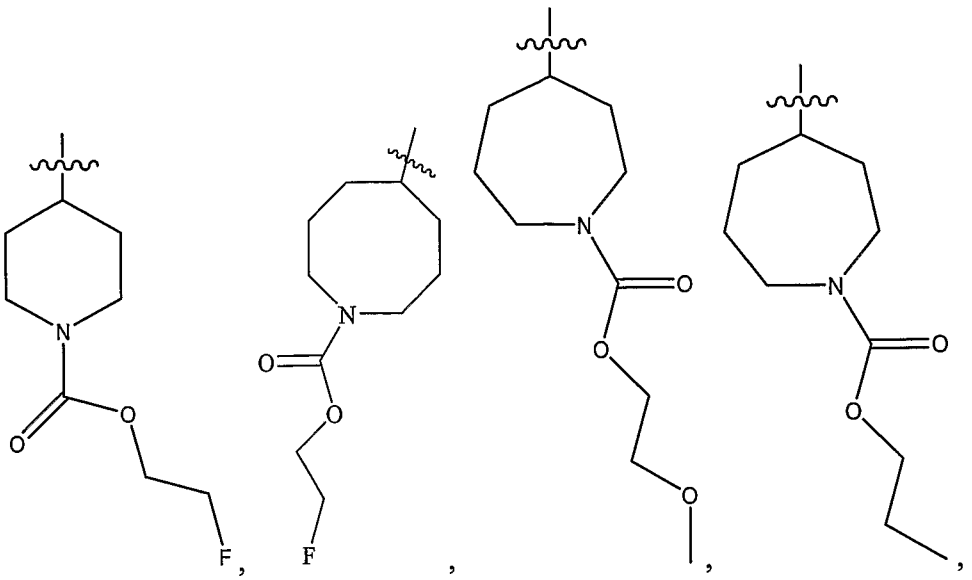
8. The method of claim 7, wherein G includes at least one N atom.

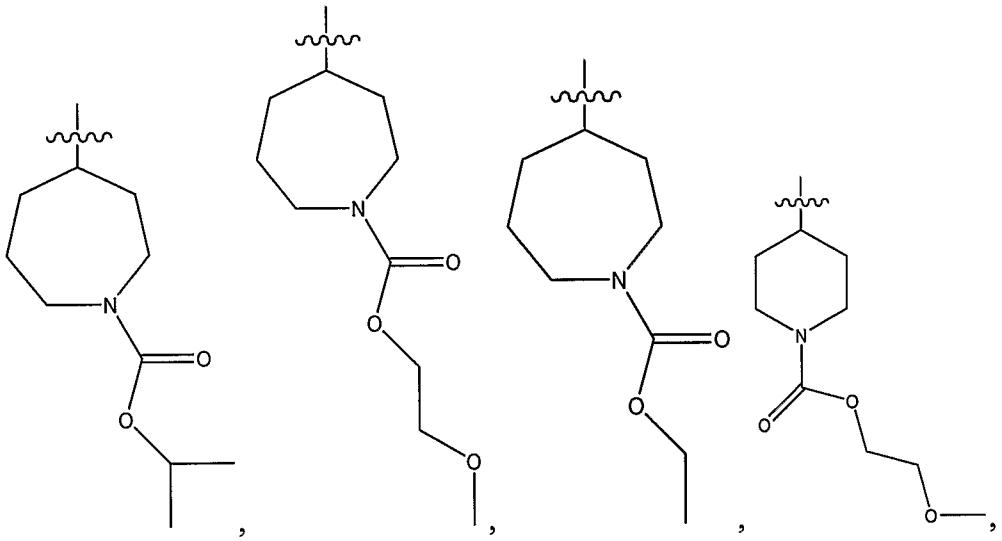
9. The method of claim 8, wherein G is substituted with 1 to 2 substituents independently selected from Q_2, and -C(O)-X_2-aliphatic, where X_2 is absent, -O-, -NH-, or -NQ_2-, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

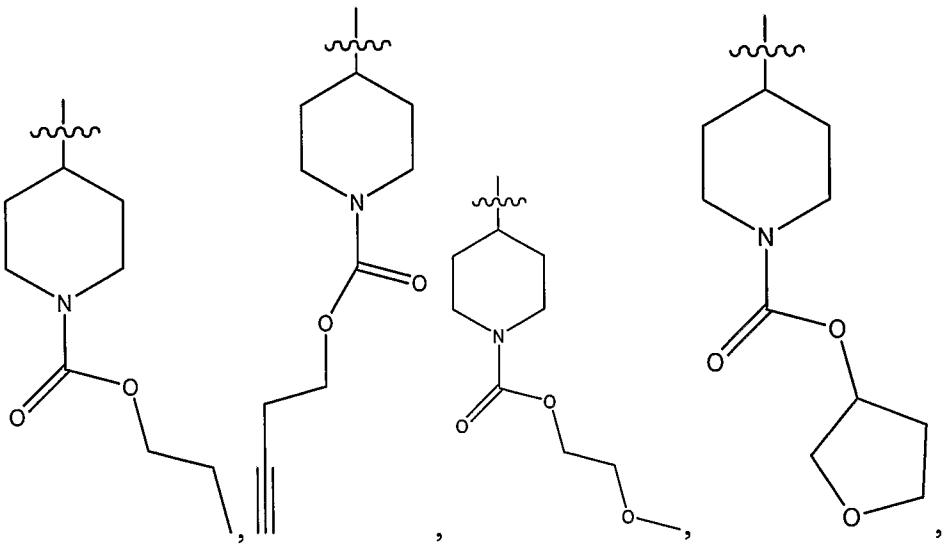
10. The method of claim 8, wherein G is substituted with 1 to 2 substituents independently selected from alkoxycarbonyl, alkynyloxycarbonyl, alkoxyalkoxycarbonyl, haloalkoxycarbonyl, heterocycloalkoxycarbonyl, and cycloalkoxycarbonyl.

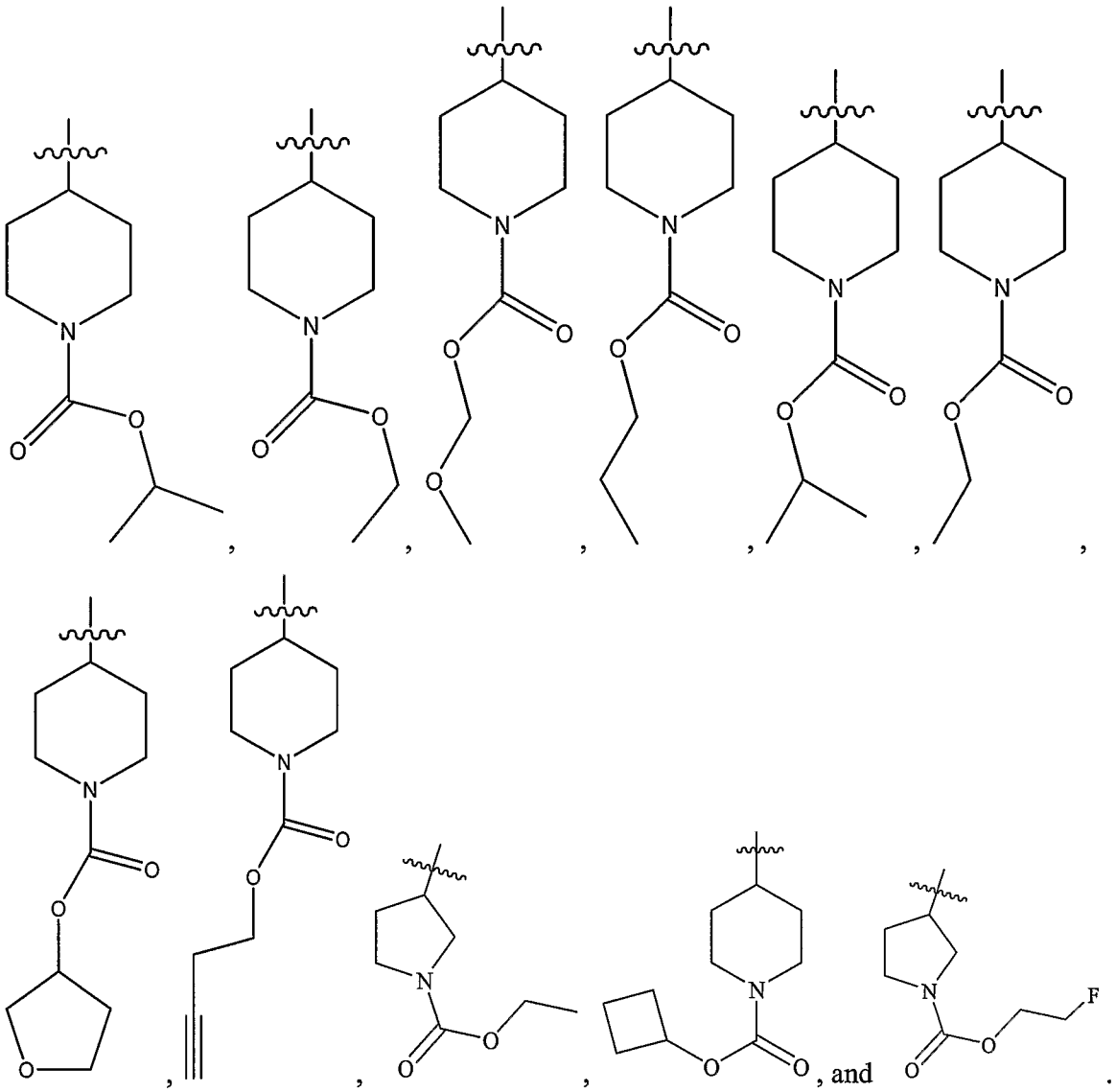
11. The method of claim 1, wherein G is one selected from











12. The method of claim 7, wherein G includes at least one O atom.

13. The method of claim 1, wherein G is an optionally substituted bicyclic group of formula (III) in which ring B is absent.

14. The method of claim 13, wherein X_1 is $-(CH_2)_i-$.

15. The method of claim 14, wherein G is optionally substituted bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[3.3.1]nonyl, bicyclo[2.2.2]octyl, or bicyclo[2.2.1]heptanyl.

16. The method of claim 15, wherein G is substituted with 1 to 2 substituents independently selected from Q_2, and -C(O)-X_2-aliphatic, where X_2 is absent, -O-, -NH-, or -NQ_2-, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

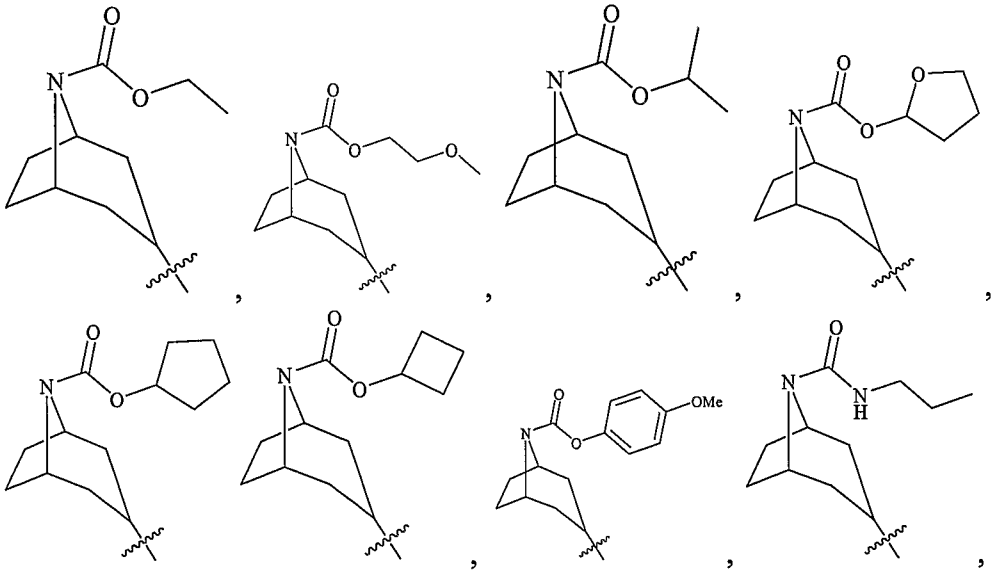
17. The method of claim 13, wherein X_1 is -N(Q_2)- or -N(-C(O)-X_2-aliphatic), where X_2 is absent, -O-, -NH-, or -NQ_2-, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

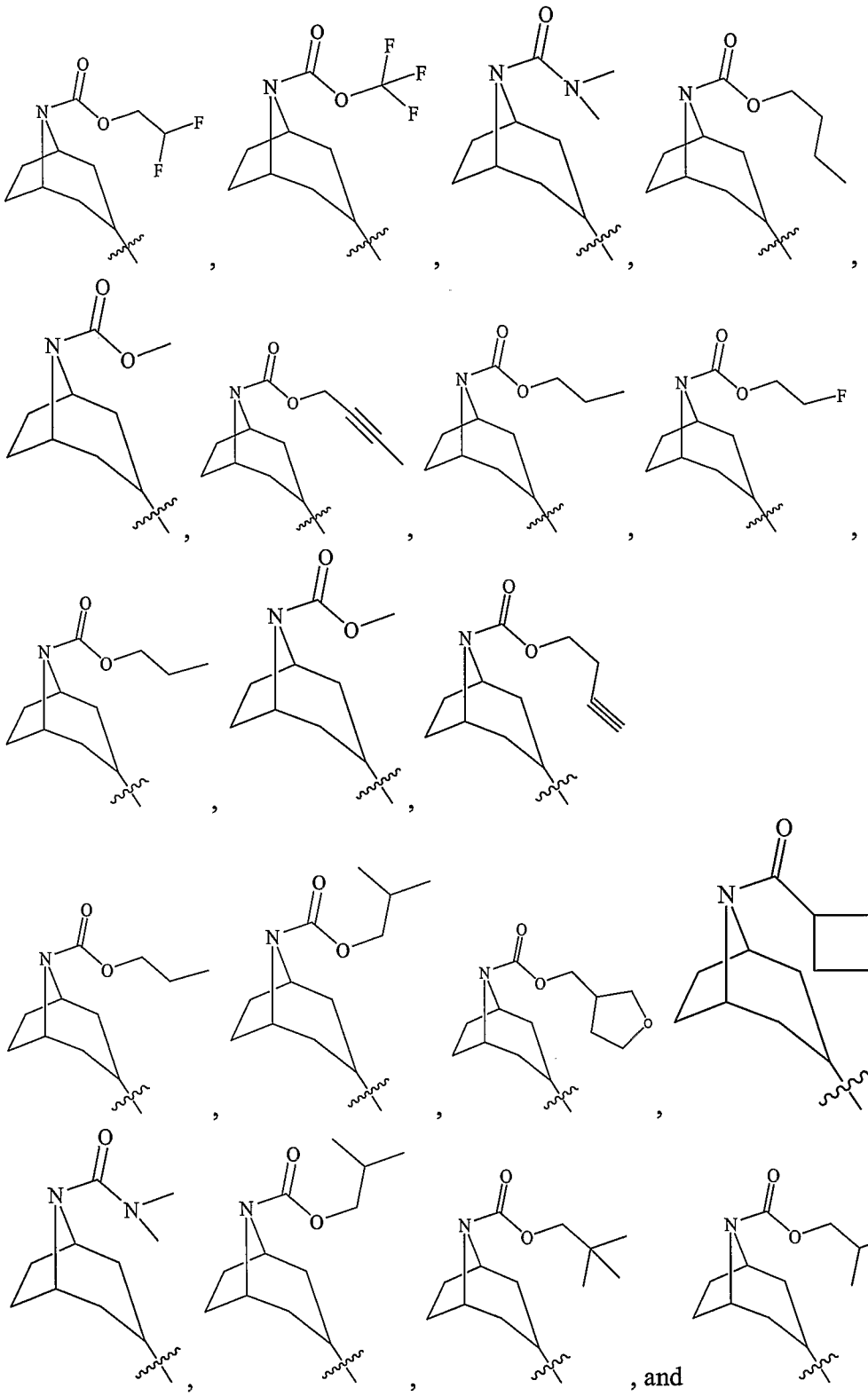
18. The method of claim 17, wherein G is an optionally substituted tropane.

19. The method of claim 18, wherein the tropane is substituted with Q_2 or -C(O)-X_2-aliphatic, where X_2 is absent, -O-, -NH-, or -NQ_2-, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

20. The method of claim 19, wherein the tropane is substituted at the tropane ring nitrogen atom with alkoxycarbonyl, alkoxyalkoxycarbonyl, heterocycloalkoxycarbonyl, cycloalkoxycarbonyl, alkoxyaryloxycarbonyl, alkylaminocarbonyl, haloalkoxycarbonyl, alkynyloxycarbonyl, or heterocycloalkylalkoxycarbonyl.

21. The method of claim 20, wherein G is selected from



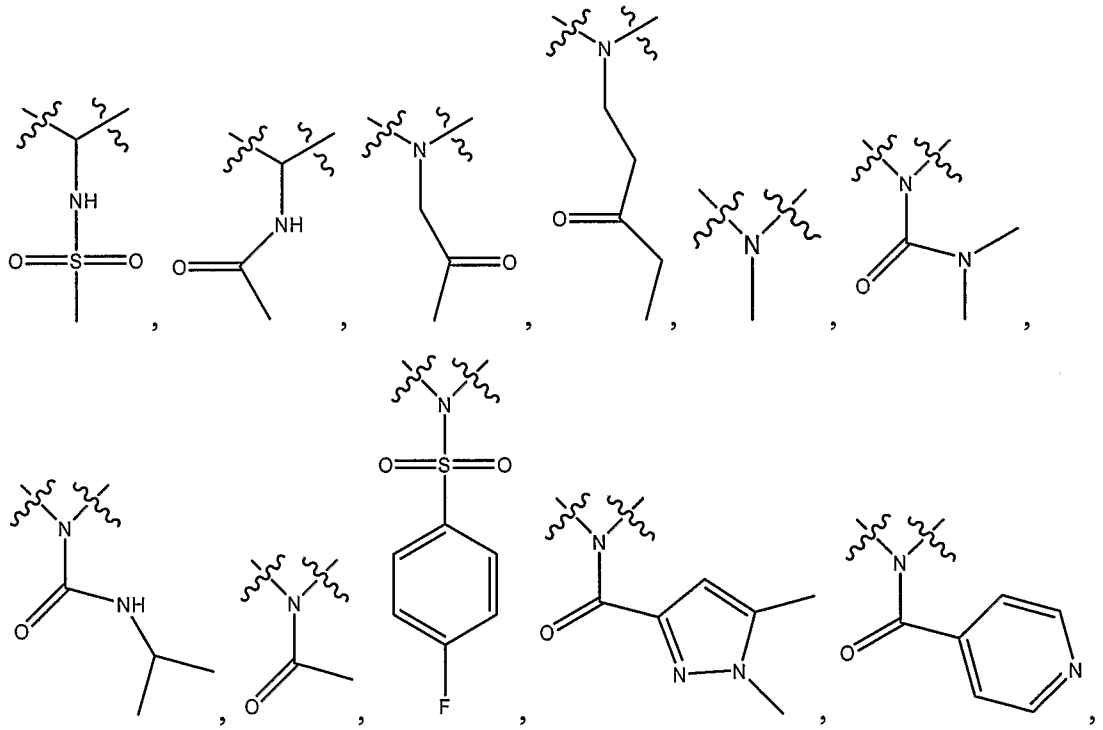


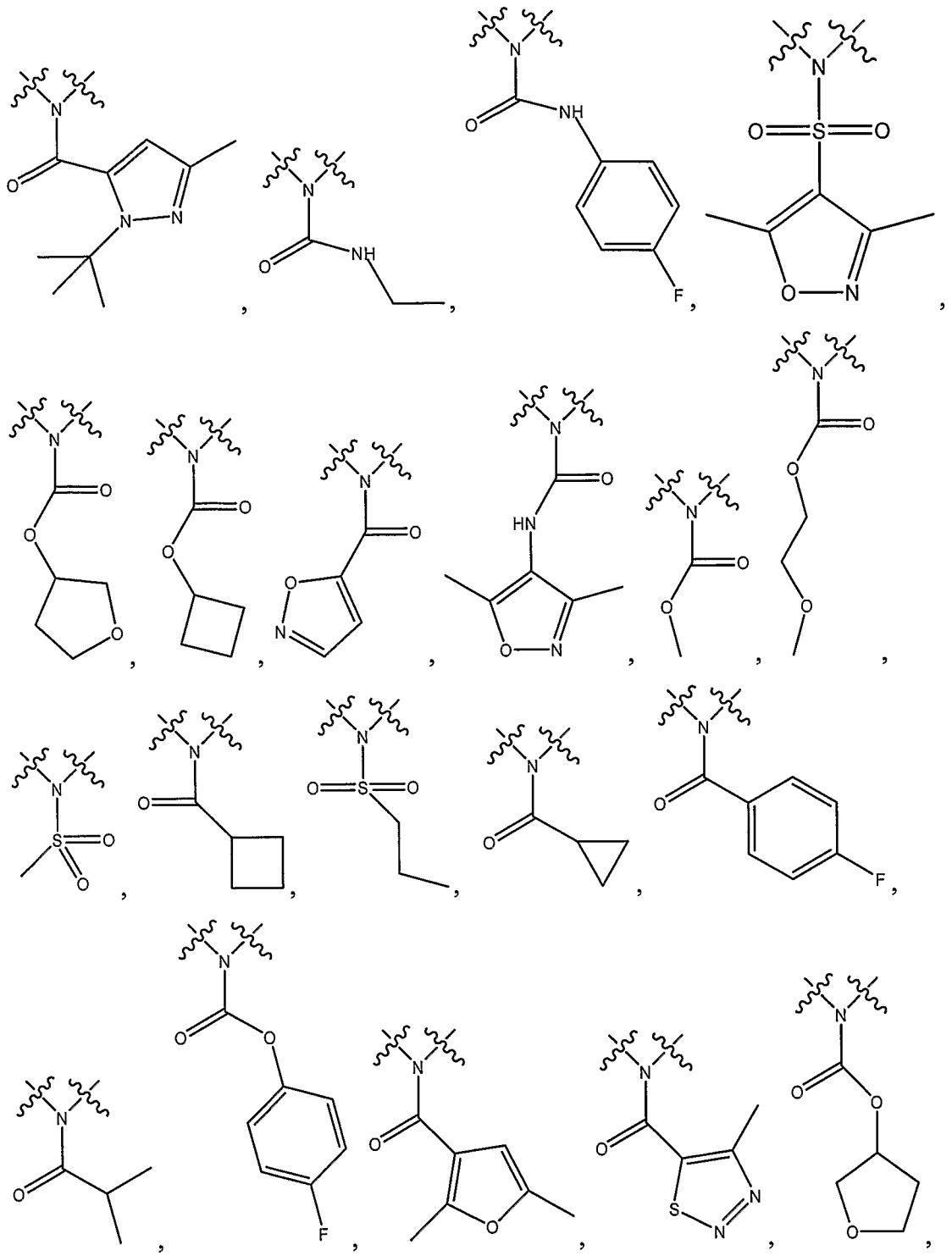
22. The method of claim 1, wherein Z_1 is -C(O)-, -CH_2-, -CH(Q_1)-, -CH(Q_5)-, -C(Q_1)$_2$-,

