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(54) Titre : ANTAGONISTES DU RECEPTEUR MUSCARINIQUE DE L'ACETYLCHOLINE M₄
(54) Title: ANTAGONISTS OF THE MUSCARINIC ACETYLCHOLINE RECEPTOR M₄

(57) **Abrégé/Abstract:**

Disclosed herein are 3-azabicyclo[3.1.0]hexan-6-amine compounds, which may be useful as antagonists of the muscarinic acetylcholine receptor M₄ (mAChR M₄). Also disclosed herein are methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of treating disorders using the compounds and compositions.

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(54) Title: ANTAGONISTS OF THE MUSCARINIC ACETYLCHOLINE RECEPTOR M₄

(57) Abstract: Disclosed herein are 3-azabicyclo[3.1.0]hexan-6-amine compounds, which may be useful as antagonists of the muscarinic acetylcholine receptor M₄ (mAChR M₄). Also disclosed herein are methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of treating disorders using the compounds and compositions.



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ANTAGONISTS OF THE MUSCARINIC ACETYLCHOLINE RECEPTOR M₄

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/625,656, filed February 2, 2018, which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates to compounds, compositions, and methods for treating disorders associated with muscarinic acetylcholine receptor dysfunction.

BACKGROUND

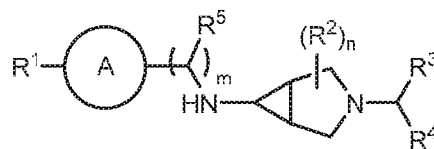
[0003] Parkinson's disease (PD) is the second most common neurodegenerative disease with an increasing prevalence as a function of age. Moreover, early-onset PD is also increasing. A hallmark of PD is the progressive degeneration and loss of dopaminergic neurons in the substantia nigra (SN) and basal ganglia (BG), leading to pronounced motor symptoms including bradykinesia, tremor, rigidity, gait dysfunction and postural instability. At present, levodopa (L-DOPA) is the standard of care for treating the motor symptoms, but it is not curative, and prolonged use can engender L-DOPA induced dyskinesia (LID).

[0004] Prior to L-DOPA, compounds with anticholinergic activity represented the preferred mode of PD treatment. Cholinergic neurons provide important neuromodulatory control of the BG motor circuit. While the actions of cholinergic pathways on basal ganglia pathways are complex, activation of muscarinic acetylcholine receptors (mAChRs) generally have actions that oppose dopamine (DA) signaling. For instance, mAChR agonists inhibit DA release, and inhibit multiple behavioral effects of drugs that increase DA levels and signaling. Interestingly, muscarinic acetylcholine receptor (mAChR) antagonists were the first available treatments for PD and are still widely used for treatment of this disorder. While many studies of the actions of mAChR antagonists were carried out before randomized controlled trials were introduced, recent well controlled double-blind cross-over design studies demonstrate significant improvement in multiple aspects of motor function in patients receiving mAChR antagonists. Unfortunately, mAChR antagonists have a number of dose-limiting adverse effects that severely limit their clinical utility, including multiple peripheral adverse effects, as well as confusion and severe cognitive disturbances.

[0005] Because adverse effects associated with mAChR antagonists limit the doses that can be tolerated, previous clinical studies may underestimate the efficacy that could be achieved if doses of mAChR antagonists could be increased to achieve more complete blockade of specific mAChR subtypes responsible for the antiparkinsonian effects of these agents. The mAChRs include five subtypes, termed M₁ – M₅. Available mAChR antagonists, such as scopolamine, are nonselective across these subtypes, and many of their adverse effects are likely mediated by mAChR subtypes that are not involved in the antiparkinsonian activity. Thus, compounds possessing a more selective profile for individual mAChRs may offer an advantage in PD, as well as related disorders such as dystonia. For example, some studies indicate that the M₄ mAChR subtype may play a dominant role in mAChR regulation of basal ganglia motor function.

SUMMARY

[0006] In one aspect, disclosed are compounds of formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is a five- or six-membered heteroarylene having 1, 2 or 3 heteroatoms independently selected from N, O and S;

m is 0 or 1;

n is 1 or 2;

R¹ is selected from heteroaryl, aryl, heterocyclyl, and cycloalkyl;

each R² is independently selected from hydrogen, C₁-C₄ alkyl, halo, and -OR^a;

R³ is selected from hydrogen and C₁-C₄ alkyl;

R⁴ is selected from -(CR^bR^c)_p-Y', C₁-C₈ alkyl, and C₁-C₈ alkenyl;

R⁵ is selected from hydrogen, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkoxy;

Y' is selected from cycloalkyl, cycloalkenyl, heterocycle, aryl, and heteroaryl;

each R^a is independently selected from hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, and aryl;

each R^b is independently selected from hydrogen and C₁-C₄ alkyl;
each R^c is independently selected from hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, and aryl;
and
p is 0, 1, 2, 3, or 4;
wherein each aryl, heteroaryl, heteroarylene, cycloalkyl, cycloalkenyl, and heterocycle is independently unsubstituted or substituted with 1, 2, or 3 substituents.

[0007] In another aspect, the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0008] In another aspect, the invention provides a method of treating a disorder in a subject, wherein the subject would benefit from antagonism of mAChR M₄, comprising administering to the subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof.

[0009] In another aspect, the invention provides a method for antagonizing mAChR M₄ in a subject, comprising administering to the subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof.