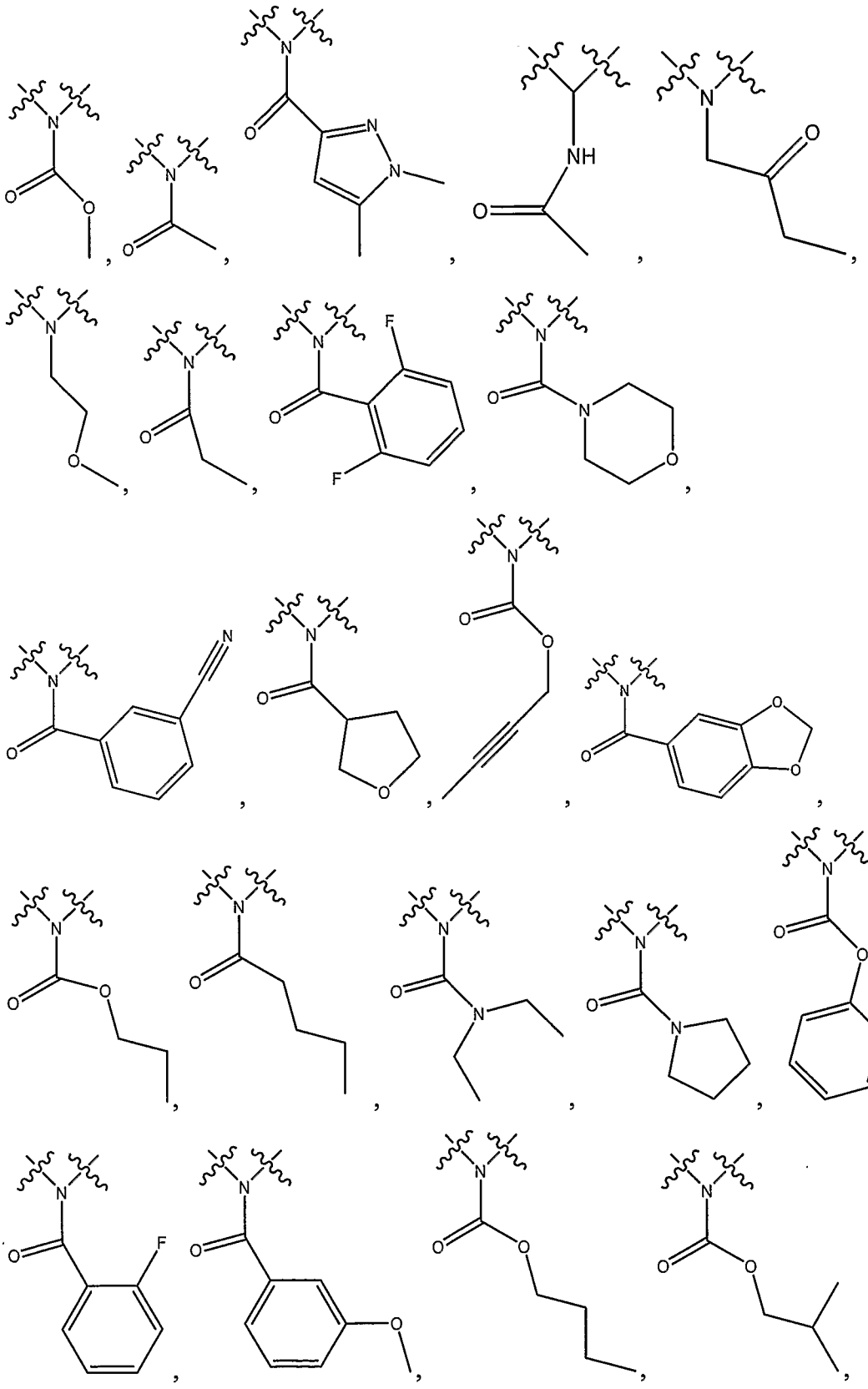
-NH-, or -N(Q_1)-.

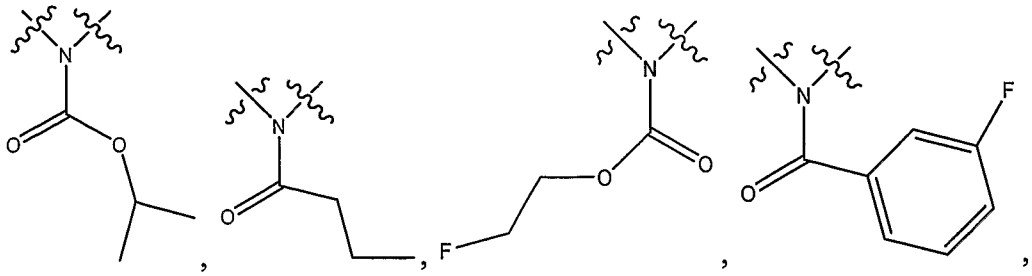
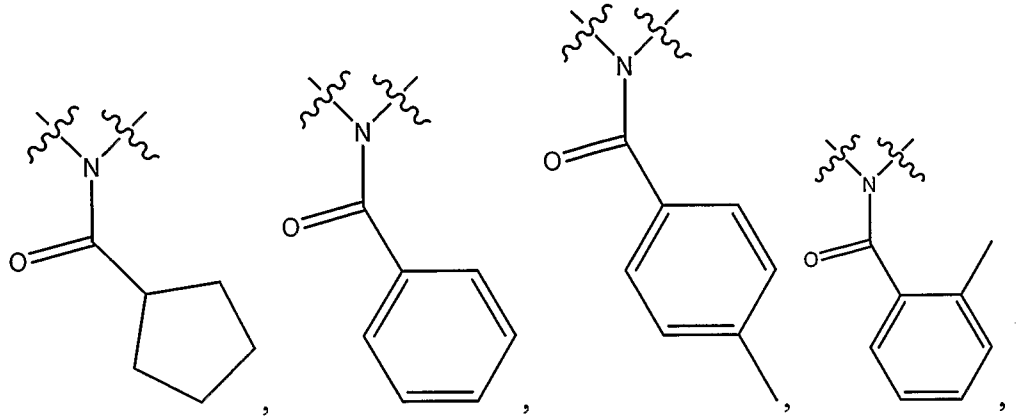
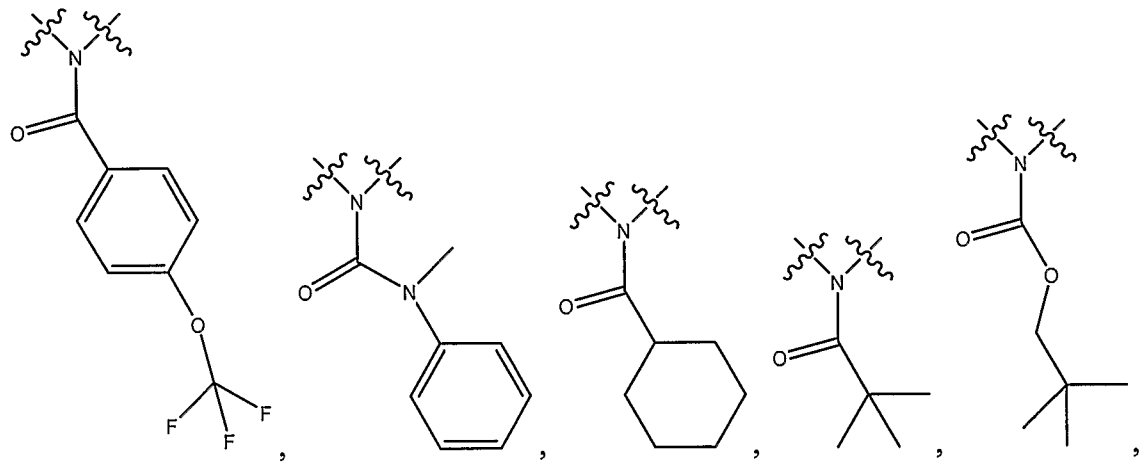
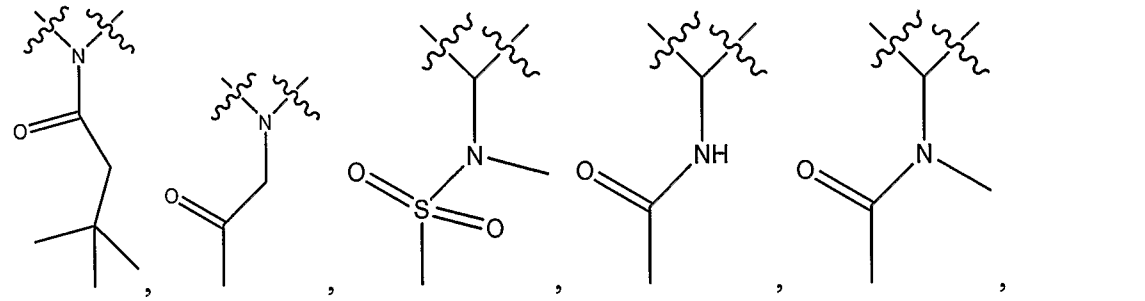
23. The method of claim 22, wherein Z_1 is -CH(Q_1)- or -N(Q_1)- and Q_1 is alkylcarbonylamino, alkylsulfonylamino, alkoxycarbonylamino, aminocarbonyl, alkylcarbonylalkyl, alkoxyalkoxycarbonyl, alkoxyalkyl, alkylaminocarbonyl, alkoxycarbonyl, haloarylcarbonyl, haloarylsulfonyl, alkylheteroarylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, haloarylaminocarbonyl, alkylheteroarylsulfonyl, cyanoalkylarylcarbonyl, heterocycloalkoxycarbonyl, alkynyloxycarbonyl, cycloalkoxycarbonyl, heterobicycloarylcarbonyl, alkylheteroarylaminocarbonyl, alkylsulfonyl, alkylcarbonylalkyl, alkoxyarylcarbonyl, haloalkoxycarbonyl, alkylarylcarbonyl, haloalkoxyarylcarbonyl, or arylaminocarbonyl.

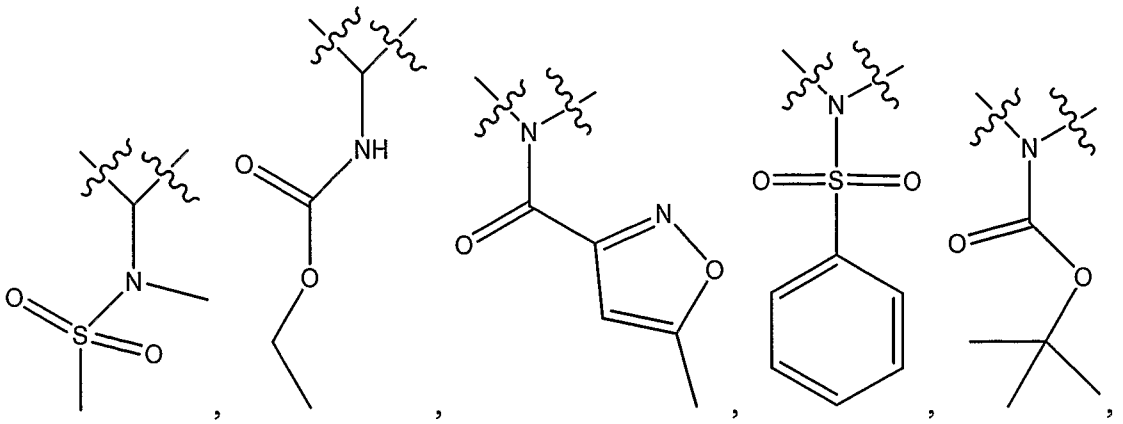
24. The method of claim 22, wherein Z_1 is one selected from -CH_2-, -C(O)-, -NH-, -O-,

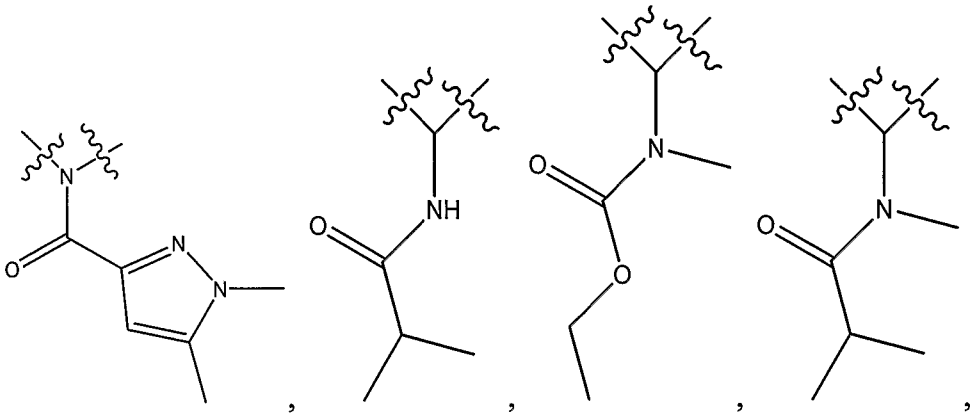


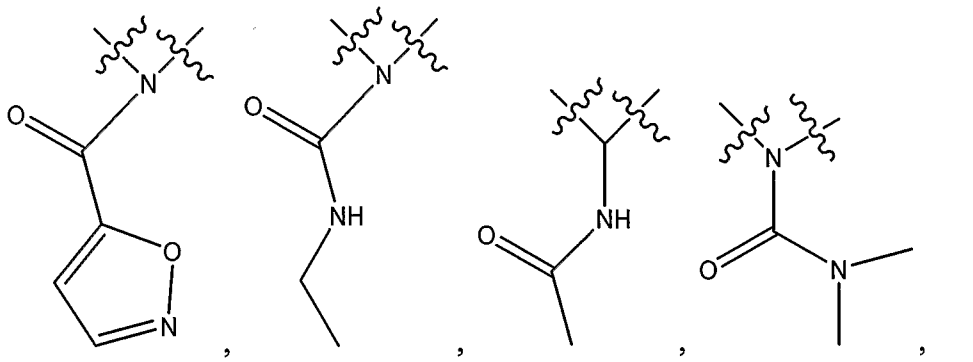


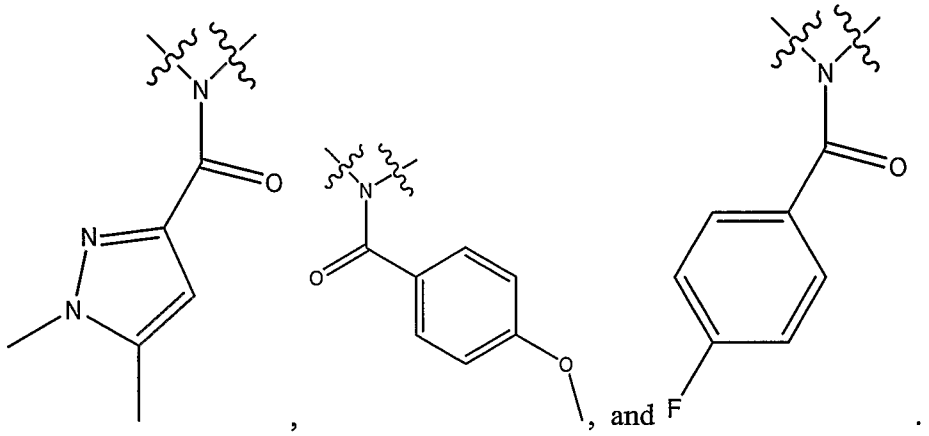



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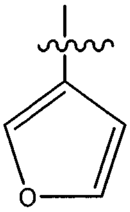
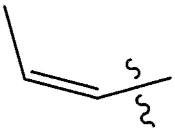
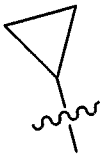
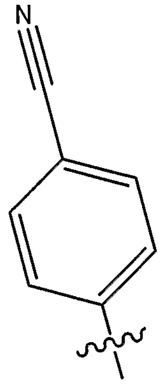
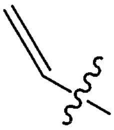
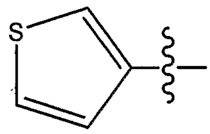

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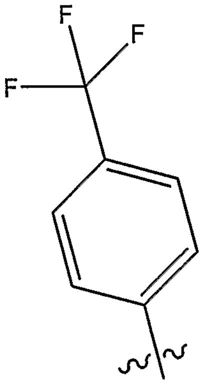
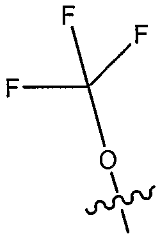
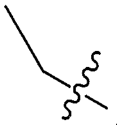
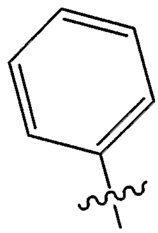
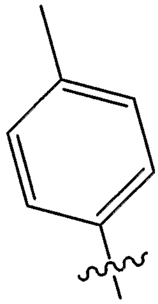
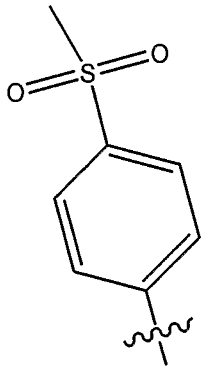

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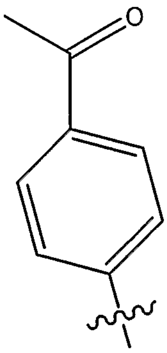
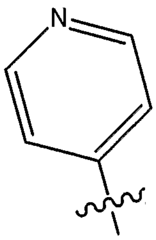
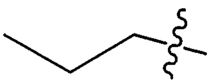
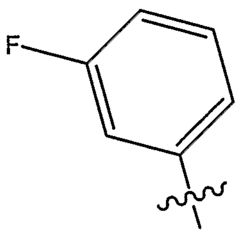
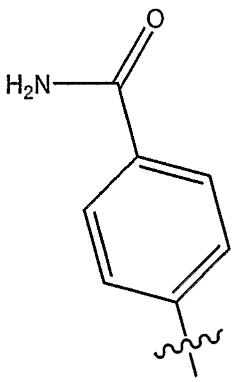
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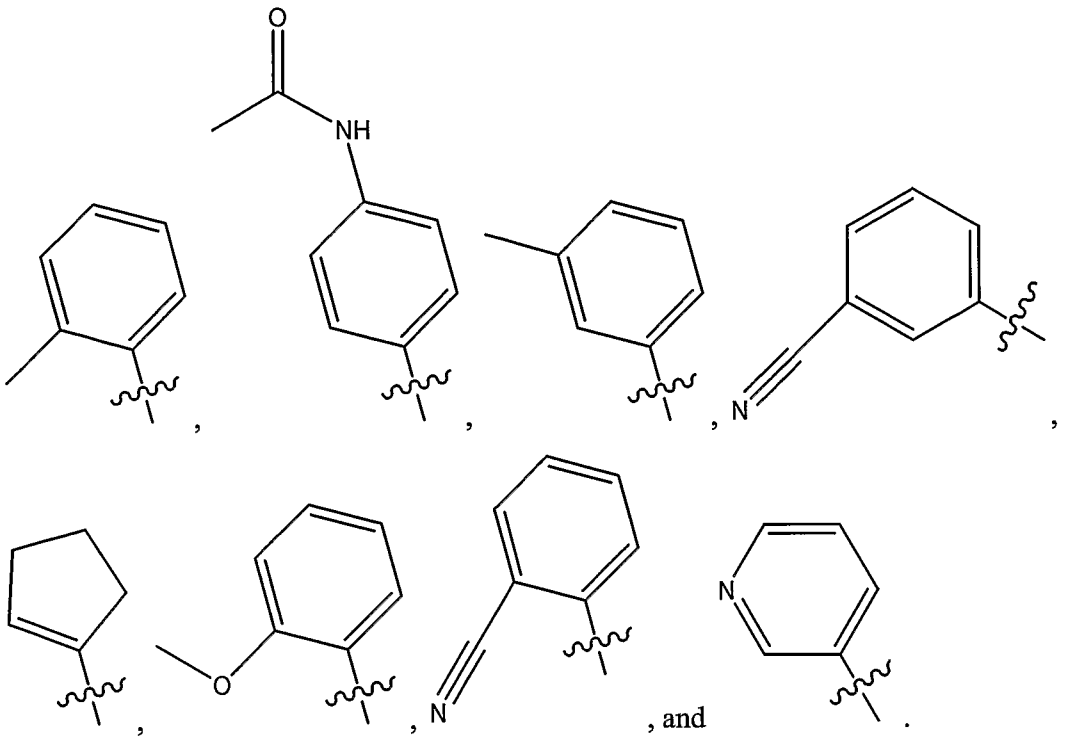
25. The method of claim 1, wherein R_1 is selected from hydrogen, halo, or optionally substituted alkyl, heteroaryl, alkoxy, alkenyl, cycloalkyl, cyanoalkylaryl, alkylaryl, alkylsulfonylaryl, alkylcarbonylaryl, aryl, aminocarbonylaryl, alkylcarbonylaminoaryl, cycloalkenyl, and alkoxyaryl.

26. The method of claim 25, wherein R_1 is selected from hydrogen, halo, methyl,

 ,  , $-OCH_3$,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,



27. The method of claim 1, wherein R_2 and R_3 are independently hydrogen, alkyl, or R_2 and R_3 together form an oxo.

28. The method of claim 27, wherein R_2 and R_3 are both hydrogen.

29. The method of claim 1, wherein p is 0.

30. The method of claim 1, wherein m and n are both 2.

31. The method of any of claims 1-30, wherein L is a bond or an aliphatic group optionally substituted with 1-3 of oxo, Q_1, or Q_2.

32. The method of claim 31, wherein L is a bond.

33. The method of claim 31, wherein L is an aliphatic group optionally substituted with 1-3 of oxo, Q_1, or Q_2.

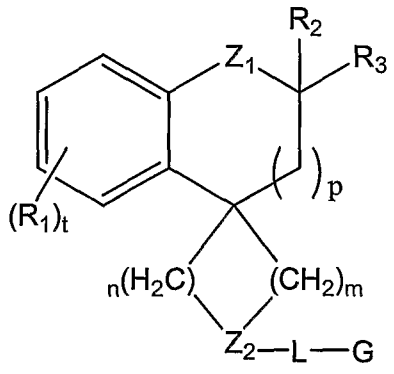
34. The method of claim 1, wherein the compound selectively modulates a M_1 or M_4 muscarinic receptor.

35. A method of treating or reducing the severity of a muscarinic receptor mediated disease in a mammal, comprising the step of administering to said mammal a compound as described in claim 1.

36. The method according to claim 35, wherein said muscarinic receptor is M_1 or M_4.

37. A method of treating or reducing the severity of a disease in a patient, wherein said disease is selected from CNS derived pathologies including cognitive disorders, Attention Deficit Hyperactivity Disorder (ADHD), obesity, Alzheimer's disease, various dementias such as vascular dementia, psychosis associated with CNS disorders including schizophrenia, mania, bipolar disorders, pain conditions including acute and chronic syndromes, Huntington's Chorea, Friederich's ataxia, Gilles de la Tourette's Syndrome, Downs Syndrome, Pick disease, clinical depression, Parkinson's disease, peripheral disorders such as reduction of intra ocular pressure in Glaucoma and treatment of dry eyes and dry mouth including Sjögren's Syndrome, bradhycardia, gastric acid secretion, asthma, GI disturbances, and wound healing, wherein said method comprises the step of contacting said patient with a compound as described in of claim 1.

38. A compound formula (I)



(I)

or pharmaceutically acceptable salts thereof, wherein

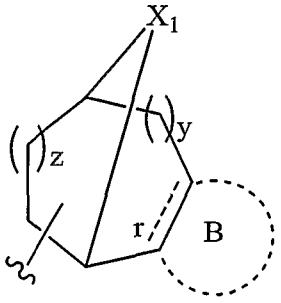
Each of R_1, R_2, R_3 is independently Q_1 or Q_2, or R_2 and R_3 together form oxo;

Z_1 is $-C(Q_1)_2-$, $-C(H)(Q_1)-$, $-C(H)(Q_5)-$, $-C(O)-$, $-CH_2-$, $-N(Q_1)-$, $-N(Q_2)-$, or O;

Z_2 is N;

L is a bond, an aliphatic group, C_3-C_6 cycloaliphatic, -O-, -$S(O)_z$-, -$S(O)_z$-(C_1-C_4)alkyl-, -$C(O)N(Q_2)$-, or -$S(O)_z$ $N(Q_2)$-, in which the aliphatic group is optionally substituted with 1-3 of oxo, Q_1, or Q_2;

G is a monocycloaliphatic group, a monocycloheteroaliphatic group, adamantyl, or a bicyclic or a tricyclic group of the formula (III)



(III)

in which the monocycloaliphatic group, the monocycloheteroalipahtic group, the adamantyl, and the bicyclic or tricyclic group are connected to L via any ring atom including those in X_1 and ring B, and the monocycloaliphatic, the monocycloheteroaliphatic, the bicyclic, and the tricyclic groups are optionally substituted with 1-3 of oxo, =N-OQ_4, fluorine, Q_2, -C(O)-X_2-aliphatic in which X_2 is absent, –O-, -NH-, -NQ_2-, or -$S(O)_z$- and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3;

Bond r is a single or double bond and when ring B is present, bond r is fused with B;

Ring B, when present, is a 5-6 membered cycloaliphatic or heterocycloaliphatic ring, and is optionally substituted with 1-3 of oxo, Q_1, or Q_2;

X_1 is -$(CH_2)_i$-, -O-, -S-, -$N(Q_2)$-, or -N(C(O)-X_2-aliphatic) in which X_2 is absent, -O-, -NH-, -NQ_2-, or -$S(O)_z$- and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3;

Each Q_1 is independently halo, -CN, -NO_2, -OQ_2, -$S(O)_zQ_2$, -$S(O)_zN(Q_2)_2$, -$N(Q_2)_2$, -$C(O)OQ_2$, -C(O)-Q_2, -$C(O)N(Q_2)_2$, -$C(O)N(Q_2)(OQ_2)$, -$N(Q_2)C(O)$-Q_2, -$N(Q_2)C(O)N(Q_2)_2$, -$N(Q_2)C(O)O$-Q_2, -$N(Q_2)S(O)_z$-Q_2 or aliphatic optionally including 1-3 substituents independently selected from Q_2 or Q_3;

Each Q_2 is independently H, aliphatic, cycloaliphatic, aryl, arylalkyl, heterocyclic, or heteroaryl ring, each optionally including 1-3 substituents independently selected from Q_3;

Each Q_3 is halo, oxo, -CN, -NO_2, -CF_3, -OCF_3, -OH, -$S(O)_zQ_4$, -$N(Q_4)_2$, -$COOQ_4$, -$C(O)Q_4$, -OQ_4, or C_1-C_4 alkyl optionally substituted with halo, oxo, -CN, -NO_2, -CF_3, -OCF_3, -OH, -SH, -$S(O)_zH$, -NH_2, or -COOH;

Each Q_4 is aliphatic, cycloaliphatic, aryl, aralkyl, heterocycloaliphatic, heteroaralky, or heteroaryl, each optionally including 1-3 substituents selected from halo, oxo, CN, NO_2, CF_3, OCF_3, OH, SH, $-S(O)_zH$, $-NH_2$, or COOH;

Each Q_5 is a heterocyclic ring optionally including 1-3 substituents selected from halo, C_1-C_4alkyl, oxo, CN, NO_2, CF_3, OCF_3, OH, SH, $-S(O)_zH$, $-NH_2$, COOH;

Each i is independently 1, 2, or 3;

Each m and n is independently 1, 2, 3, or 4 provided that m + n is at least 4;

Each p is 0 or 1;

Each y is independently 0 or 1;

Each z is independently 0, 1, or 2;

Each t is 1 to 4; and

Provided that when

Z_1 is $-CH_2-$ or $-N(CH_3)-$, L is a bond, and G is an optionally substituted monocycloaliphatic, an optionally substituted monocycloheteroaliphatic group, or a norbornyl group; the R_1 substituent is other than H;

L is $-C(O)-CH_2-$ and Z_1 is $-N(Q_1)-$, where Q_1 is $-S(O)_2$-optionally substituted phenyl; the R_1 substituent is other than H;

L is $-S(O)_2-(C_1-C_4)$alkyl- and Z_1 is $-CH_2-$; the R_1 substituent is other than H;

L is $-S(O)_2-(C_1-C_4)$alkyl-, and R_2 and R_3 form =O, and Z_1 is $-N(Q_1)-$, where Q_1 is aliphatic or $-S(O)_2$-aliphatic; the R_1 substituent is other than H; and

L is aliphatic, and R_2 and R_3 form =O, and Z_1 is $-N(Q_1)-$, where Q_1 is aliphatic, and G is a substituted monocycloheteroaliphatic group; the R_1 substituent is other than H.

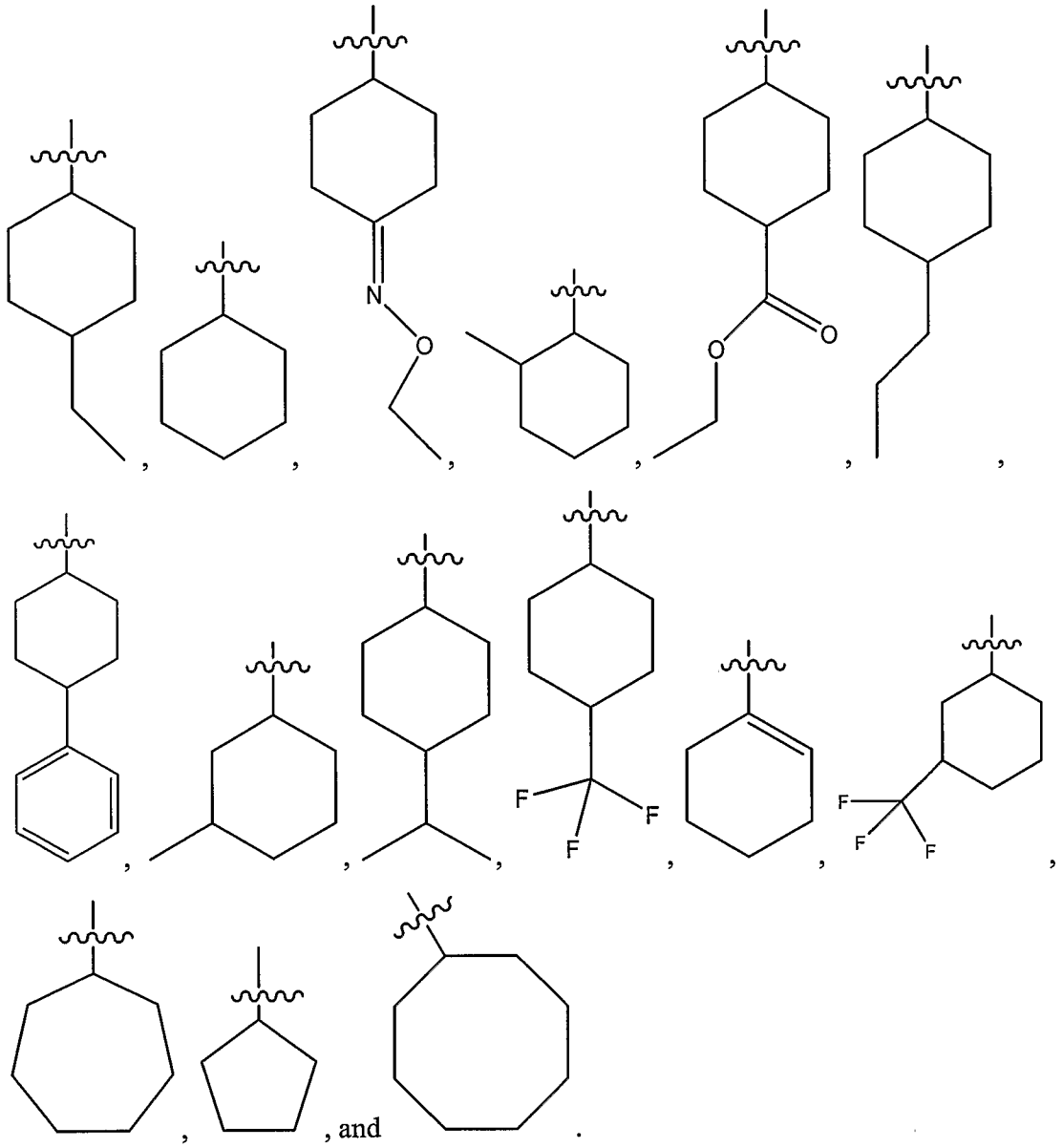
39. The compound of claim 38, wherein G is an optionally substituted 5 to 8 membered monocycloaliphatic group.

40. The compound of claim 39, wherein G is optionally substituted cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, or cyclooctyl.

41. The compound of claim 40, wherein G is optionally substituted with Q_2, or $-C(O)-X_2-$ aliphatic, where X_2 is absent, -O-, -NH-, or $-NQ_2-$, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

42. The compound of claim 38, wherein G is substituted with alkyl, aryl, haloalkyl, alkoxycarbonyl, or alkoxyamino.

43. The compound of claim 38, wherein G is selected from



, and .

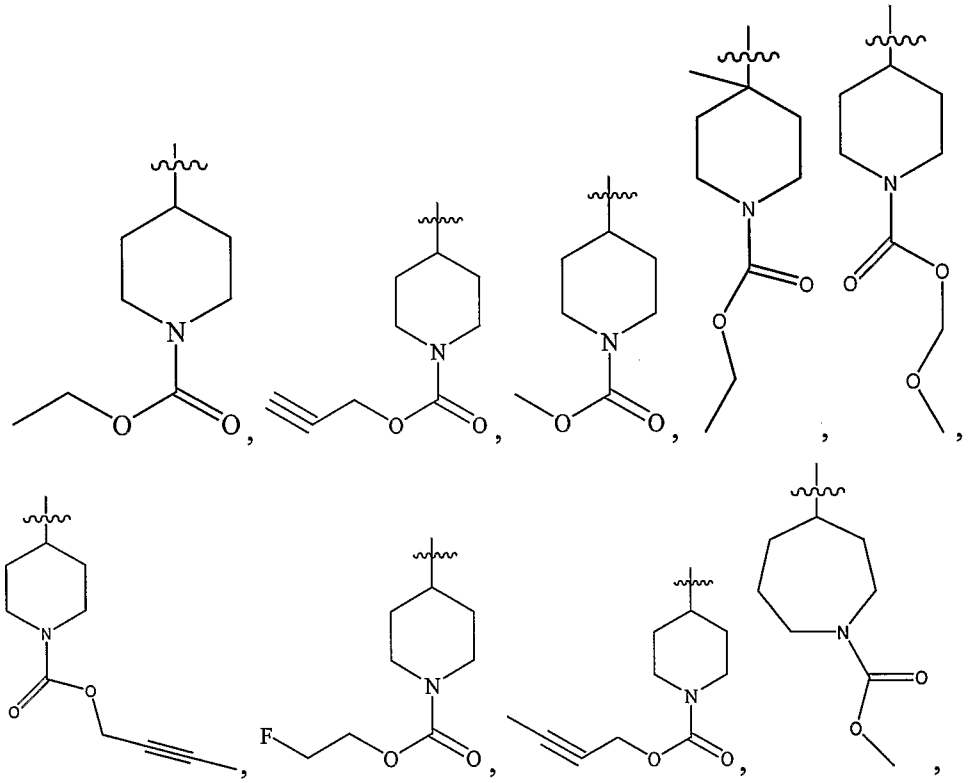
44. The compound of claim 38, wherein G is an optionally substituted 5 to 7 membered monoheterocycloaliphatic group.

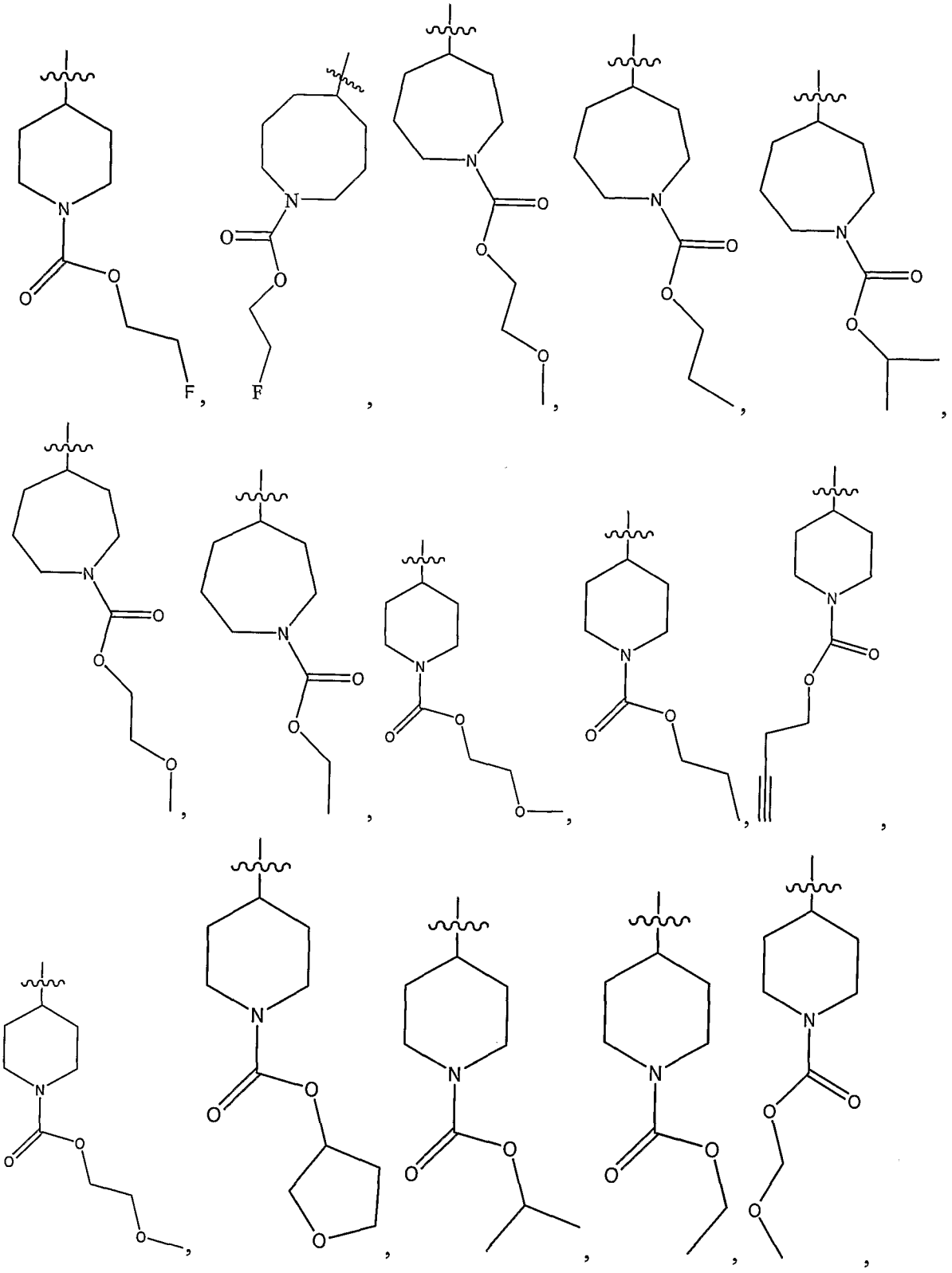
45. The compound of claim 44, wherein G includes at least one N atom.

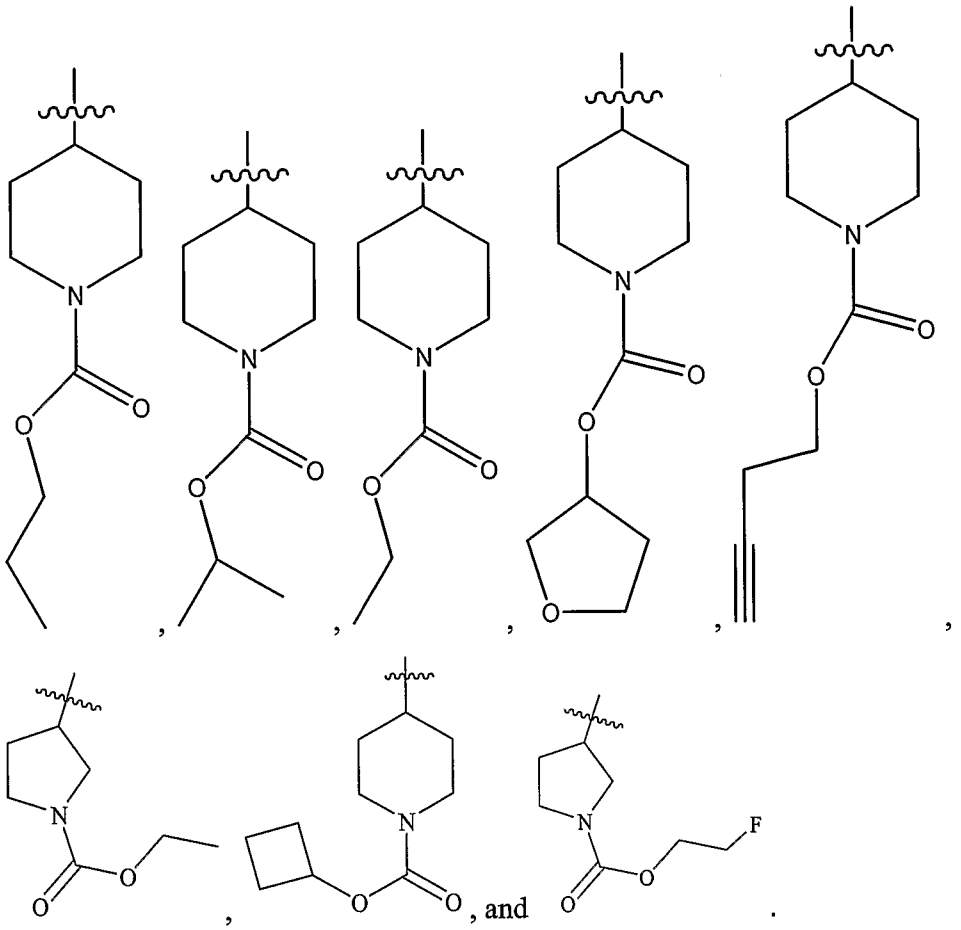
46. The compound of claim 45, wherein G is substituted with 1 to 2 substituents independently selected from Q_2, and -C(O)-X_2-aliphatic, where X_2 is absent, -O-, -NH-, or -NQ_2-, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

47. The compound of claim 46, wherein G is substituted with 1 to 2 substituents independently selected from alkoxycarbonyl, alkynyloxycarbonyl, alkoxyalkoxycarbonyl, haloalkoxycarbonyl, heterocycloalkoxycarbonyl, and cycloalkoxycarbonyl.

48. The compound of claim 37, wherein G is one selected from







49. The compound of claim 38, wherein G is an optionally substituted bicyclic group of formula (III) in which ring B is absent.

50. The compound of claim 49, wherein X_1 is $-(CH_2)_i-$.

51. The compound of claim 49, wherein G is optionally substituted bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[3.3.1]nonyl, bicyclo[2.2.2]octyl, or bicyclo[2.2.1]heptanyl.