[0010] In another aspect, the invention provides a method for the treatment of a neurodegenerative disorder, a movement disorder, or a brain disorder comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof.

[0011] In another aspect, the invention provides a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, for use in the treatment of a neurodegenerative disorder, a movement disorder, or a brain disorder.

[0012] In another aspect, the invention provides a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, for use in antagonizing mAChR M₄ in a subject.

[0013] In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, in the manufacture of a medicament for the treatment of a neurodegenerative disorder, a movement disorder, or a brain disorder.

[0014] In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, in the manufacture of a medicament for antagonizing mAChR M₄ in a subject.

[0015] In another aspect, the invention provides a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, and instructions for use.

[0016] Also disclosed are pharmaceutical compositions comprising the compounds, methods of making the compounds, kits comprising the compounds, and methods of using the compounds, compositions and kits for treatment of disorders, such as neurological and/or psychiatric disorders, associated with muscarinic acetylcholine receptor dysfunction in a mammal.

DETAILED DESCRIPTION

[0017] Disclosed herein are compounds that are antagonists of the muscarinic acetylcholine receptor M₄ (mAChR M₄), methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of treating disorders using the compounds and pharmaceutical compositions. The compounds include substituted 3-azabicyclo[3.1.0]hexan-6-amine compounds.

1. Definitions

[0018] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

[0019] The terms “comprise(s),” “include(s),” “having,” “has,” “can,” “contain(s),” and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments “comprising,” “consisting of” and

“consisting essentially of,” the embodiments or elements presented herein, whether explicitly set forth or not.

[0020] The modifier “about” used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (for example, it includes at least the degree of error associated with the measurement of the particular quantity). The modifier “about” should also be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression “from about 2 to about 4” also discloses the range “from 2 to 4.” The term “about” may refer to plus or minus 10% of the indicated number. For example, “about 10%” may indicate a range of 9% to 11%, and “about 1” may mean from 0.9-1.1. Other meanings of “about” may be apparent from the context, such as rounding off, so, for example “about 1” may also mean from 0.5 to 1.4.

[0021] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

[0022] The term “alkoxy,” as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy and tert-butoxy.

[0023] The term “alkyl,” as used herein, means a straight or branched, saturated hydrocarbon chain containing from 1 to 10 carbon atoms. The term “lower alkyl” or “C₁-C₆-alkyl” means a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. The term “C₁-C₃-alkyl” means a straight or branched chain hydrocarbon containing from 1 to 3 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-

propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, 4,4-dimethylpentan-2-yl, *n*-heptyl, *n*-octyl, *n*-nonyl, and *n*-decyl.

[0024] The term “alkenyl,” as used herein, means a straight or branched, hydrocarbon chain containing at least one carbon-carbon double bond and from 1 to 10 carbon atoms.

[0025] The term “alkoxyalkyl,” as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

[0026] The term “alkoxyfluoroalkyl,” as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a fluoroalkyl group, as defined herein.

[0027] The term “alkylene,” as used herein, refers to a divalent group derived from a straight or branched chain hydrocarbon of 1 to 10 carbon atoms, for example, of 2 to 5 carbon atoms. Representative examples of alkylene include, but are not limited to, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$.

[0028] The term “alkylamino,” as used herein, means at least one alkyl group, as defined herein, is appended to the parent molecular moiety through an amino group, as defined herein.

[0029] The term “amide,” as used herein, means $-\text{C}(\text{O})\text{NR}-$ or $-\text{NRC}(\text{O})-$, wherein R may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0030] The term “aminoalkyl,” as used herein, means at least one amino group, as defined herein, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0031] The term “amino,” as used herein, means $-\text{NR}_x\text{R}_y$, wherein R_x and R_y may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl. In the case of an aminoalkyl group or any other moiety where amino appends together two other moieties, amino may be $-\text{NR}_x-$, wherein R_x may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0032] The term “aryl,” as used herein, refers to a phenyl group, or a bicyclic fused ring system. Bicyclic fused ring systems are exemplified by a phenyl group appended to the parent molecular moiety and fused to a cycloalkyl group, as defined herein, a phenyl group, a heteroaryl group, as defined herein, or a heterocycle, as defined herein. Representative examples of aryl include, but are not limited to, indolyl, naphthyl, phenyl, benzodioxolyl, and tetrahydroquinoliny.

[0033] The term “cyanoalkyl,” as used herein, means at least one -CN group, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0034] The term “cyanofluoroalkyl,” as used herein, means at least one -CN group, is appended to the parent molecular moiety through a fluoroalkyl group, as defined herein.

[0035] The term “cycloalkoxy,” as used herein, refers to a cycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

[0036] The term “cycloalkyl,” as used herein, refers to a carbocyclic ring system containing three to ten carbon atoms, zero heteroatoms and zero double bonds. The cycloalkyl may be monocyclic, bicyclic, bridged, fused, or spirocyclic. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, and bicyclo[1.1.1]pentanyl. “Cycloalkyl” also includes carbocyclic ring systems in which a cycloalkyl group is appended to the parent molecular moiety and is fused to an aryl group as defined herein (e.g., a phenyl group), a heteroaryl group as defined herein, or a heterocycle as defined herein. Representative examples of such cycloalkyl groups include, but are not limited to, 2,3-dihydro-1*H*-indenyl (e.g., 2,3-dihydro-1*H*-inden-1-yl and 2,3-dihydro-1*H*-inden-2-yl), 6,7-dihydro-5*H*-cyclopenta[*b*]pyridinyl (e.g., 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-6-yl), oxaspiro[3.3]heptanyl (e.g., 2-oxaspiro[3.3]heptan-6-yl), and 5,6,7,8-tetrahydroquinolinyl (e.g., 5,6,7,8-tetrahydroquinolin-5-yl).