52. The compound of claim 51, wherein G is substituted with 1 to 2 substituents independently selected from Q_2, and $-C(O)-X_2$-aliphatic, where X_2 is absent, -O-, -NH-, or $-NQ_2-$, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

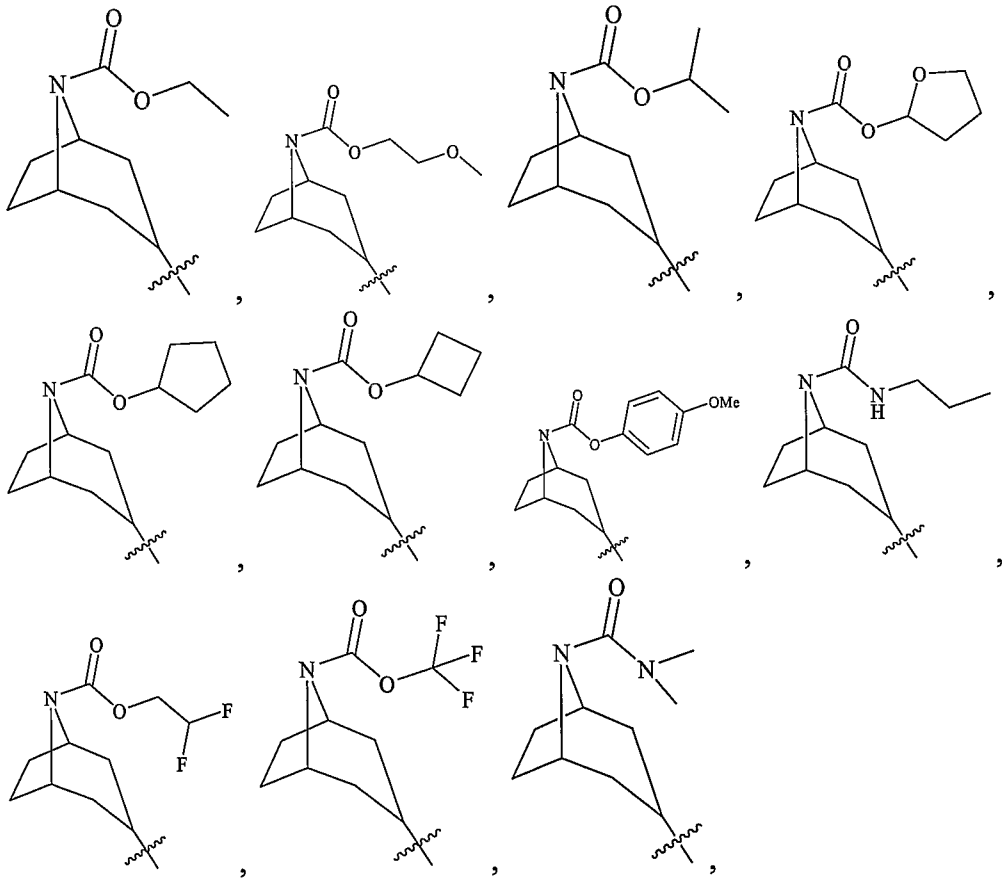
53. The compound of claim 50, wherein X_1 is $-N(Q_2)-$ or $-N(C(O)-X_2-$aliphatic, where X_2 is absent, -O-, -NH-, or $-NQ_2-$, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

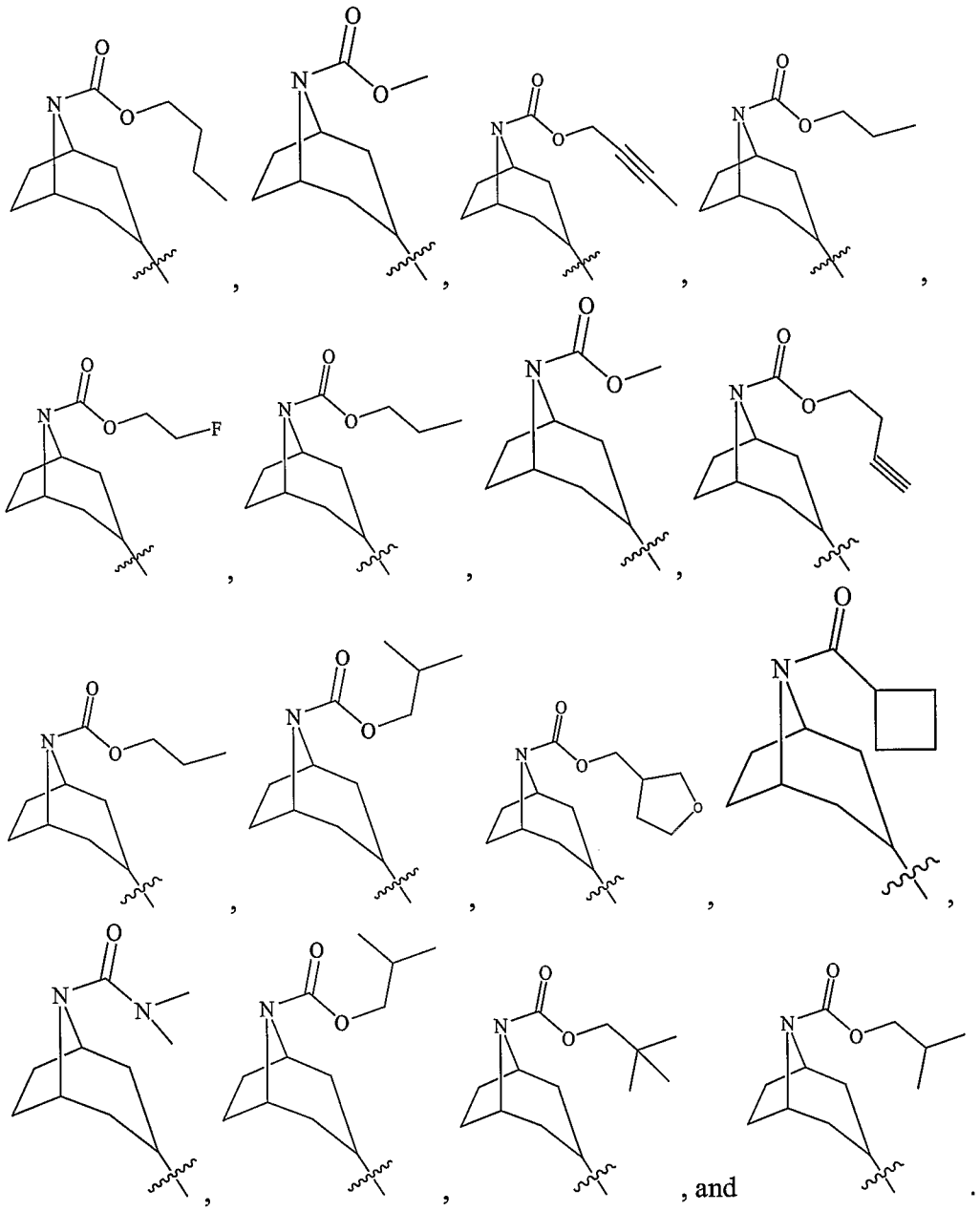
54. The compound of claim 53, wherein G is an optionally substituted tropane.

55. The compound of claim 54, wherein the tropane is substituted with Q_2, and $-C(O)-X_2-$aliphatic, where X_2 is absent, -O-, -NH-, or $-NQ_2-$, and the aliphatic group is optionally substituted with 1-3 substituents independently selected from Q_3.

56. The compound of claim 55, wherein the tropane is substituted at the tropane ring nitrogen atom with alkoxycarbonyl, alkoxyalkoxycarbonyl, heterocycloalkoxycarbonyl, cycloalkoxycarbonyl, alkoxyaryloxycarbonyl, alkylaminocarbonyl, haloalkoxycarbonyl, alkynyloxycarbonyl, or heterocycloalkylalkoxycarbonyl.

57. The compound of claim 56, wherein G is selected from



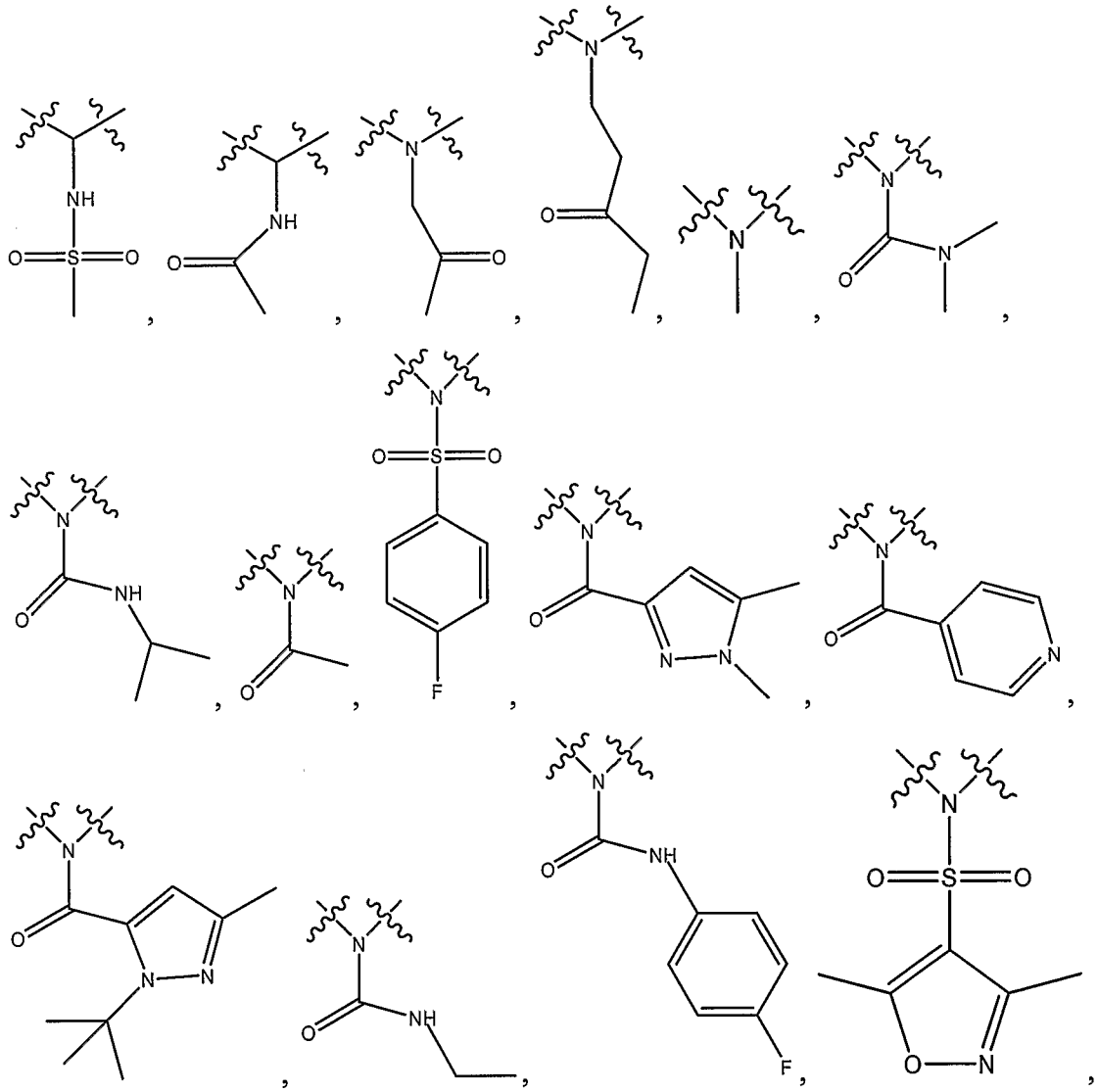


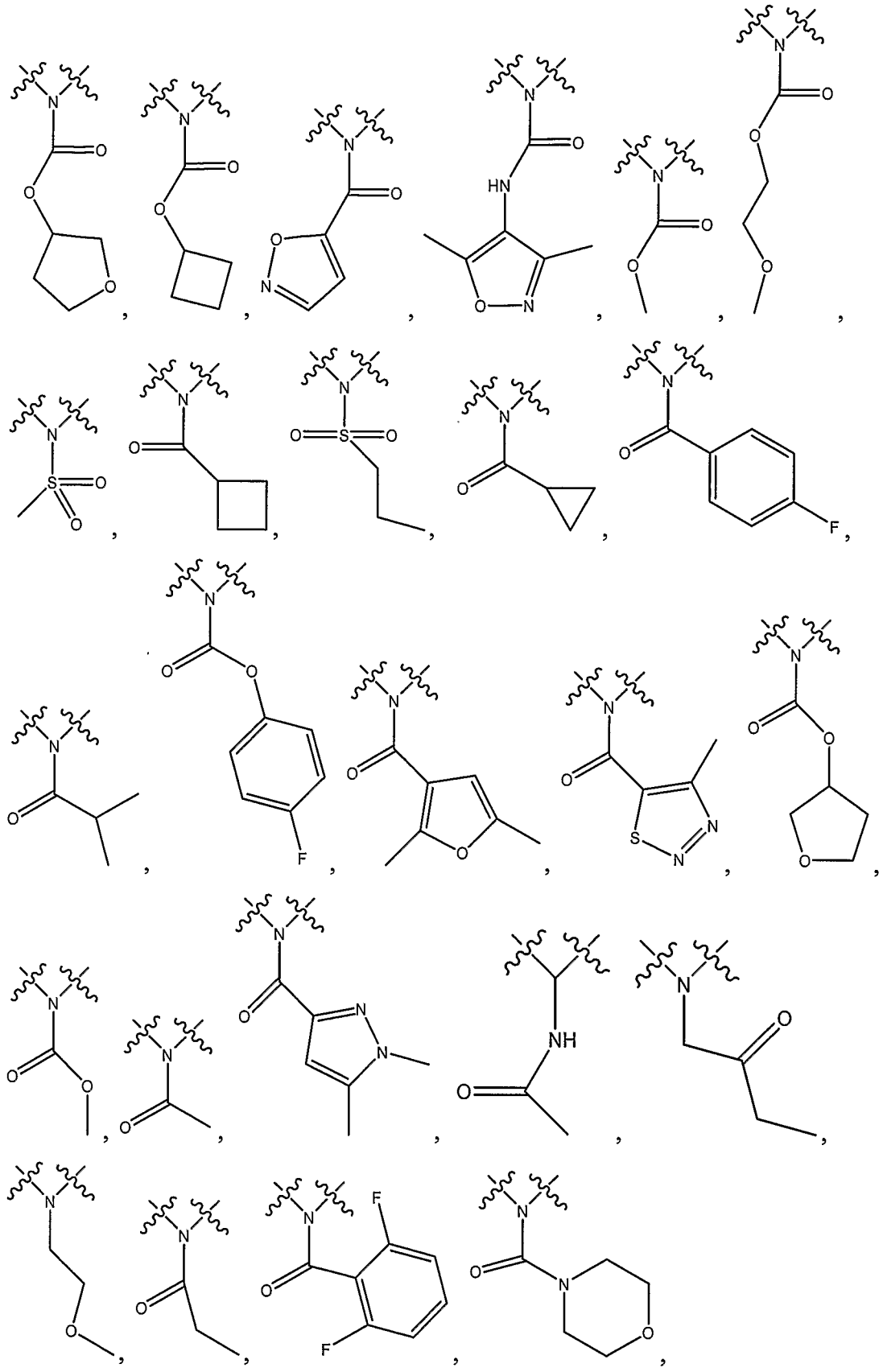
58. The compound of claim 38, wherein Z_1 is -C(O)-, -CH_2-, -CH(Q_1)-, -CH(Q_5)-, -C(Q_1)$_2$-, -NH-, or -N(Q_1)-.

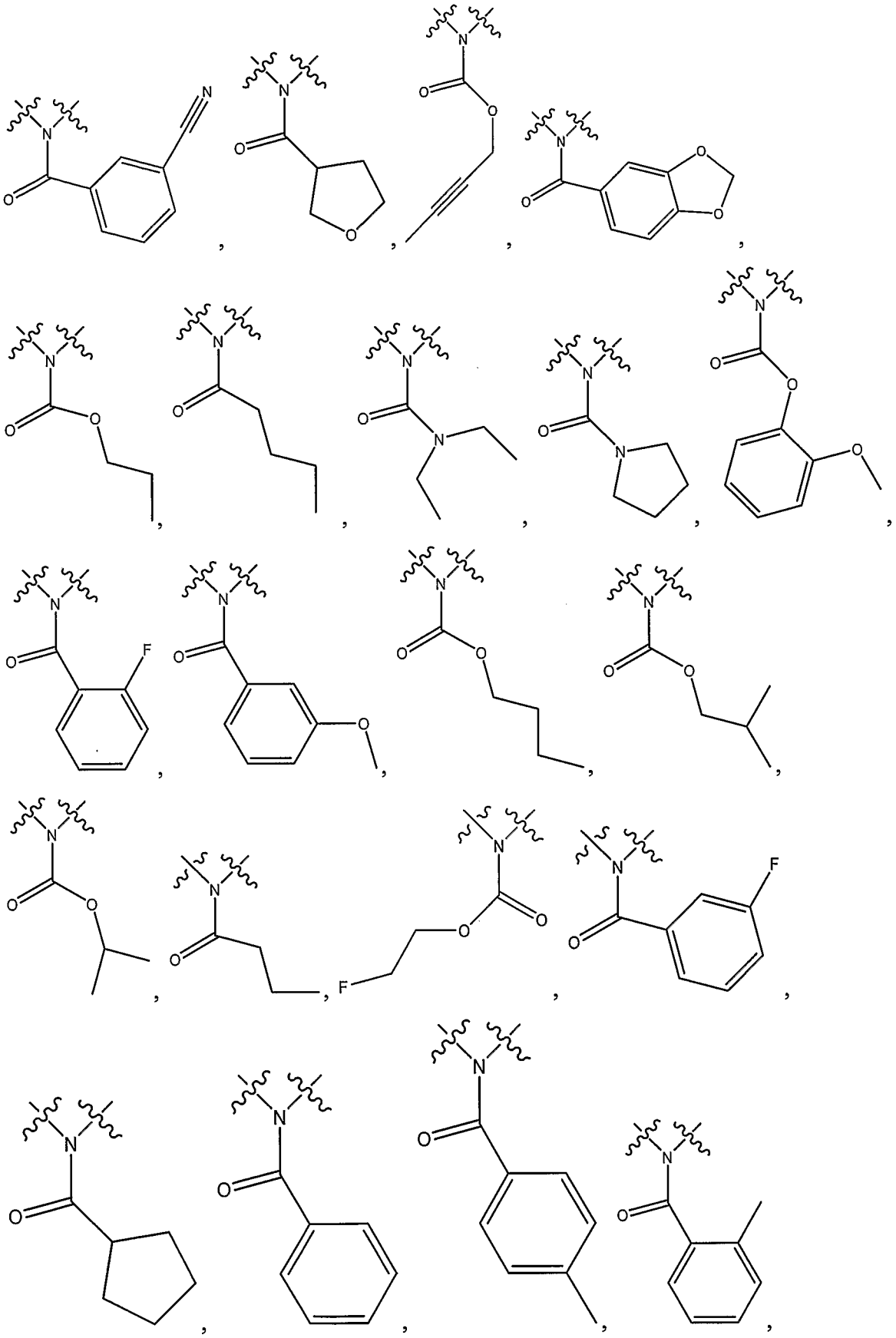
59. The compound of claim 58, wherein Z_1 is -CH(Q_1)- or -N(Q_1)- and Q_1 is alkylcarbonylamino, alkylsulfonylamino, alkoxycarbonylamino, aminocarbonyl, alkylcarbonylalkyl, alkoxyalkoxycarbonyl, alkoxyalkyl, alkylaminocarbonyl, alkoxycarbonyl, haloarylcarbonyl, haloarylsulfonyl, alkylheteroarylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, haloarylaminocarbonyl, alkylheteroarylsulfonyl,

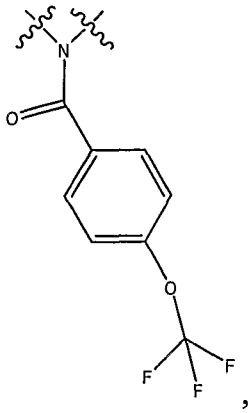
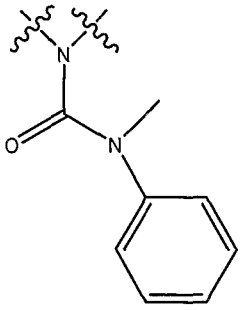
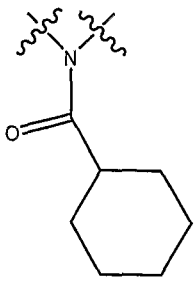
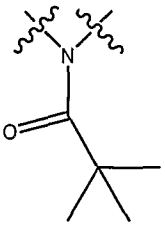
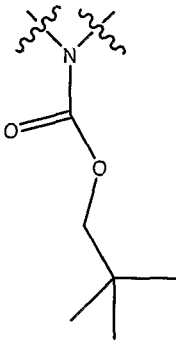
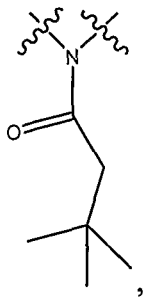
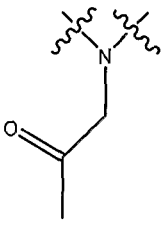
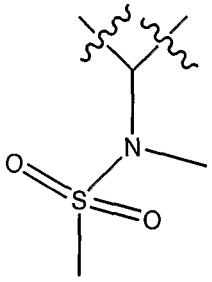
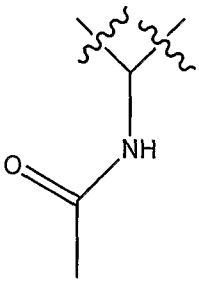
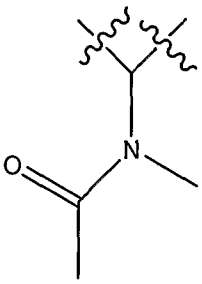
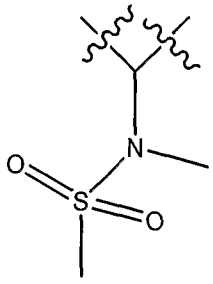
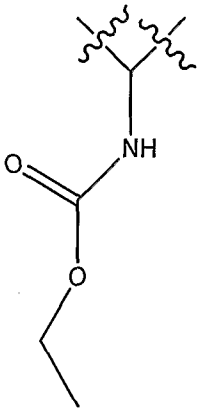
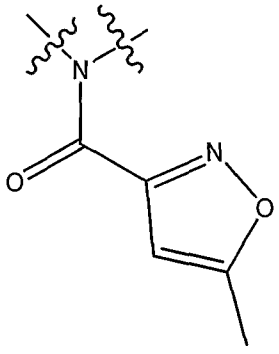
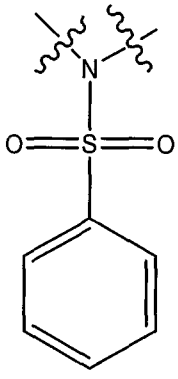
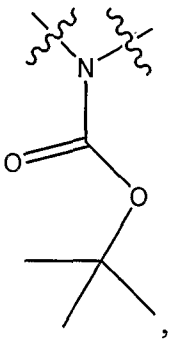
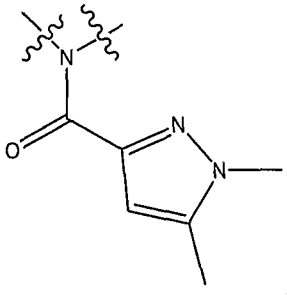
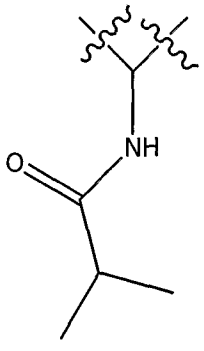
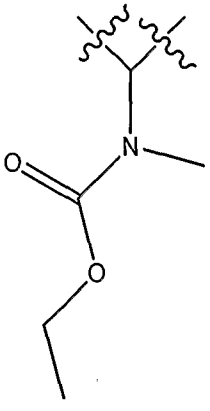
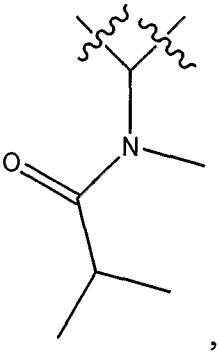
cyanoalkylarylcarbonyl, heterocycloalkoxycarbonyl, alkynyloxycarbonyl, cycloalkoxycarbonyl, heterobicycloarylcarbonyl, alkylheteroarylaminocarbonyl, alkylsulfonyl, alkylcarbonylalkyl, alkoxyarylcarbonyl, haloalkoxycarbonyl, alkylarylcarbonyl, haloalkoxyarylcarbonyl, or arylaminocarbonyl.