[0037] The term “cycloalkenyl,” as used herein, means a non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. The cycloalkenyl may be monocyclic, bicyclic, bridged, fused, or spirocyclic. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl, cycloheptenyl, and bicyclo[2.2.1]heptenyl.

[0038] The term “fluoroalkyl,” as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by fluorine. Representative examples of fluoroalkyl include, but are not limited to, 2-fluoroethyl, 2,2,2-trifluoroethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, and trifluoropropyl such as 3,3,3-trifluoropropyl.

[0039] The term “fluoroalkoxy,” as used herein, means at least one fluoroalkyl group, as defined herein, is appended to the parent molecular moiety through an oxygen atom.

Representative examples of fluoroalkoxy include, but are not limited to, difluoromethoxy, trifluoromethoxy and 2,2,2-trifluoroethoxy.

[0040] The term “halogen” or “halo,” as used herein, means Cl, Br, I, or F.

[0041] The term “haloalkyl,” as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by a halogen.

[0042] The term “haloalkoxy,” as used herein, means at least one haloalkyl group, as defined herein, is appended to the parent molecular moiety through an oxygen atom.

[0043] The term “halocycloalkyl,” as used herein, means a cycloalkyl group, as defined herein, in which one or more hydrogen atoms are replaced by a halogen.

[0044] The term “heteroalkyl,” as used herein, means an alkyl group, as defined herein, in which one or more of the carbon atoms has been replaced by a heteroatom selected from S, O, P and N. Representative examples of heteroalkyls include, but are not limited to, alkyl ethers, secondary and tertiary alkyl amines, amides, and alkyl sulfides.

[0045] The term “heteroaryl,” as used herein, refers to an aromatic monocyclic ring or an aromatic bicyclic ring system. The aromatic monocyclic rings are five or six membered rings containing at least one heteroatom independently selected from the group consisting of N, O and S (e.g. 1, 2, 3, or 4 heteroatoms independently selected from O, S, and N). The five membered aromatic monocyclic rings have two double bonds and the six membered six membered aromatic monocyclic rings have three double bonds. The bicyclic heteroaryl groups are exemplified by a monocyclic heteroaryl ring appended to the parent molecular moiety and fused to a monocyclic cycloalkyl group, as defined herein, a monocyclic aryl group, as defined herein, a monocyclic heteroaryl group, as defined herein, or a monocyclic heterocycle, as defined herein.

Representative examples of heteroaryl include, but are not limited to, indolyl, pyridinyl (including pyridin-2-yl, pyridin-3-yl, pyridin-4-yl), pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrrolyl, benzopyrazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, thienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, furanyl, oxazolyl, isoxazolyl, purinyl, isoindolyl, quinoxaliny, indazolyl, quinazoliny, 1,2,4-triazinyl, 1,3,5-triazinyl, isoquinoliny, quinoliny, 6,7-dihydro-1,3-benzothiazolyl, imidazo[1,2-*a*]pyridinyl, naphthyridinyl, pyridoimidazolyl, thiazolo[5,4-*b*]pyridin-2-yl, thiazolo[5,4-*d*]pyrimidin-2-yl.

[0046] The term “heterocycle” or “heterocyclic,” as used herein, means a monocyclic heterocycle, a bicyclic heterocycle, or a tricyclic heterocycle. The monocyclic heterocycle is a three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S. The three- or four-membered ring contains zero or one double bond, and one heteroatom selected from the group consisting of O, N, and S. The five-membered ring contains zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The six-membered ring contains zero, one or two double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. The seven- and eight-membered rings contains zero, one, two, or three double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Representative examples of monocyclic heterocycles include, but are not limited to, azetidiny, azepanyl, aziridiny, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazoliny, imidazolidiny, isothiazoliny, isothiazolidiny, isoxazoliny, isoxazolidiny, morpholiny, 2-oxo-3-piperidiny, 2-oxoazepan-3-yl, oxadiazoliny, oxadiazolidiny, oxazoliny, oxazolidiny, oxetanyl, oxepanyl, oxocanyl, piperaziny, piperidiny, pyranyl, pyrazoliny, pyrazolidiny, pyrroliny, pyrrolidiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridiny, tetrahydrothienyl, thiadiazoliny, thiadiazolidiny, 1,2-thiazinanyl, 1,3-thiazinanyl, thiazoliny, thiazolidiny, thiomorpholiny, 1,1-dioxidothiomorpholiny (thiomorpholine sulfone), thiopyranyl, and trithianyl. The bicyclic heterocycle is a monocyclic heterocycle fused to a phenyl group, or a monocyclic heterocycle fused to a monocyclic cycloalkyl, or a monocyclic heterocycle fused to a monocyclic cycloalkenyl, or a monocyclic heterocycle fused to a monocyclic heterocycle, or a spiro heterocycle group, or a bridged monocyclic heterocycle ring system in which two non-adjacent atoms of the ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. Representative examples of bicyclic heterocycles include, but are not limited to, benzopyranyl, benzothiopyranyl, chromanyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydroisoquinoline, 2-azaspiro[3.3]heptan-2-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, azabicyclo[2.2.1]heptyl (including 2-azabicyclo[2.2.1]hept-2-yl), oxabicyclo[2.2.1]heptanyl (including 7-oxabicyclo[2.2.1]heptan-3-yl), azabicyclo[3.1.0]hexanyl (including 3-azabicyclo[3.1.0]hexan-3-yl), 2,3-dihydro-1*H*-indolyl, isoindoliny, octahydrocyclopenta[*c*]pyrrolyl, octahydropyrrolopyridiny, and

tetrahydroisoquinolinyl. Tricyclic heterocycles are exemplified by a bicyclic heterocycle fused to a phenyl group, or a bicyclic heterocycle fused to a monocyclic cycloalkyl, or a bicyclic heterocycle fused to a monocyclic cycloalkenyl, or a bicyclic heterocycle fused to a monocyclic heterocycle, or a bicyclic heterocycle in which two non-adjacent atoms of the bicyclic ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. Examples of tricyclic heterocycles include, but are not limited to, octahydro-2,5-epoxypentalene, hexahydro-2*H*-2,5-methanocyclopenta[*b*]furan, hexahydro-1*H*-1,4-methanocyclopenta[*c*]furan, aza-adamantane (1-azatricyclo[3.3.1.1^{3,7}]decane), and oxa-adamantane (2-oxatricyclo[3.3.1.1^{3,7}]decane). The monocyclic, bicyclic, and tricyclic heterocycles are connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the rings, and can be unsubstituted or substituted.

[0047] The term “hydroxyl” or “hydroxy,” as used herein, means an -OH group.

[0048] The term “hydroxyalkyl,” as used herein, means at least one -OH group, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0049] The term “hydroxyfluoroalkyl,” as used herein, means at least one -OH group, is appended to the parent molecular moiety through a fluoroalkyl group, as defined herein.

[0050] In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl or cycloalkyl) is indicated by the prefix “C_x-C_y,” wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, “C₁-C₃-alkyl” refers to an alkyl substituent containing from 1 to 3 carbon atoms.

[0051] The term “sulfonamide,” as used herein, means -S(O)₂NR^d- or -NR^dS(O)-, wherein R^d may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0052] The term “substituents” refers to a group “substituted” on an aryl, heteroaryl, phenyl or pyridinyl group at any atom of that group. Any atom can be substituted.

[0053] The term “substituted” refers to a group that may be further substituted with one or more non-hydrogen substituent groups. Substituent groups include, but are not limited to, halogen, =O (oxo), =S (thioxo), cyano, nitro, fluoroalkyl, alkoxyfluoroalkyl, fluoroalkoxy, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, heteroalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycle, cycloalkylalkyl, heteroarylalkyl, arylalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkylene, aryloxy, phenoxy, benzyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl,

sulfinyl, -COOH, ketone, amide, carbamate, and acyl. For example, if a group is described as being “optionally substituted” (such as an alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heteroalkyl, heterocycle or other group such as an R group), it may have 0, 1, 2, 3, 4 or 5 substituents independently selected from halogen, =O (oxo), =S (thioxo), cyano, nitro, fluoroalkyl, alkoxyfluoroalkyl, fluoroalkoxy, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, heteroalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycle, cycloalkylalkyl, heteroarylalkyl, arylalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkylene, aryloxy, phenoxy, benzyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, -COOH, ketone, amide, carbamate, and acyl.

[0054] The term “—” designates a single bond (—) or a double bond (==).

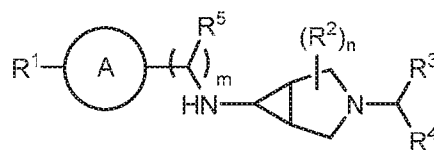
[0055] For compounds described herein, groups and substituents thereof may be selected in accordance with permitted valence of the atoms and the substituents, such that the selections and substitutions result in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[0056] The term “mAChR M₄ receptor antagonist” as used herein refers to any exogenously administered compound or agent that directly or indirectly antagonizes mAChR M₄, for example in an animal, in particular a mammal (e.g., a human).

[0057] For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the numbers 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

2. Compounds

[0058] In one aspect, disclosed is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A is a five- or six-membered heteroarylene having 1, 2 or 3 heteroatoms independently selected from N, O and S;

m is 0 or 1;

n is 1 or 2;

R¹ is selected from heteroaryl, aryl, heterocyclyl, and cycloalkyl;

each R² is independently selected from hydrogen, C₁-C₄ alkyl, halo, and -OR^a;

R³ is selected from hydrogen and C₁-C₄ alkyl;

R⁴ is selected from -(CR^bR^c)_p-Y', C₁-C₈ alkyl, and C₁-C₈ alkenyl;

R⁵ is selected from hydrogen, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkoxy;

Y' is selected from cycloalkyl, cycloalkenyl, heterocycle, aryl, and heteroaryl;

each R^a is independently selected from hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, and aryl;

each R^b is independently selected from hydrogen and C₁-C₄ alkyl;

each R^c is independently selected from hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, and aryl;

and

p is 0, 1, 2, 3, or 4;

wherein each aryl, heteroaryl, heteroarylene, cycloalkyl, cycloalkenyl, and heterocycle is independently unsubstituted or substituted with 1, 2, or 3 substituents.