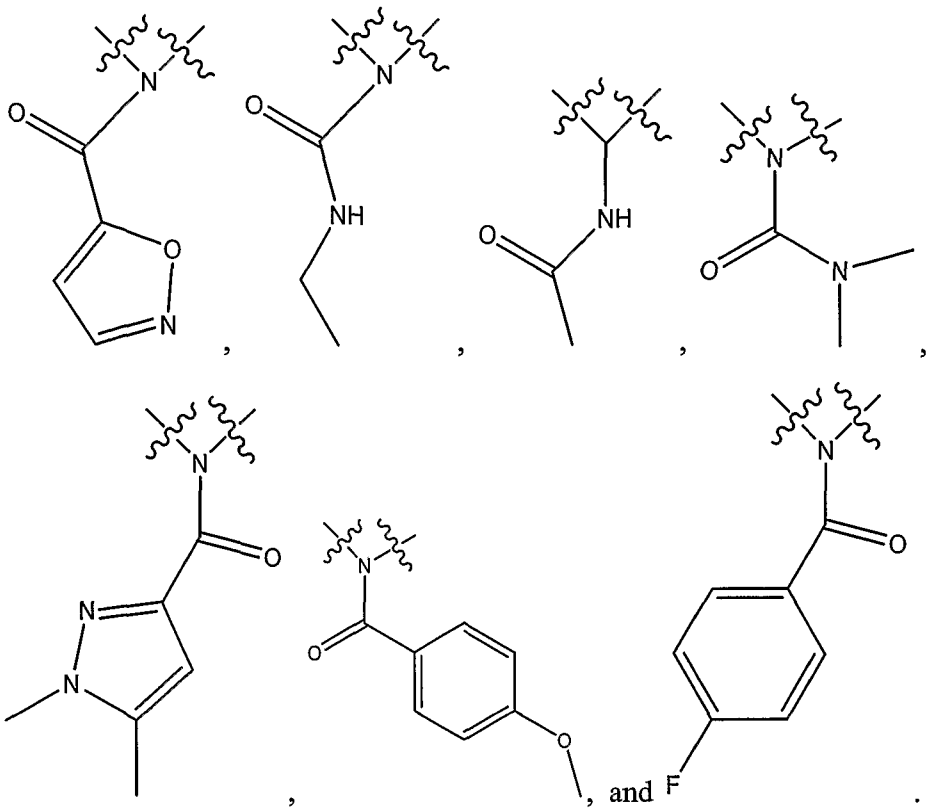
60. The compound of claim 59, wherein Z_1 is one selected from $-CH_2-$, -C(O)-, -NH-, -O-,





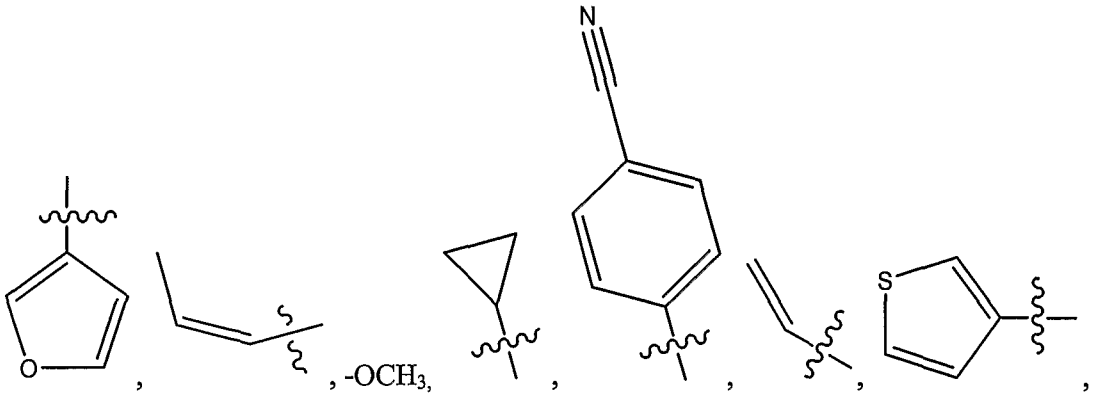


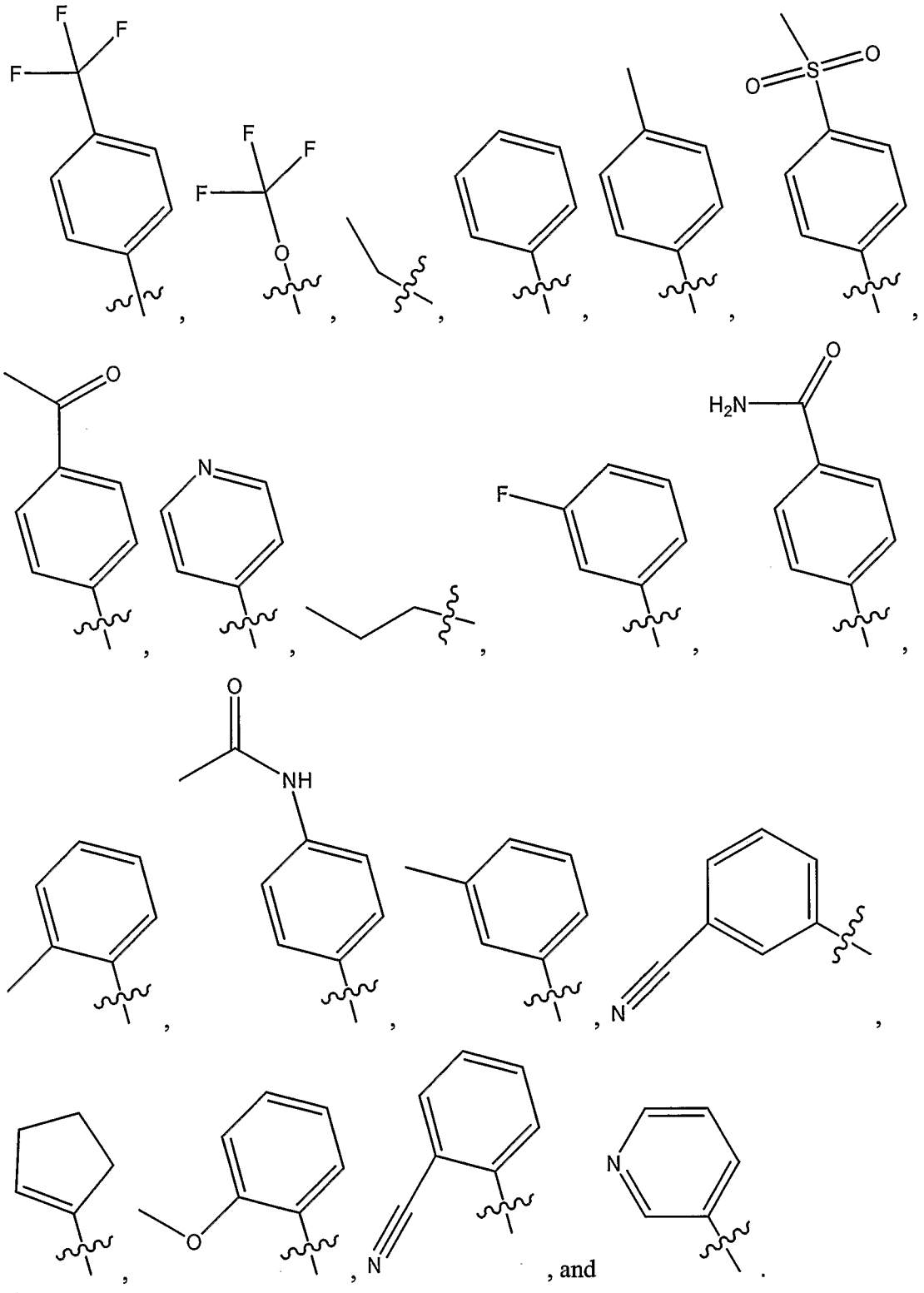

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61. The compound of claim 38, wherein R_1 is selected from hydrogen, halo, or optionally substituted alkyl, heteroaryl, alkoxy, alkenyl, cycloalkyl, cyanoalkylaryl, alkylaryl, alkylsulfonylaryl, alkylcarbonylaryl, aryl, aminocarbonylaryl, alkylcarbonylaminoaryl, cycloalkenyl, and alkoxyaryl.

62. The compound of claim 61, wherein R_1 is selected from hydrogen, halo, methyl,





63. The compound of claim 38, wherein R_2 and R_3 are independently hydrogen, alkyl, or R_2 and R_3 together form an oxo.

64. The compound of claim 63, wherein R_2 and R_3 are both hydrogen.

65. The compound of claim 38, wherein p is 0.

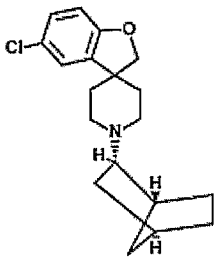
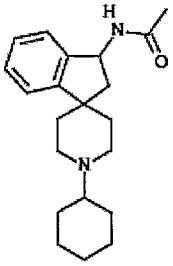
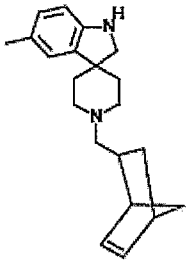
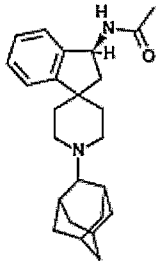
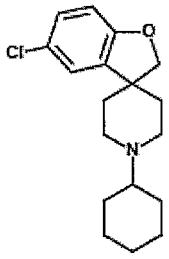
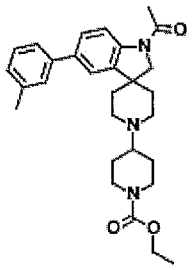
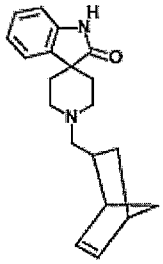
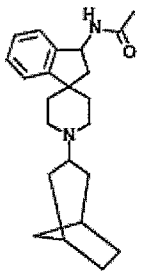
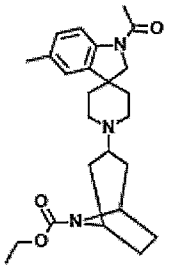
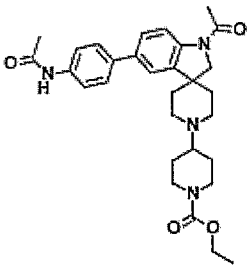
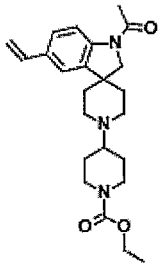
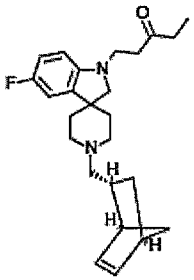
66. The compound of claim 38, wherein m and n are both 2.

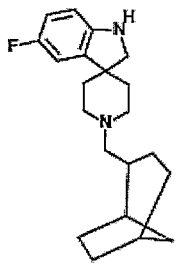
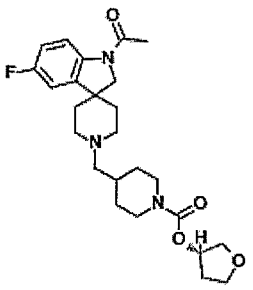
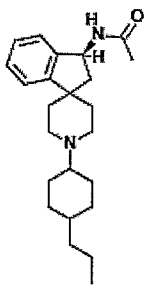
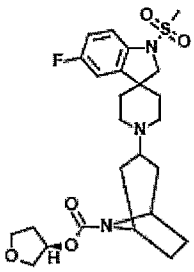
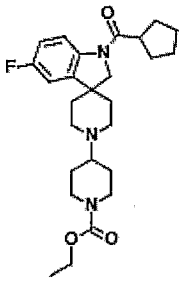
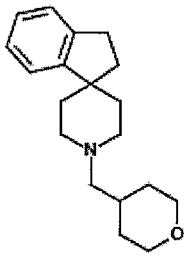
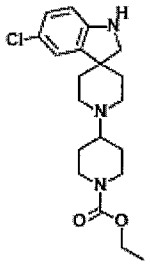
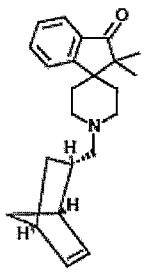
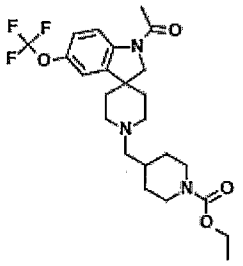
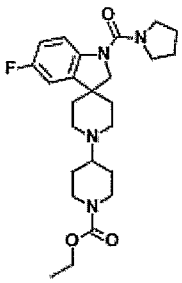
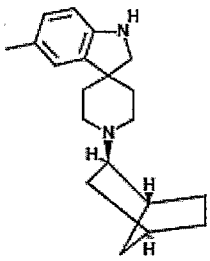
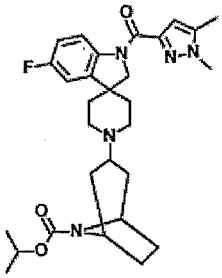
67. The compound of any of claims 38-66, wherein L is a bond or an aliphatic group optionally substituted with 1-3 of oxo, Q_1, or Q_2.

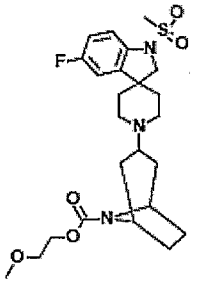
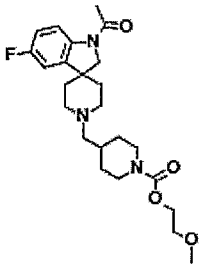
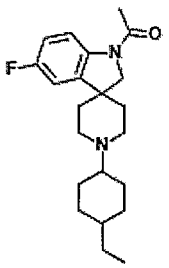
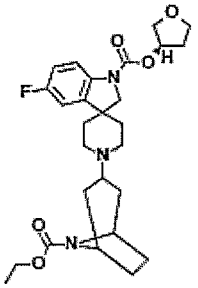
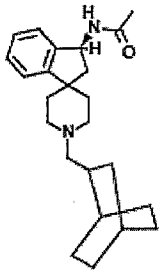
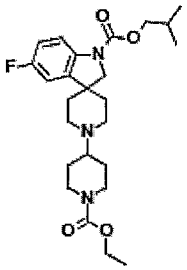
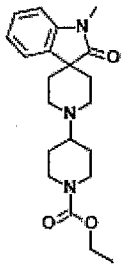
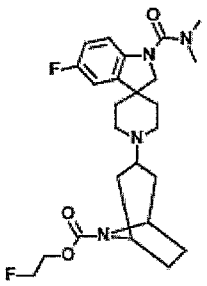
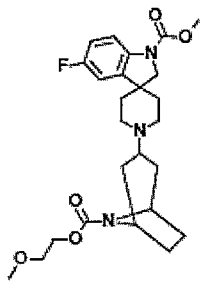
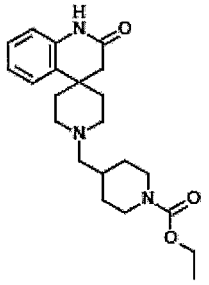
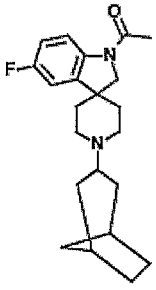
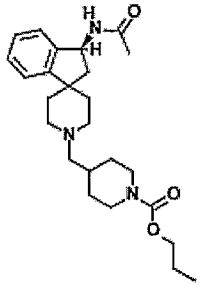
68. The compound of claim 67, wherein L is a bond.

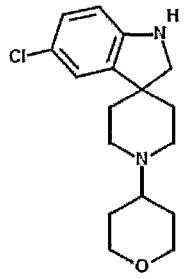
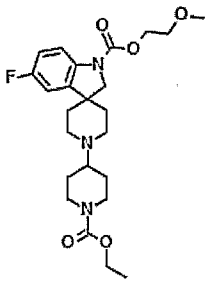
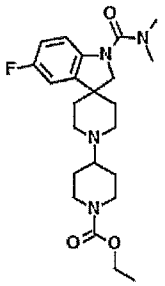
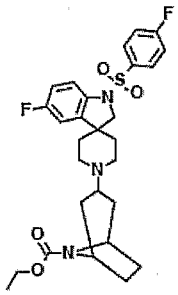
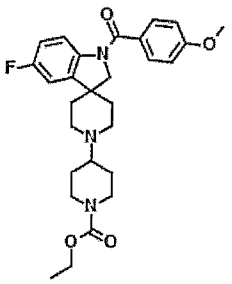
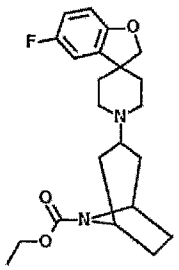
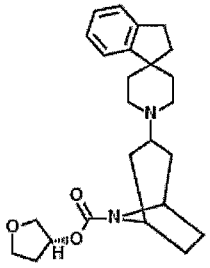
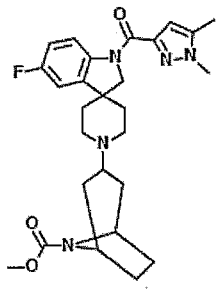
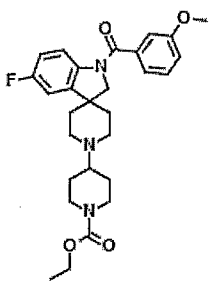
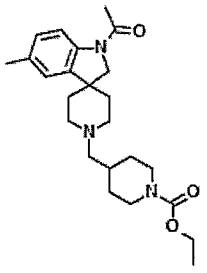
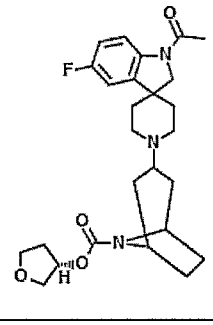
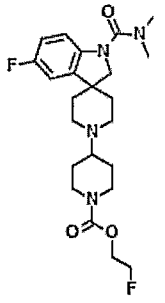
69. The compound of claim 67, wherein L is $-CH_2-$.

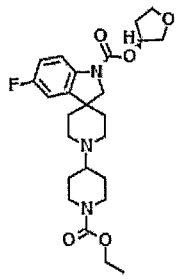
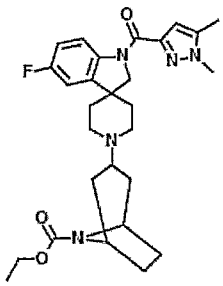
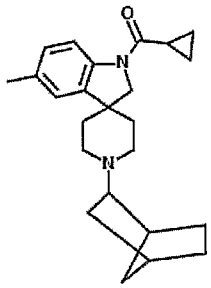
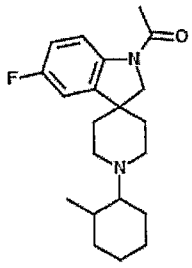
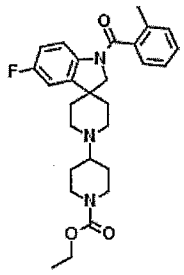
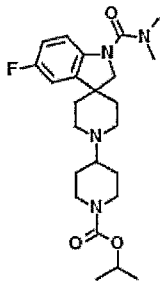
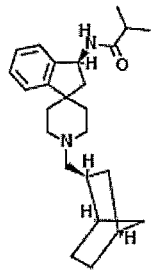
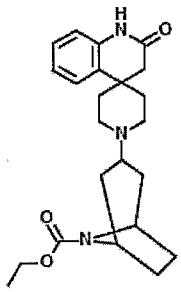
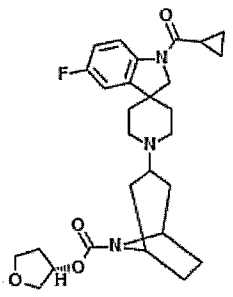
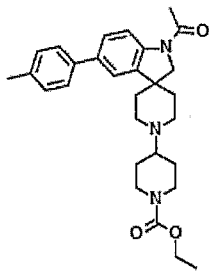
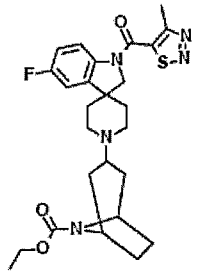
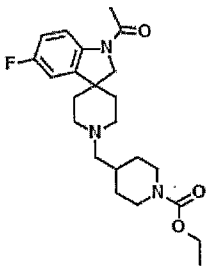
70. The compound of claim 38, wherein the compound is selected from