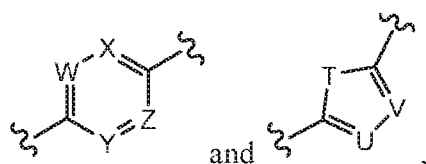
[0059] In some embodiments, each aryl, heteroaryl, heteroarylene, cycloalkyl, cycloalkenyl, and heterocycle is independently unsubstituted or substituted with 1, 2, or 3 substituents independently selected from C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ hydroxyalkyl, hydroxy, cyano, -NHCOR^e, and benzyl.

[0060] In the embodiments herein, R^e may be hydrogen or C₁-C₄ alkyl.

[0061] In some embodiments, each aryl, heteroaryl, heteroarylene, cycloalkyl, cycloalkenyl, and heterocycle is independently unsubstituted or substituted with 1, 2, or 3 substituents independently selected from C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ hydroxyalkyl, hydroxy, cyano, -NHCOR^e, C₃-C₆cycloalkyl, and benzyl; and R^e is hydrogen or C₁-C₄ alkyl.

[0062] In some embodiments, ring A is unsubstituted.

[0063] In some embodiments, A is selected from:



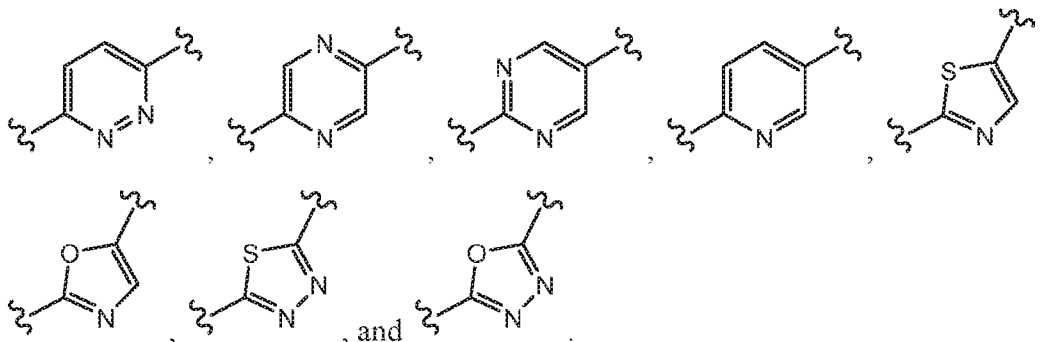
wherein:

T is selected from O, S and NH;

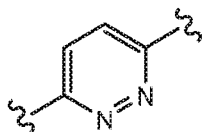
U, V, W, X, Y and Z are independently selected from N and CR^d; and

each R^d is independently selected from hydrogen, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, and hydroxy.

[0064] In some embodiments, A is selected from:



[0065] In some embodiments, A is:



[0066] In some embodiments, m is 0.

[0067] In some embodiments, m is 1.

[0068] In some embodiments, m is 1, and R⁵ is hydrogen.

[0069] In some embodiments, R¹ is selected from aryl (e.g., phenyl or benzodioxolyl), heteroaryl (e.g., 5- or 6- membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, such as pyrazolyl or isoxazolyl), heterocyclyl (e.g., a 5- or 6- membered heterocycle having 1, 2, or 3 heteroatoms independently selected from N, O, and S, such as morpholino), and cycloalkyl (e.g., a C₃-C₇ cycloalkyl). The aryl, heteroaryl, heterocyclyl, and cycloalkyl may be substituted with 1, 2, or 3 substituents independently selected from C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ hydroxyalkyl, hydroxy, cyano, -NHCOR^e, C₃-C₆cycloalkyl, and benzyl; and R^e is hydrogen or C₁-C₄ alkyl.

[0070] In some embodiments, R¹ is selected from phenyl and a 5- or 6- membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, wherein the phenyl or

heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, and -NHCOR^e (wherein R^e is selected from hydrogen and C₁-C₄ alkyl).

[0071] In some embodiments, R¹ is selected from phenyl and a 5- or 6- membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, wherein the phenyl or heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from halo, C₁-C₄ alkyl, and C₁-C₄ haloalkyl.

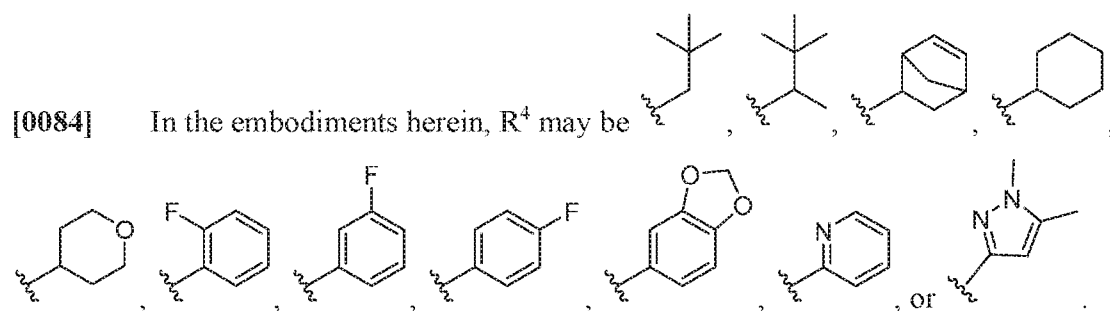
[0072] In some embodiments, R¹ is phenyl that is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, and -NHCOR^e. In some embodiments, R¹ is phenyl that is substituted with 1 or 2 substituents independently selected from halo and C₁-C₄ haloalkyl. In some embodiments, R¹ is phenyl that is substituted with fluoro and chloro. In some embodiments, R¹ is 2-chloro-5-fluoro-phenyl.

[0073] In some embodiments, R¹ is a 5- or 6- membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, and -NHCOR^e. In some embodiments, R¹ is a 5- membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N and O, and is substituted with 1, 2, or 3 substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, and -NHCOR^e. In some embodiments, R¹ is selected from pyrazolyl and isoxazolyl, each of which is substituted with two substituents independently selected from C₁-C₄ alkyl. In some embodiments, R¹ is selected from 2,4-dimethylpyrazol-3-yl, 1,3-dimethylpyrazol-4-yl, and 3,5-dimethylisoxazolyl. In some embodiments, R¹ is 2,4-dimethylpyrazol-3-yl.

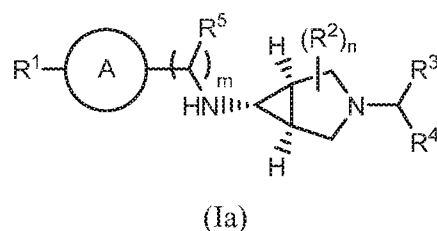
[0074] In some embodiments, R¹ is phenyl or pyrazolyl, wherein the phenyl or pyrazolyl is substituted with two substituents independently selected from halo and C₁-C₄ alkyl.

[0075] In some embodiments, R¹ is aryl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C₁-C₄alkyl, C₁-C₄ haloalkyl, -NHCOR^e, and C₃-C₆cycloalkyl. The aryl at R¹ may be phenyl or a phenyl bonded to the parent molecular moiety and fused to a 5- or 6-membered heteroaryl (e.g., quinolin-6-yl, 2H-indazol-5-yl), a 5- to 6-membered heterocycle containing 1-2 oxygen atoms (e.g., benzo[d][1,3]dioxol-5-yl), or a second phenyl (i.e., naphthyl). In further embodiments, R¹ is a) phenyl, b) a phenyl bonded to the parent molecular moiety and fused to a second ring selected from the group

may be unsubstituted or substituted with 1 or 2 substituents independently selected from halo (e.g., fluoro) and C₁-C₄ alkyl (e.g., methyl). In some embodiments, Y' is a 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S (e.g., pyridyl) which is unsubstituted or substituted with 1 or 2 substituents independently selected from halo (e.g., fluoro) and C₁-C₄ alkyl (e.g., methyl). In some embodiments, Y' is a 5-, 6-, or 7-membered heterocycle having 1, 2, or 3 heteroatoms independently selected from N, O, and S (e.g., tetrahydropyranyl or oxabicyclo[2.2.1]heptanyl). In the embodiments herein, Y' may be C₃-C₁₀ cycloalkyl; C₃-C₈ cycloalkenyl; phenyl; a phenyl bonded to the parent molecular moiety and fused to a 5- to 6-membered heterocycle containing 1-2 oxygen atoms (e.g., benzo[d][1,3]dioxol-5-yl); a 5- or 6-membered heteroaryl having 1, 2, or 3 nitrogen atoms (e.g., pyridinyl, pyrazolyl); and a 5-, 6-, or 7-membered heterocycle containing 1 oxygen atom (e.g., tetrahydropyranyl), wherein Y' is unsubstituted or substituted with one or two substituents independently selected from halo and C₁-C₄ alkyl. In the embodiments herein, Y' may be C₃-C₇ cycloalkyl; C₃-C₈ cycloalkenyl; phenyl; benzo[d][1,3]dioxolyl; pyridinyl, pyrazolyl, or tetrahydropyranyl, wherein Y' is unsubstituted or substituted with one or two substituents independently selected from halo and C₁-C₄ alkyl.

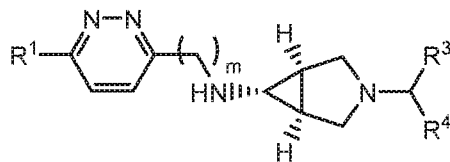


[0085] In some embodiments, the compound is a compound of formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, R⁴, R⁵, A, m, and n are as defined in the aspects and embodiments described herein.

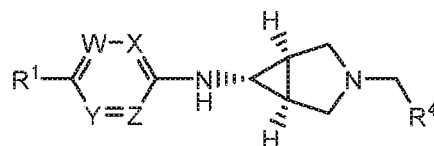
[0086] In some embodiments, the compound is a compound of formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^3 , R^4 , and m are as defined in the aspects and embodiments described herein.