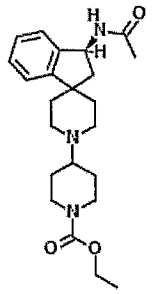
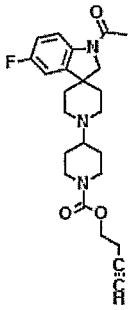
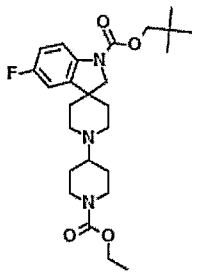
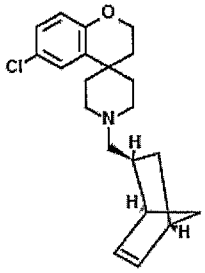
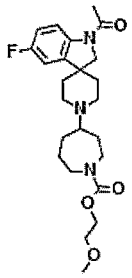
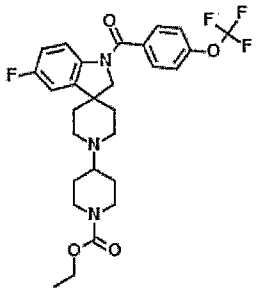
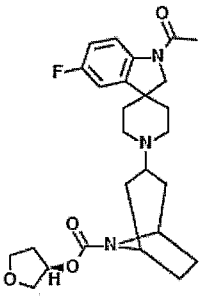
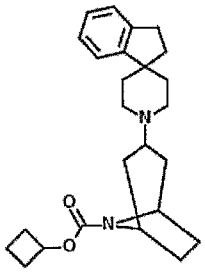
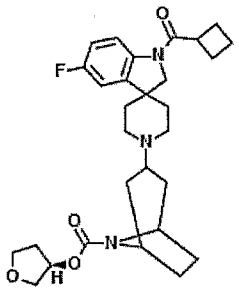
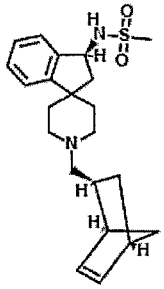
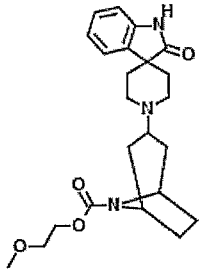
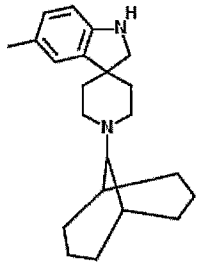
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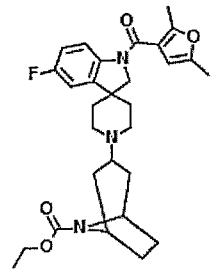
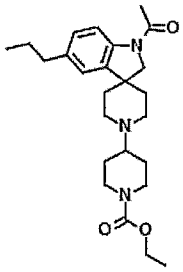
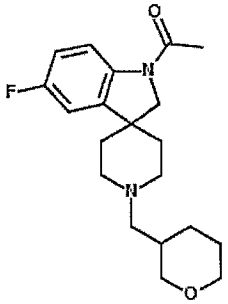
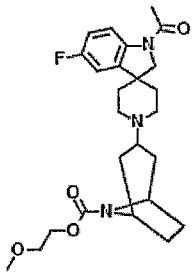
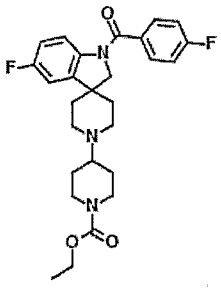
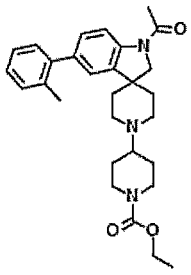
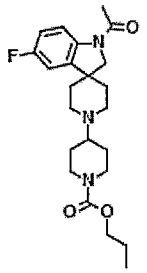
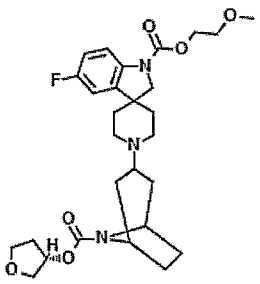
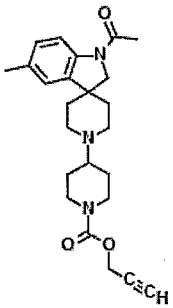
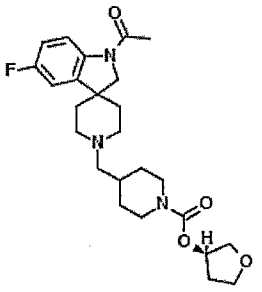
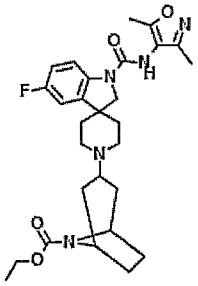
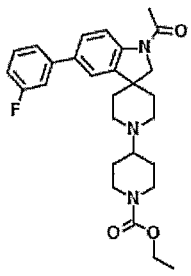
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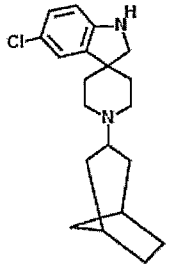
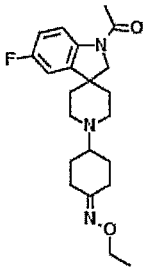
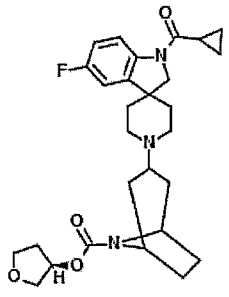
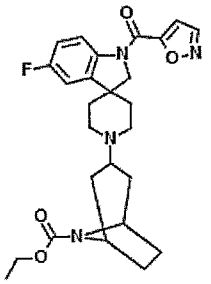
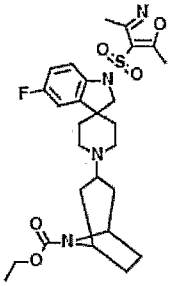
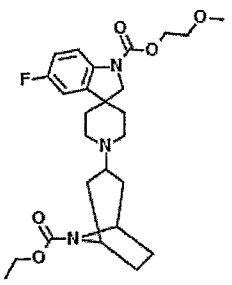
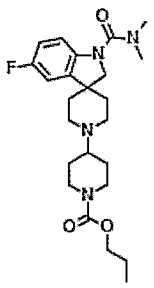
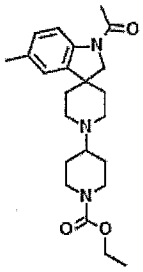
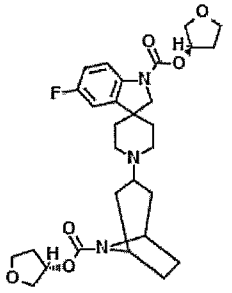
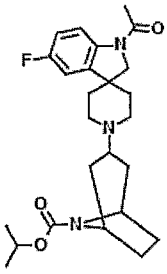
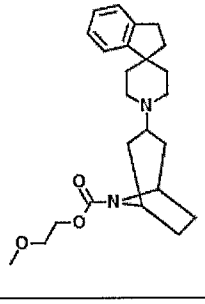
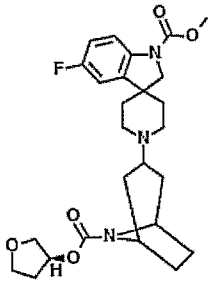
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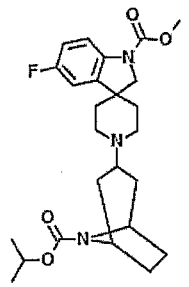
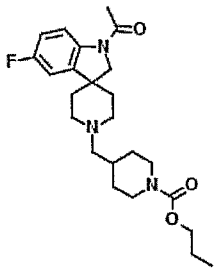
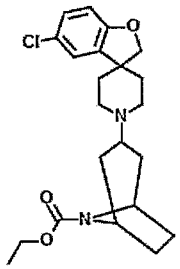
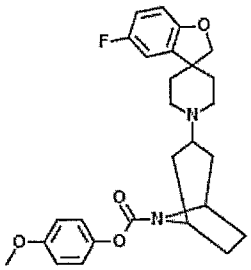
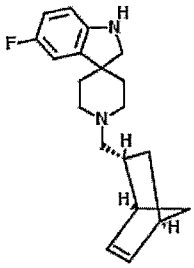
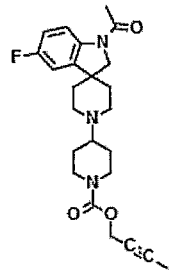
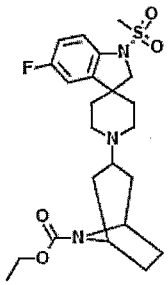
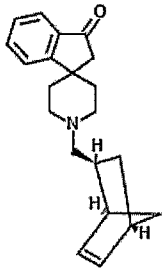
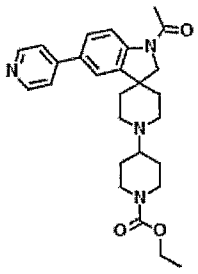
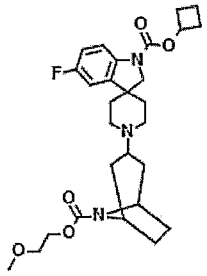
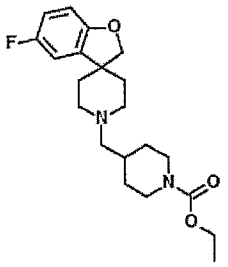
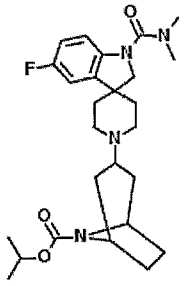
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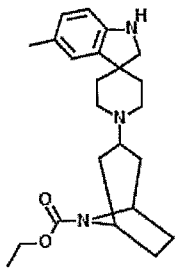
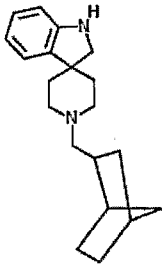
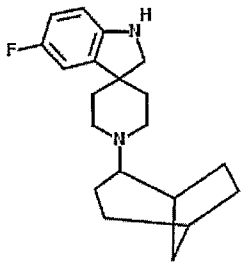
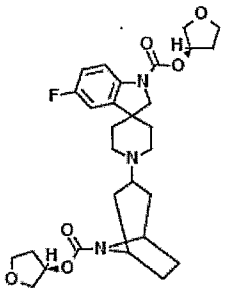
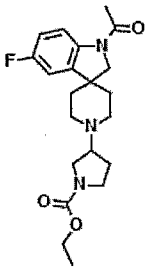
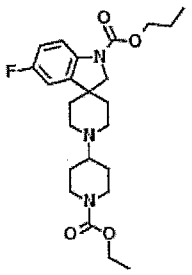
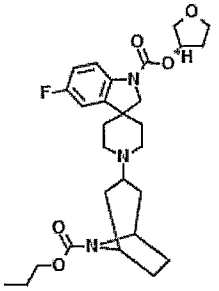
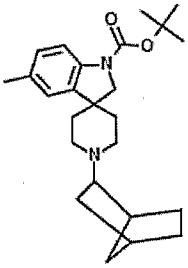
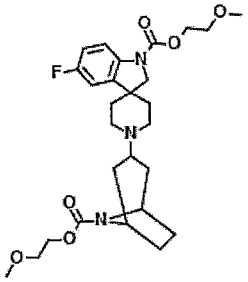
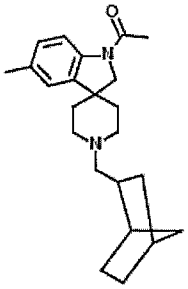
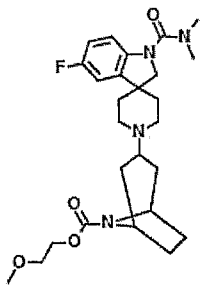
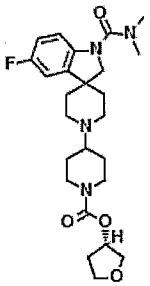
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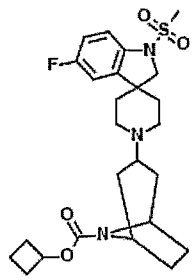
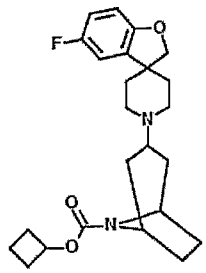
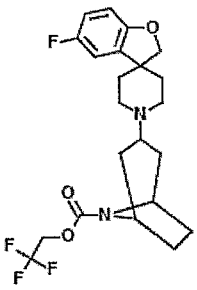
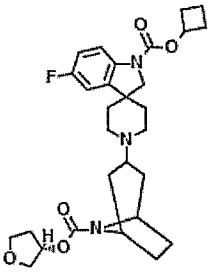
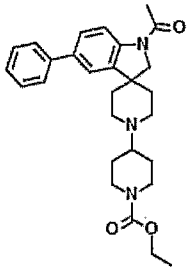
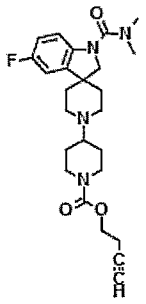
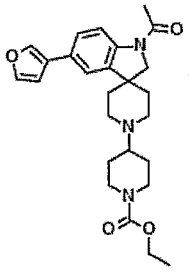
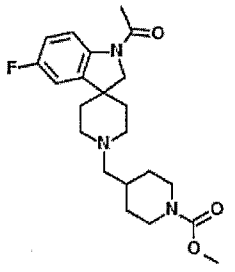
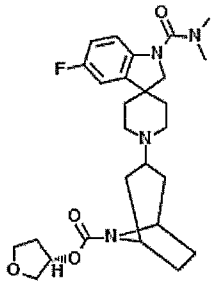
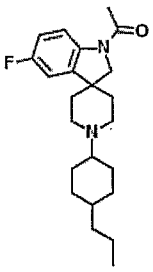
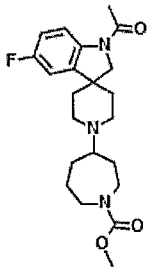
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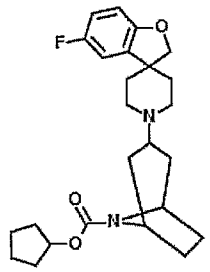
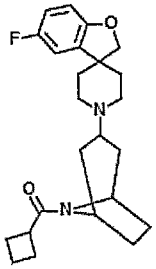
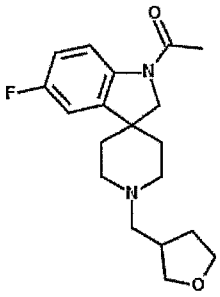
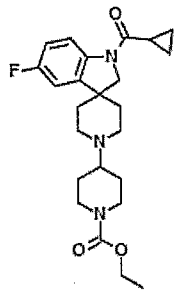
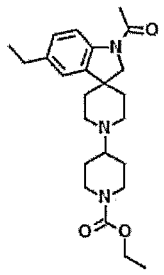
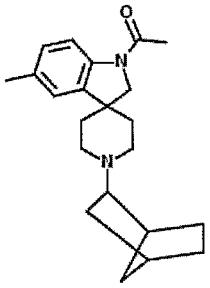
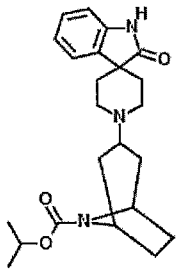
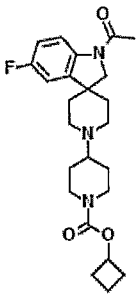
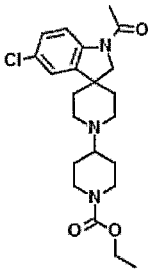
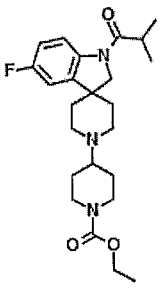
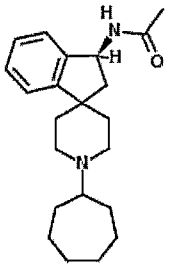
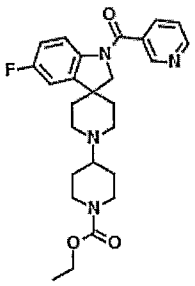
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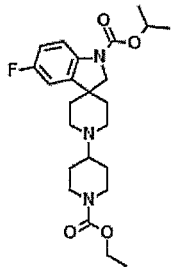
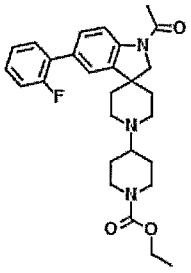
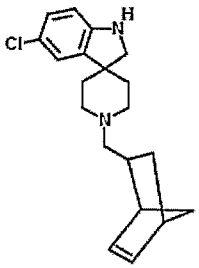
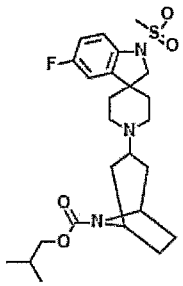
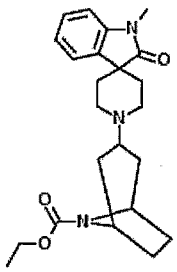
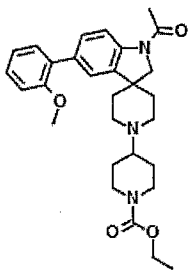
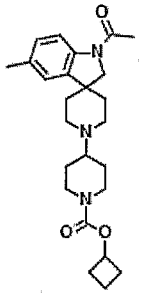
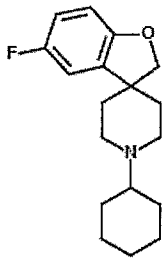
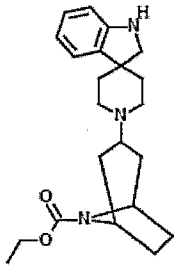
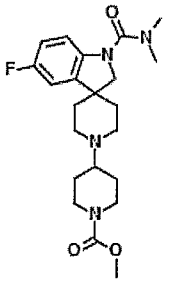
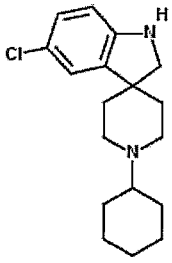
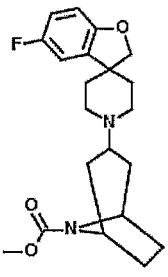
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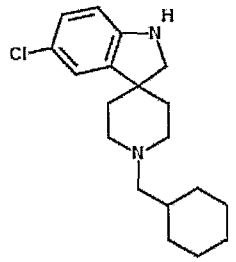
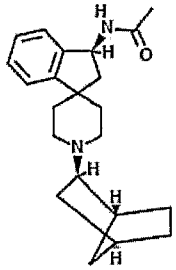
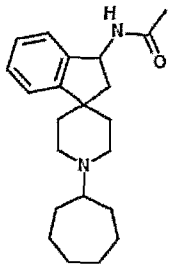
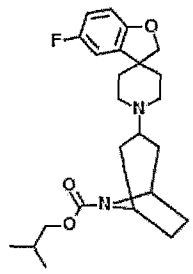
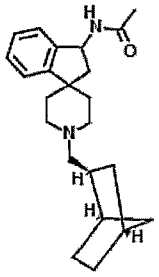
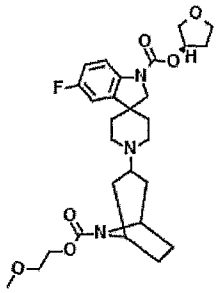
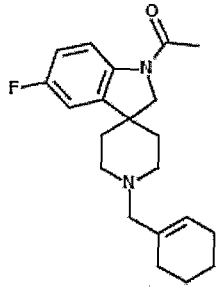
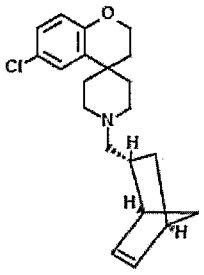
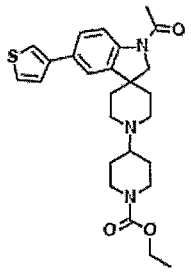
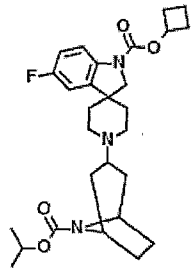
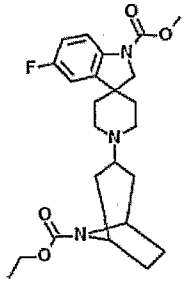
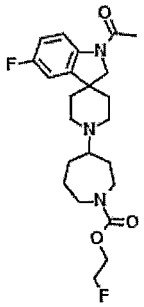
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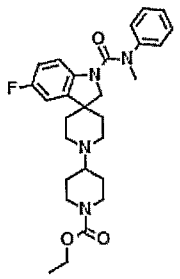
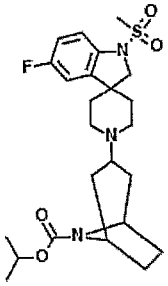
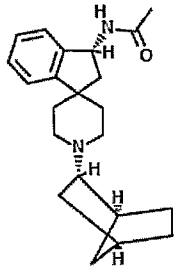
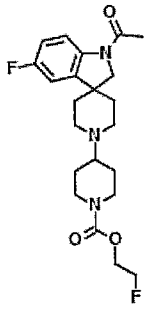
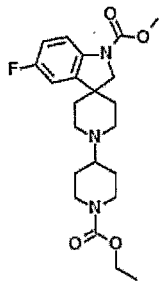
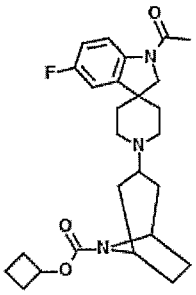
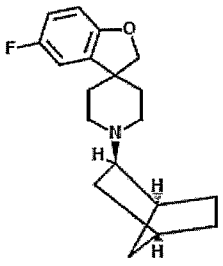
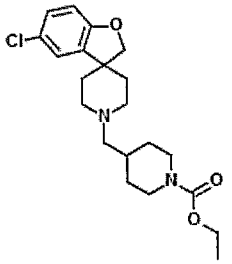
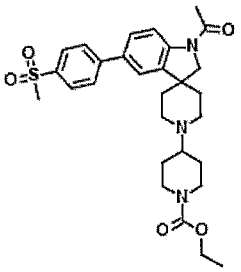
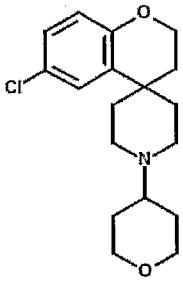
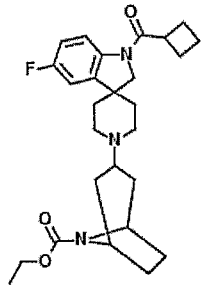
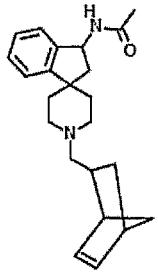
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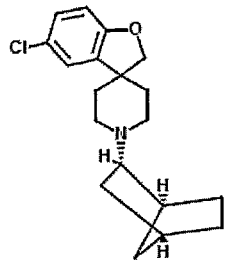
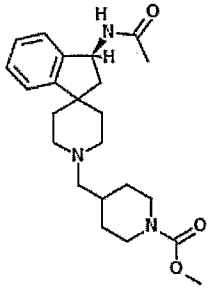
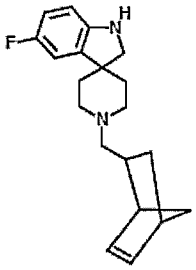
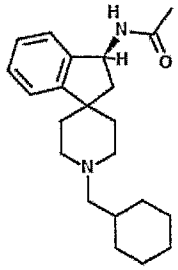
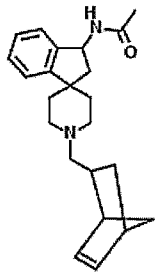