[0087] In some embodiments, the compound of formula (I) has formula (Ic)



(Ic)

wherein the ring containing W, X, Y and Z is a 6-membered heteroaryl ring containing two or one nitrogen atoms and W, X, Y and Z are independently N or CH (e.g., pyridazine, pyridine, pyrimidine); R^1 is a 5- to 10-membered aromatic ring system optionally containing 1-2 nitrogen atoms and optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C₁-C₄alkyl, C₁-C₄ haloalkyl, -NHCOR^c, and C₃-C₆cycloalkyl; R^c is hydrogen or C₁-C₄ alkyl; R^d is C₄-C₆ alkyl or -(CR^bR^c)_p-Y'; each R^b is independently hydrogen or C₁-C₄ alkyl; each R^c is independently hydrogen or C₁-C₄ alkyl; p is 0, 1, 2, 3, or 4; and Y' is C₃-C₁₀ cycloalkyl; C₃-C₈ cycloalkenyl; aryl; a 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S; or a 5-, 6-, or 7-membered heterocycle having 1, 2, or 3 heteroatoms independently selected from N, O, and S; wherein Y' is unsubstituted or substituted with one or two substituents independently selected from halo and C₁-C₄ alkyl. The 5- to 10-membered aromatic ring system optionally containing 1-2 nitrogen atoms at R¹ is a mono or bicyclic aryl or heteroaryl as defined herein, such as phenyl, naphthyl, quinolinyl, indazolyl, benzo[d][1,3]dioxol-5-yl, pyridinyl, and pyrazolyl.

[0088] Representative compounds of formula (I) include, but are not limited to:

(1*S*,5*R*,6*s*)-3-(3,3-dimethylbutyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-3-(3,3-dimethylbutyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*,6*s*)-3-(5-bicyclo[2.2.1]hept-2-enylmethyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-3-(5-bicyclo[2.2.1]hept-2-enylmethyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*,6*s*)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-(2,3,3-trimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-(2,3,3-trimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-((6-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridazin-3-yl)methyl)-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-((6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl)methyl)-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-((6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl)methyl)-3-(cyclohexylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-3-(cyclohexylmethyl)-*N*-((6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(3-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(4-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2-chlorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2-chloro-3-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2-chloro-4-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2-chloro-6-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-

ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(6-quinolyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

N-[4-[6-[(1*R*,5*S*,6*S*)-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-yl]amino]pyridazin-3-yl]phenyl]acetamide;

(1*R*,5*S*,6*S*)-3-(tetrahydropyran-4-ylmethyl)-N-[6-[6-(trifluoromethyl)-3-pyridyl]pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(6-cyclopropyl-3-pyridyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(3-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(4-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-3-(1,3-benzodioxol-5-ylmethyl)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-(6-phenylpyridazin-3-yl)-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(2-naphthyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*S*)-N-[6-(1,3-benzodioxol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2,3-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2,4-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(2-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-3-(1,3-benzodioxol-5-ylmethyl)-*N*-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-3-[(1,5-dimethylpyrazol-3-yl)methyl]-*N*-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine; and

(1*R*,5*S*,6*s*)-3-(3,3-dimethylbutyl)-*N*-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine,

trans-3-(3,3-dimethylbutyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

trans-3-(5-bicyclo[2.2.1]hept-2-enylmethyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-(2,3,3-trimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-((6-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridazin-3-yl)methyl)-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-((6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl)methyl)-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-((6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl)methyl)-3-(cyclohexylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-3-(cyclohexylmethyl)-*N*-((6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl)methyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(3-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(4-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chlorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chloro-3-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chloro-4-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chloro-6-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(6-quinolyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

N-[4-[6-[[trans-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-

yl]amino]pyridazin-3-yl]phenyl]acetamide;

trans-3-(tetrahydropyran-4-ylmethyl)-N-[6-[6-(trifluoromethyl)-3-pyridyl]pyridazin-3-

yl]-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(6-cyclopropyl-3-pyridyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(3-fluorophenyl)methyl]-3-

azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(4-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-3-(1,3-benzodioxol-5-ylmethyl)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-(6-phenylpyridazin-3-yl)-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2-naphthyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(1,3-benzodioxol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2,3-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2,4-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(2-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-3-(1,3-benzodioxol-5-ylmethyl)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

trans-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

trans-3-[(1,5-dimethylpyrazol-3-yl)methyl]-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-

3-azabicyclo[3.1.0]hexan-6-amine; and

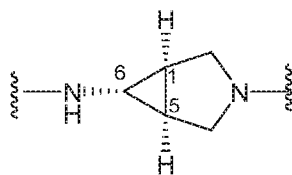
trans-3-(3,3-dimethylbutyl)-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine,

or a pharmaceutically acceptable salt thereof.

[0089] Compound names and/or structures can be assigned/determined by using the Struct=Name naming algorithm as part of CHEMDRAW® ULTRA.

[0090] The compound may exist as a stereoisomer wherein asymmetric or chiral centers are present. The stereoisomer is “*R*” or “*S*” depending on the configuration of substituents around the chiral carbon atom. The terms “*R*” and “*S*” used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, in Pure Appl. Chem., 1976, 45: 13-30. The disclosure contemplates various stereoisomers and mixtures thereof and these are specifically included within the scope of this invention. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of the compounds may be prepared synthetically from commercially available starting materials, which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by methods of resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and optional liberation of the optically pure product from the auxiliary as described in Furniss, Hannaford, Smith, and Tatchell, “Vogel's Textbook of Practical Organic Chemistry,” 5th edition (1989), Longman Scientific & Technical, Essex CM20 2JE, England, or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns, or (3) fractional recrystallization methods.

[0091] Compounds have a 3-azabicyclo[3.1.0]hexane core structure that can have a plane of symmetry as in the following representative structure A.