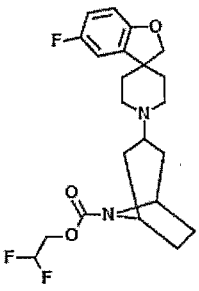
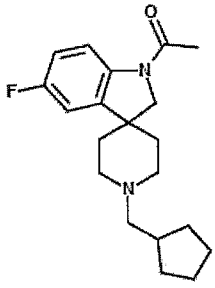
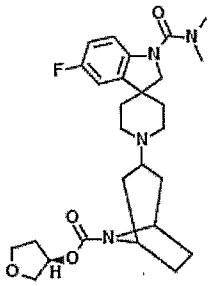
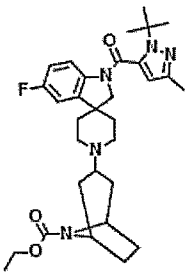
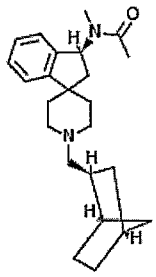
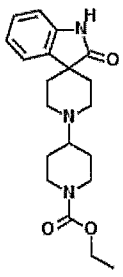
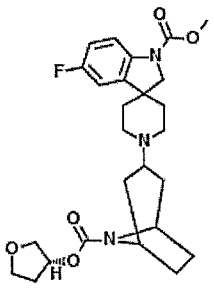
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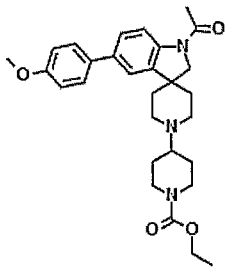
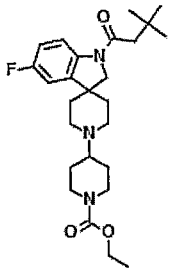
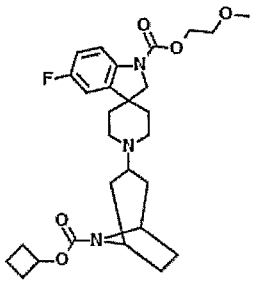
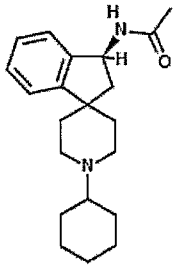
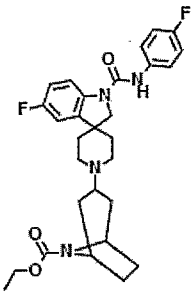
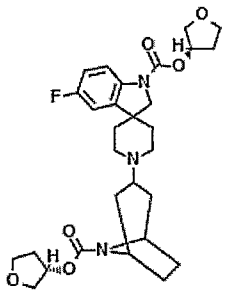
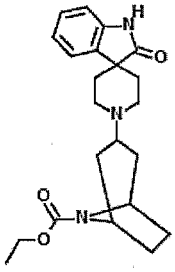
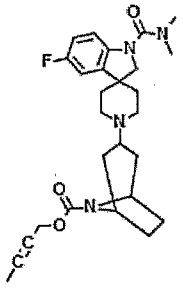
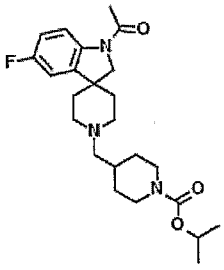
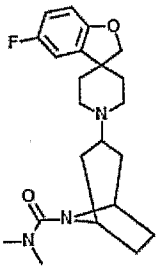
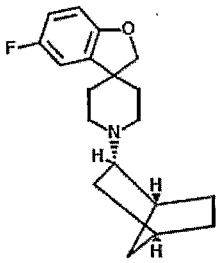
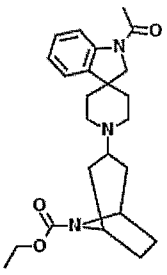
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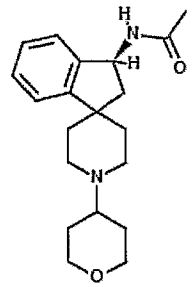
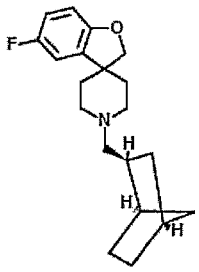
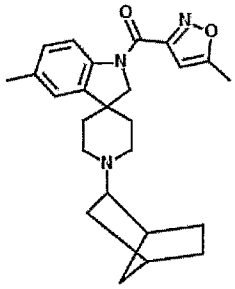
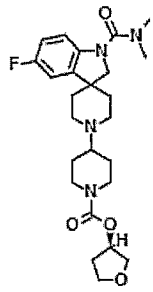
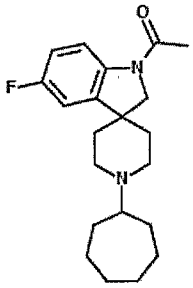
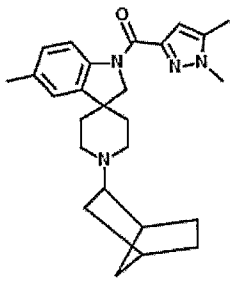
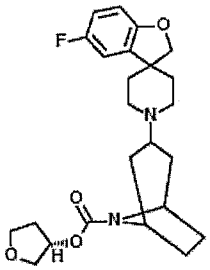
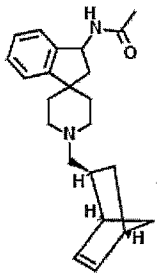
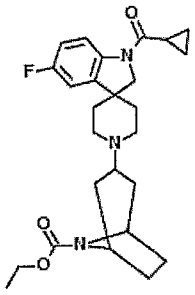
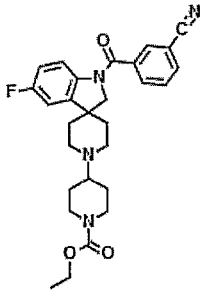
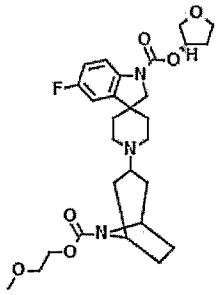
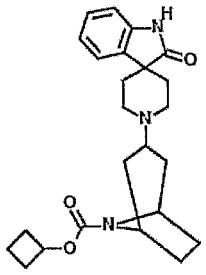
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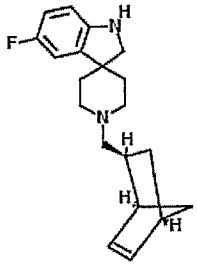
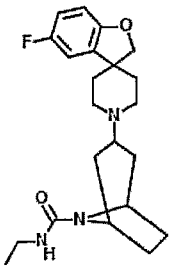
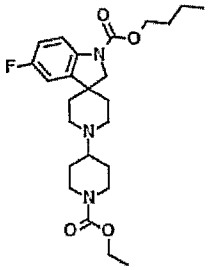
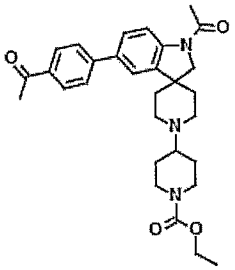
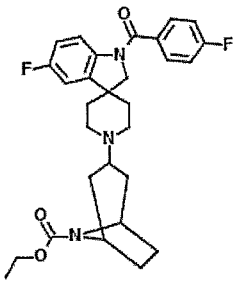
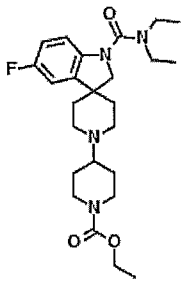
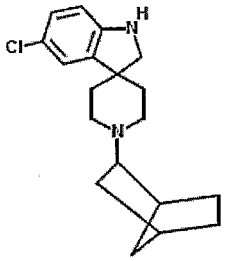
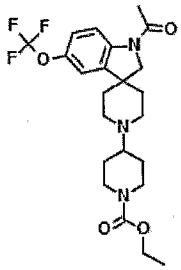
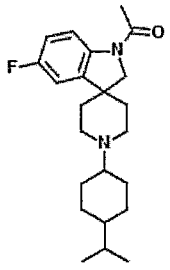
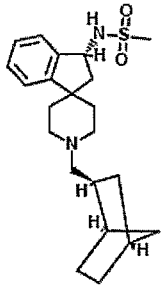
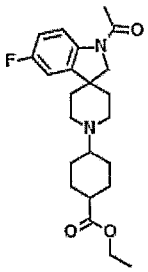
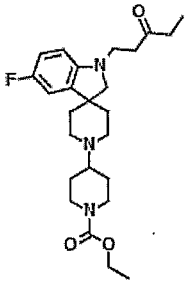
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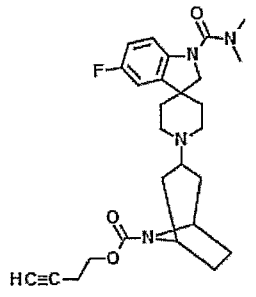
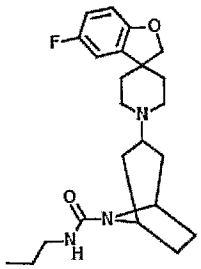
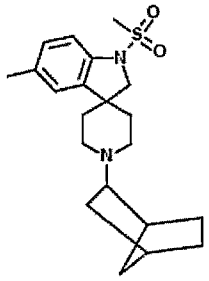
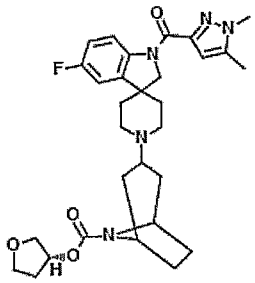
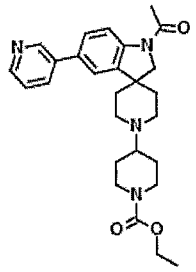
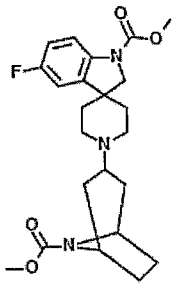
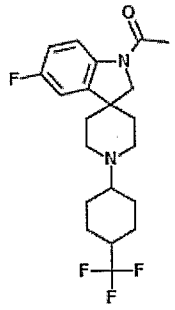
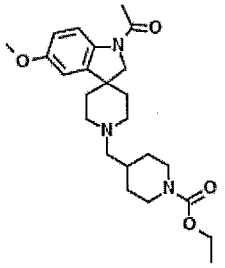
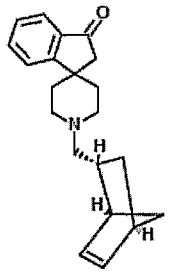
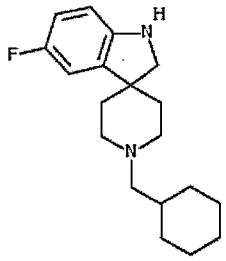
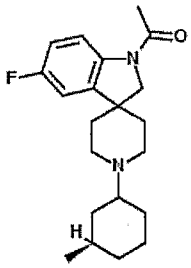
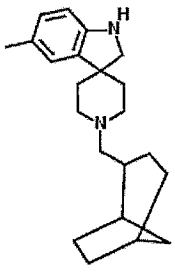
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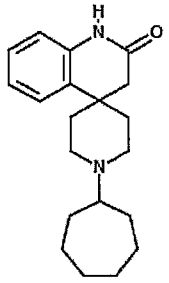
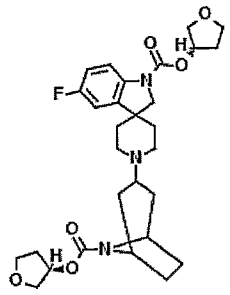
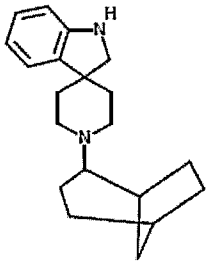
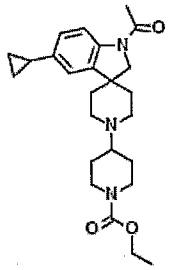
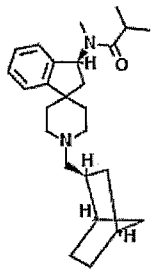
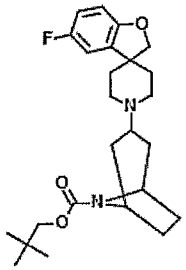
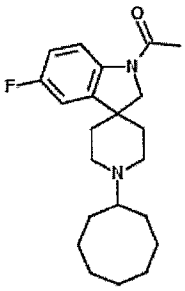
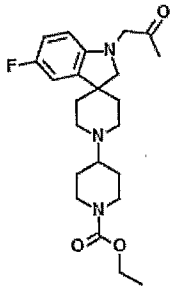
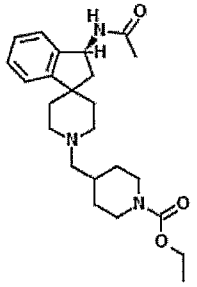
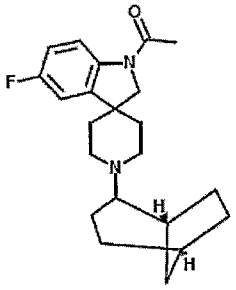
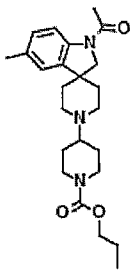
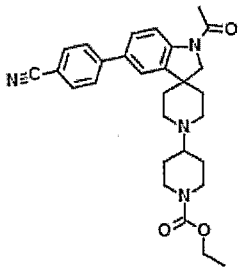
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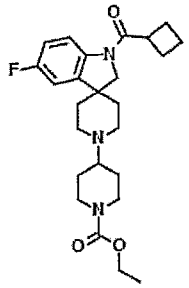
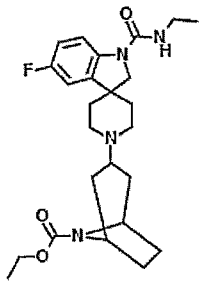
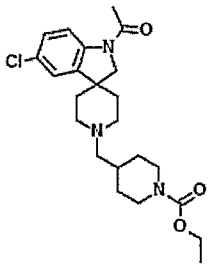
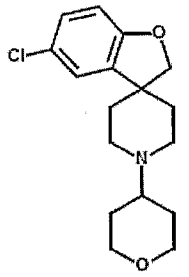
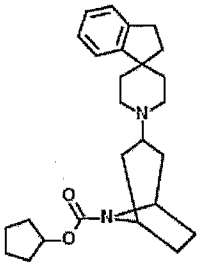
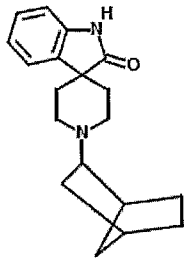
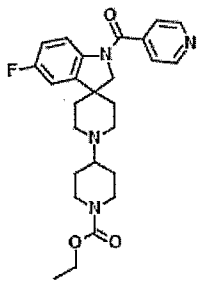
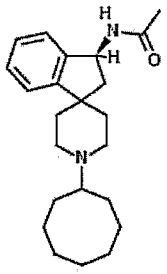
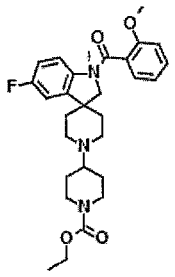
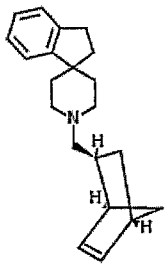
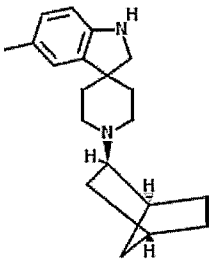
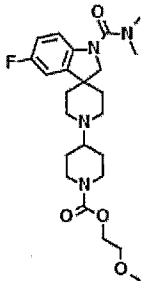
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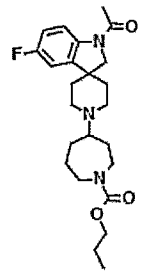
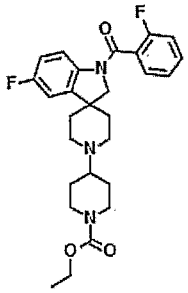
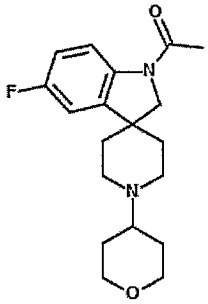
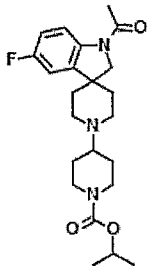
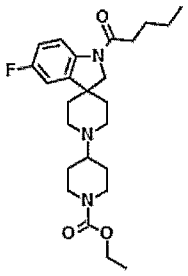
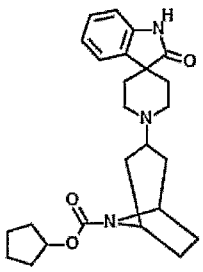
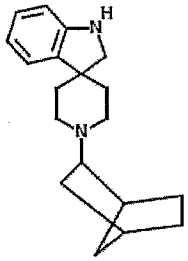
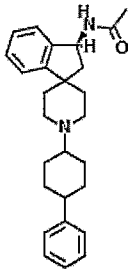
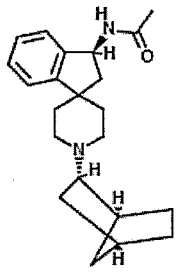
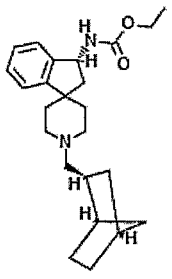
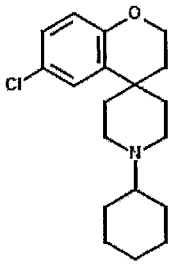
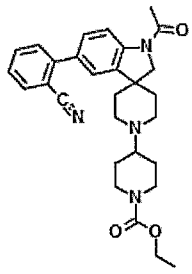
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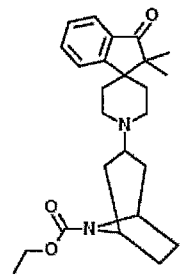
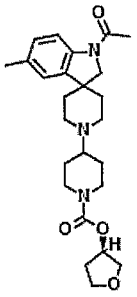
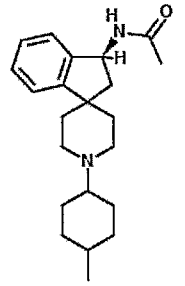
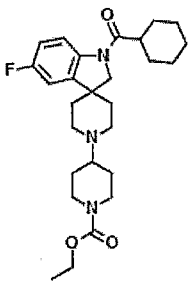
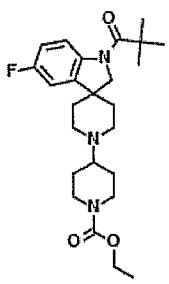
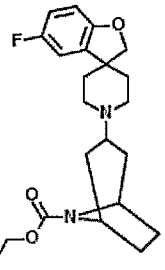
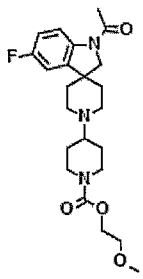
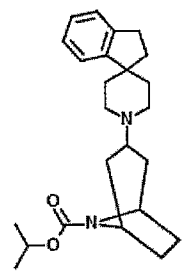
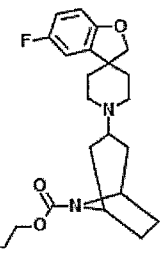
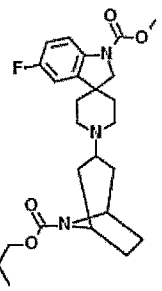
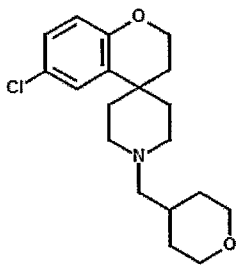
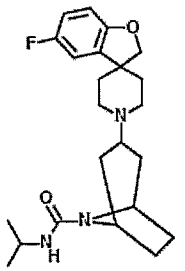
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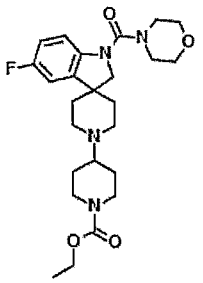
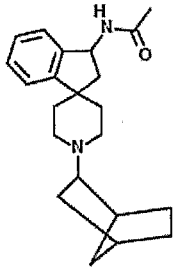
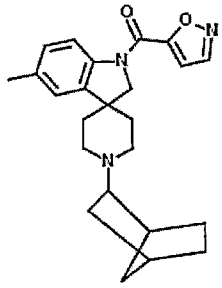
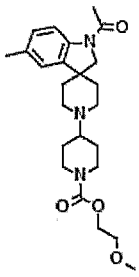
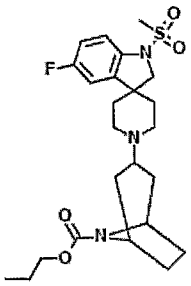
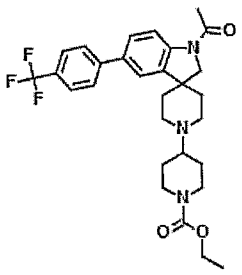
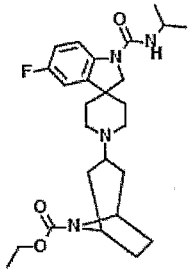
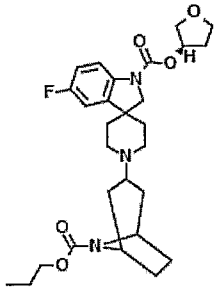
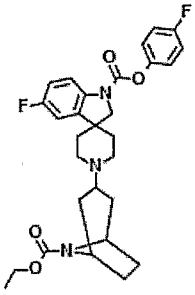
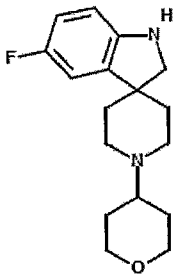
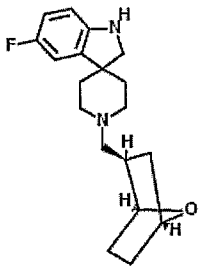
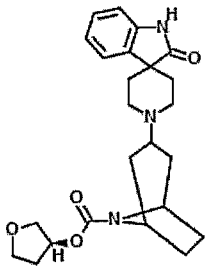
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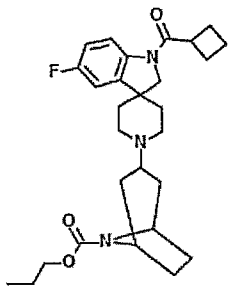
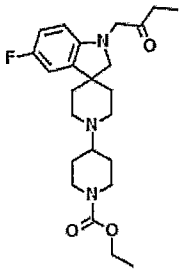
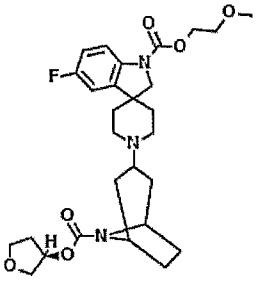
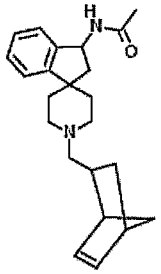
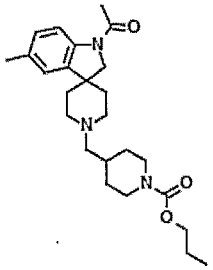
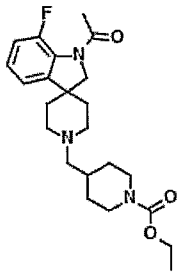
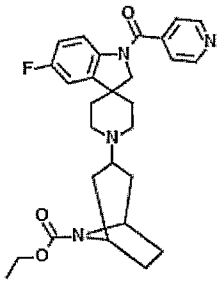
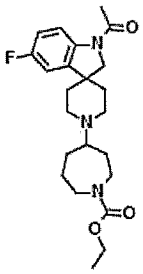
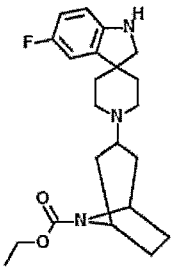
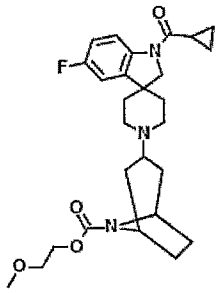
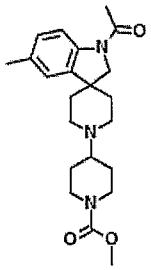
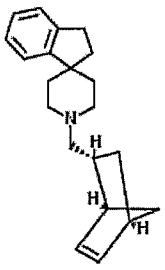
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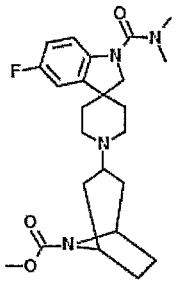
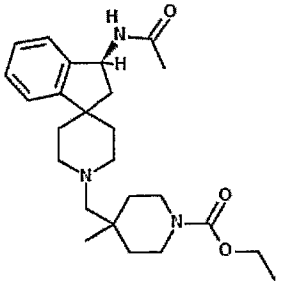
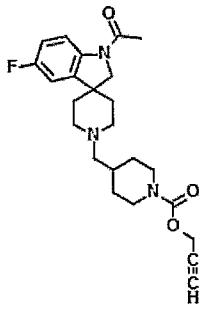
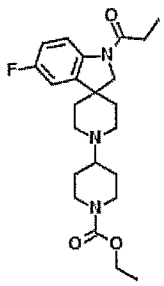
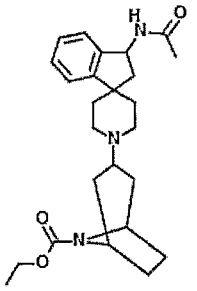
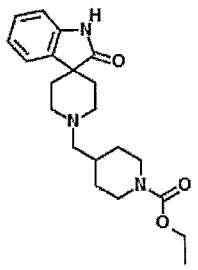
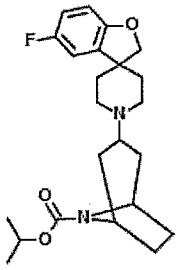
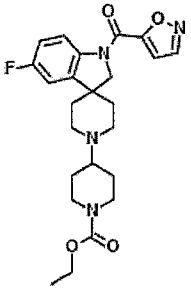
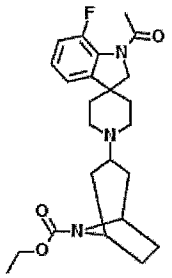
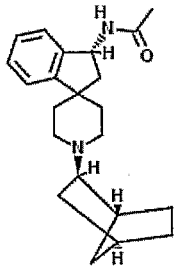
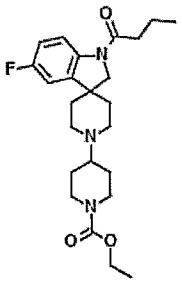
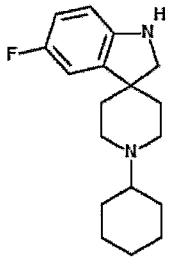
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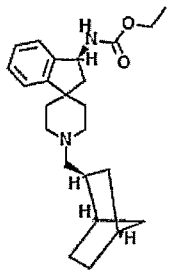
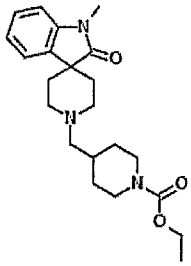
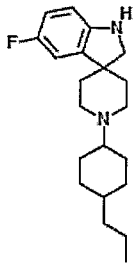
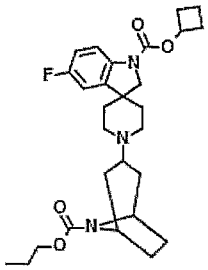
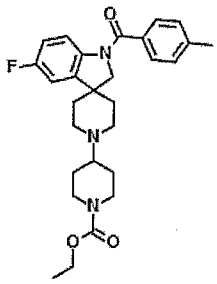
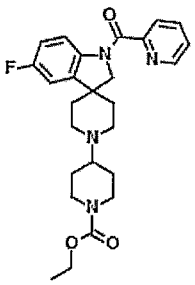
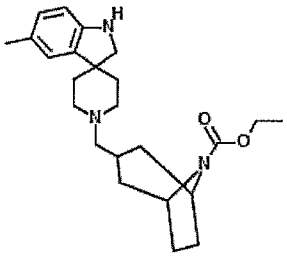
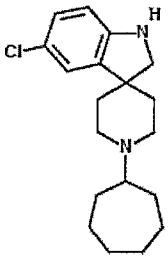
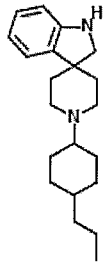
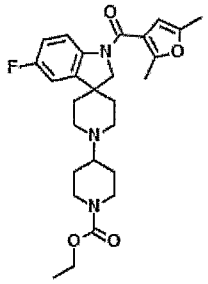
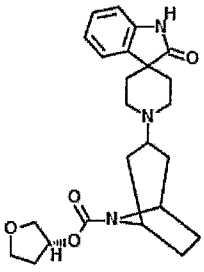
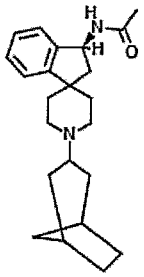
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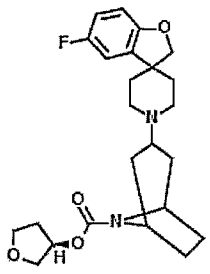
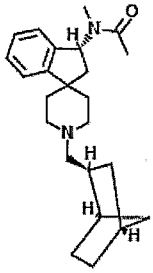
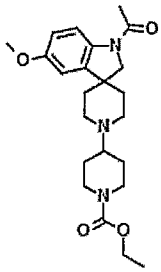
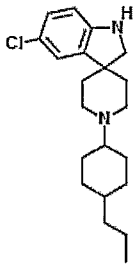
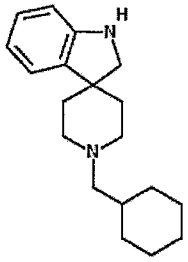
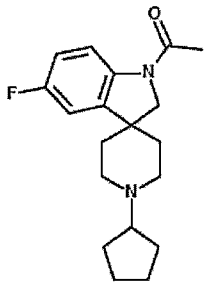
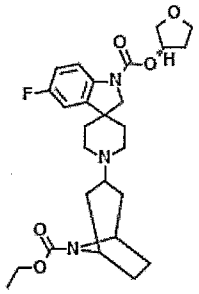
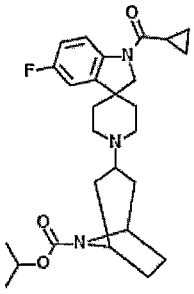
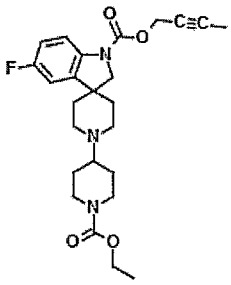
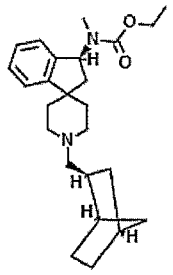
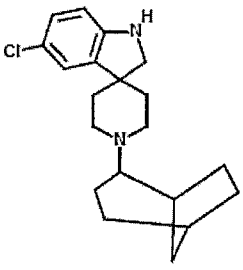
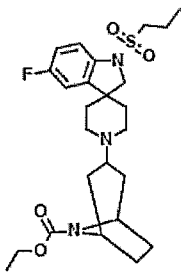
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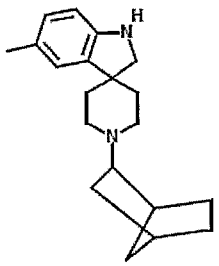
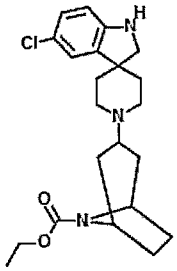
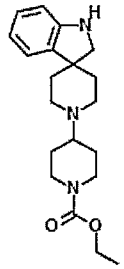
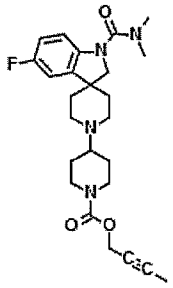
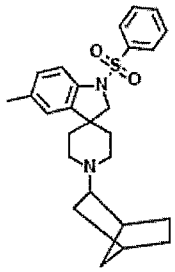
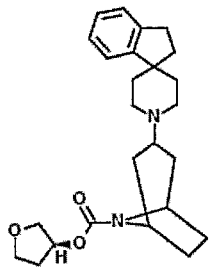
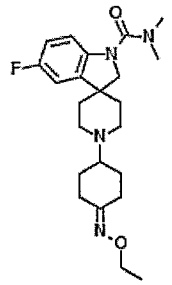
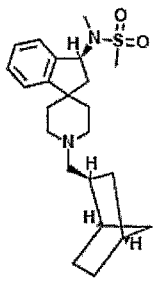
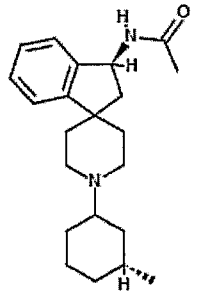
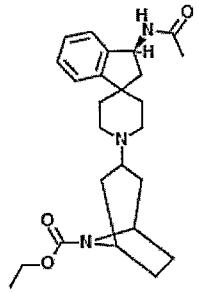
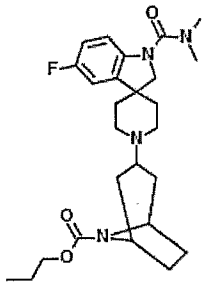
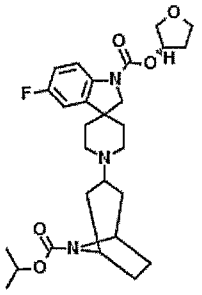
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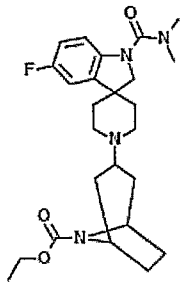
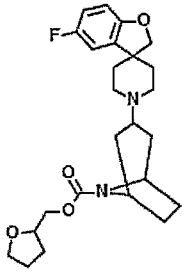
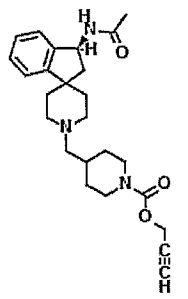
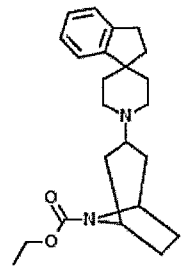
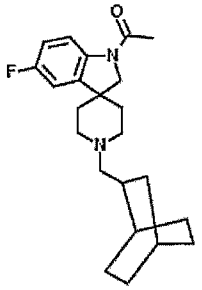
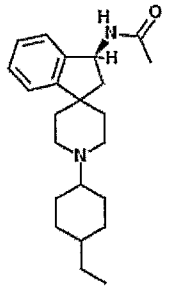
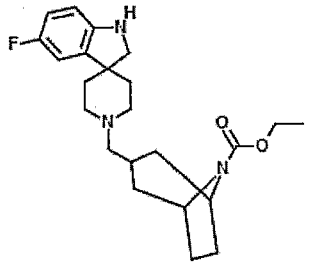
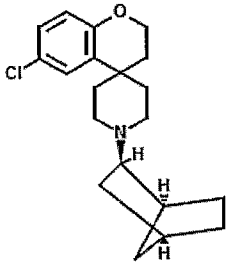
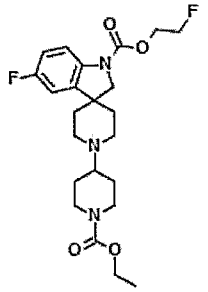
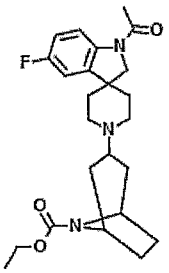
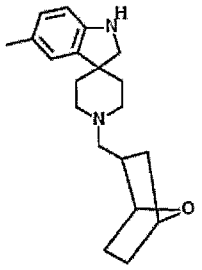
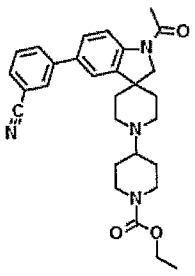
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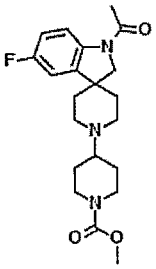
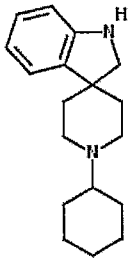
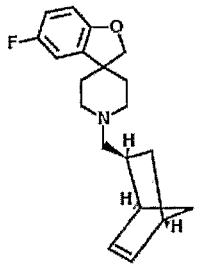
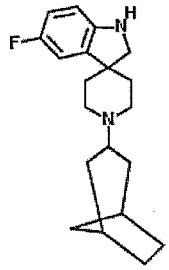
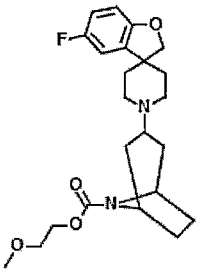
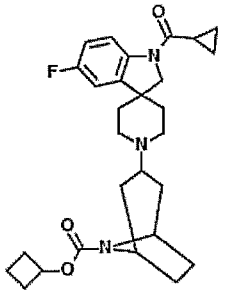
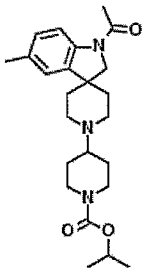
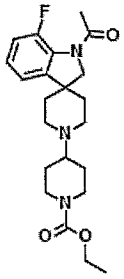
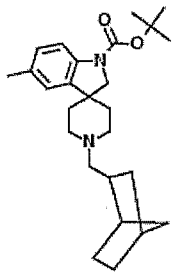
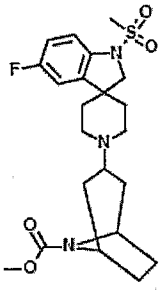
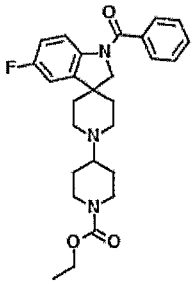
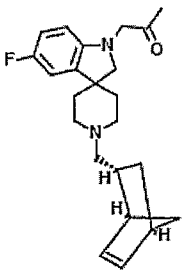
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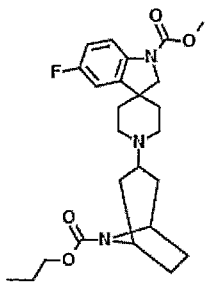
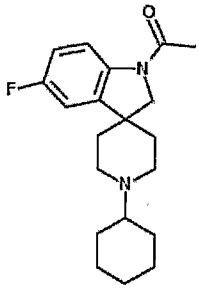
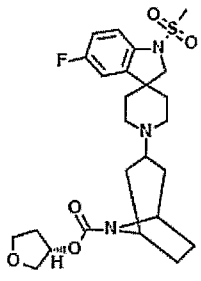
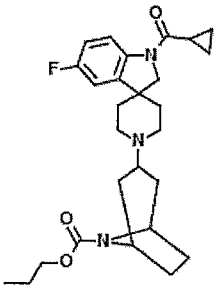
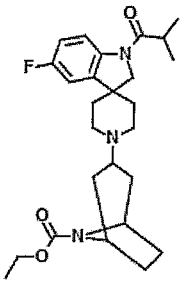
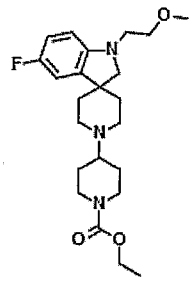
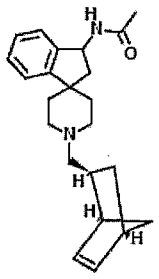
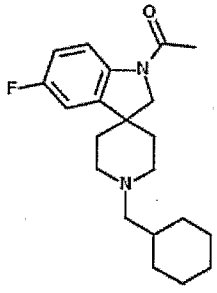
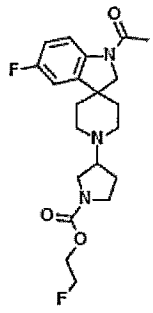
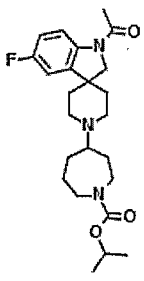
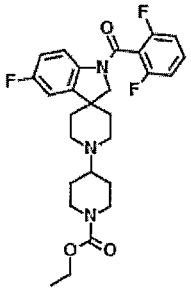
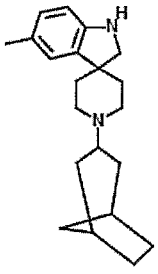
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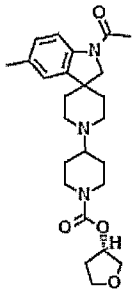
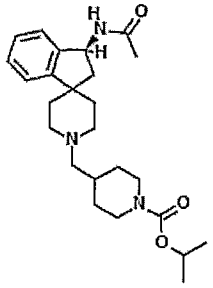
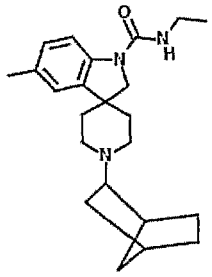
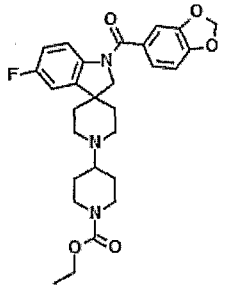
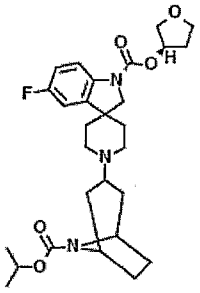
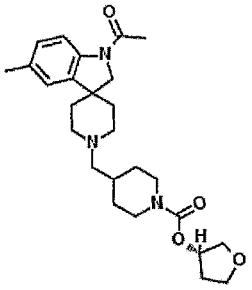
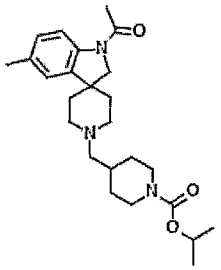
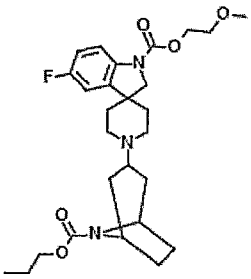
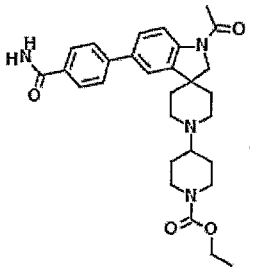
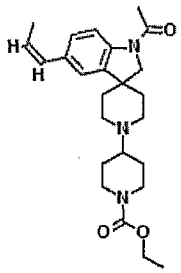
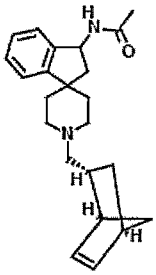
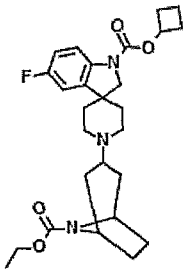
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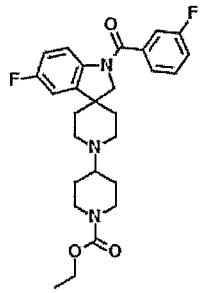
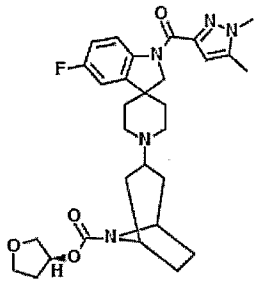
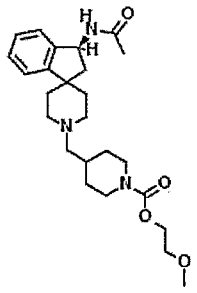
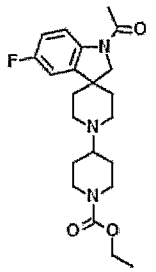
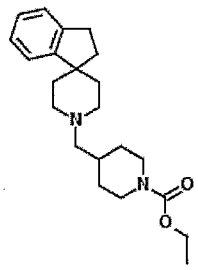
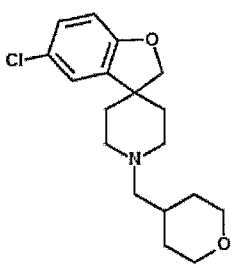
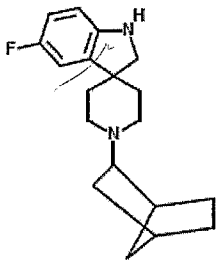
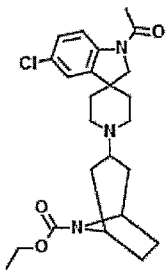
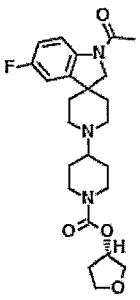
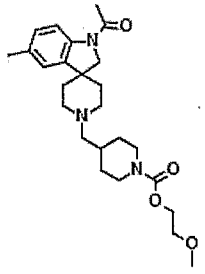
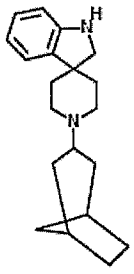
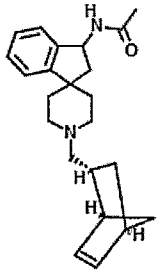
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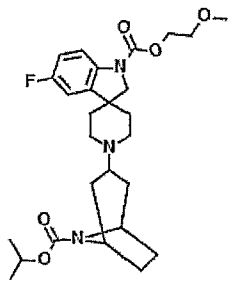
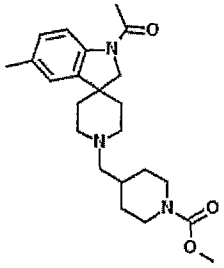
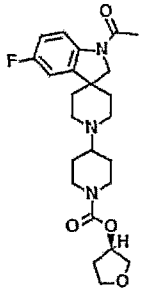
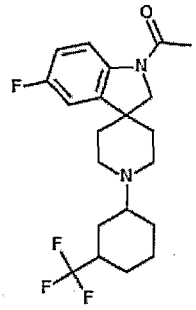
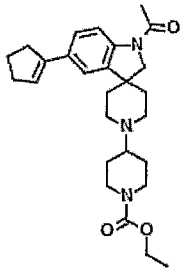
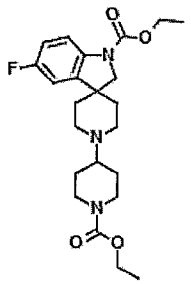
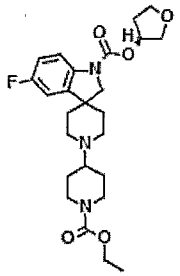
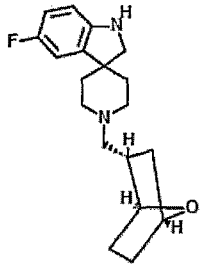
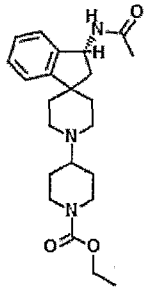
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71. A pharmaceutical composition comprising a compound according to claims 38 or 70 and a pharmaceutical carrier.