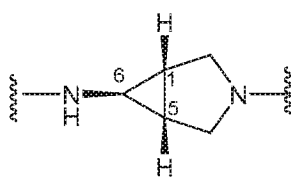


A

trans

(1*R*,5*S*,6*s*)

[0092] Structure A is meso since its mirror image B is superimposable. The 1, 5, and 6 stereochemical designations are used herein for symmetrical structures of type A to designate relative stereochemistry between the ring fusion and the 6-position. Thus, when drawn in the orientation depicted above 1R,5s,6r refers to trans relative stereochemistry between the 6-position substituent and the ring fusion. Lower case s and r designations at the 6-position refer to pseudo asymmetry as described by G.P. Moss in "Basic terminology of stereochemistry (IUPAC Recommendations)" in *Pure and Applied Chemistry* (1996), 68 (12) 2193-2222. The person skilled in the art will understand that when structure A is drawn as the mirror image B,



B

trans

(1S,5R,6s)

chemical naming programs may, depending on the program, reverse the stereochemical designation for 1 and 5 positions from R to S and S to R, respectively, but that the pseudo asymmetry at the 6-position remains invariant, due to R having priority over S according to priority rules and the reversal of the carbons having R and S designations. Due to a plane of symmetry A and B are the same.

[0093] It should be understood that the compound may possess tautomeric forms, as well as geometric isomers, and that these also constitute embodiments of the disclosure.

[0094] The present disclosure also includes an isotopically-labeled compound, which is identical to those recited in formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Substitution with heavier isotopes such as deuterium, i.e. ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. The compound may incorporate positron-emitting isotopes for medical imaging and positron-emitting

tomography (PET) studies for determining the distribution of receptors. Suitable positron-emitting isotopes that can be incorporated in compounds of formula (I) are ^{11}C , ^{13}N , ^{15}O , and ^{18}F . Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using appropriate isotopically-labeled reagent in place of non-isotopically-labeled reagent.

a. Pharmaceutically Acceptable Salts

[0095] The disclosed compounds may exist as pharmaceutically acceptable salts. The term “pharmaceutically acceptable salt” refers to salts or zwitterions of the compounds which are water or oil-soluble or dispersible, suitable for treatment of disorders without undue toxicity, irritation, and allergic response, commensurate with a reasonable benefit/risk ratio and effective for their intended use. The salts may be prepared during the final isolation and purification of the compounds or separately by reacting an amino group of the compounds with a suitable acid. For example, a compound may be dissolved in a suitable solvent, such as but not limited to methanol and water and treated with at least one equivalent of an acid, like hydrochloric acid. The resulting salt may precipitate out and be isolated by filtration and dried under reduced pressure. Alternatively, the solvent and excess acid may be removed under reduced pressure to provide a salt. Representative salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, isethionate, fumarate, lactate, maleate, methanesulfonate, naphthylsulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, oxalate, maleate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, glutamate, para-toluenesulfonate, undecanoate, hydrochloric, hydrobromic, sulfuric, phosphoric and the like. The amino groups of the compounds may also be quaternized with alkyl chlorides, bromides and iodides such as methyl, ethyl, propyl, isopropyl, butyl, lauryl, myristyl, stearyl and the like.

[0096] Basic addition salts may be prepared during the final isolation and purification of the disclosed compounds by reaction of a carboxyl group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation such as lithium, sodium, potassium, calcium, magnesium, or aluminum, or an organic primary, secondary, or tertiary amine. Quaternary amine salts can be prepared, such as those derived from methylamine, dimethylamine, trimethylamine,

triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-phenamine and *N,N'*-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine, and the like.

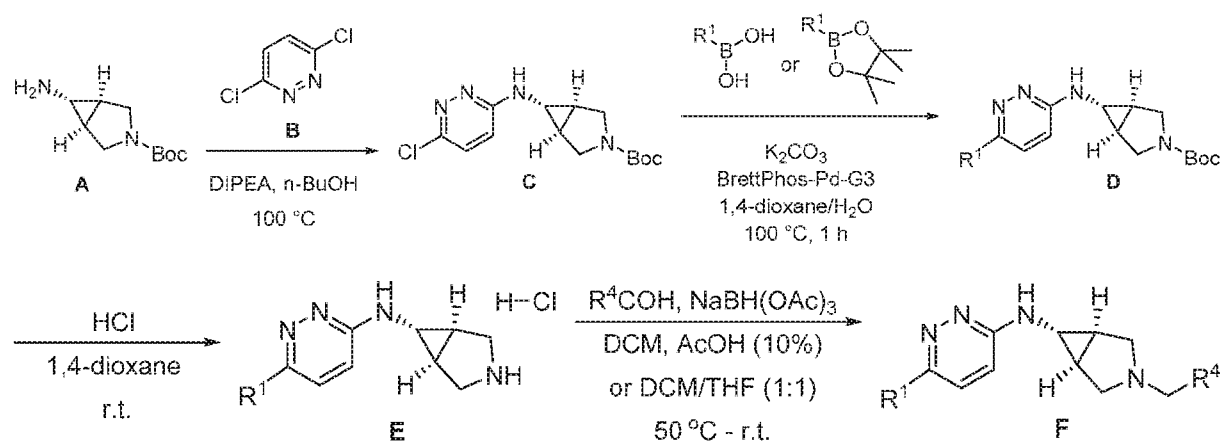
b. General Synthesis

[0097] Compounds of formula (I) may be prepared by synthetic processes or by metabolic processes. Preparation of the compounds by metabolic processes includes those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

[0098] Abbreviations used in the descriptions of the Schemes that follow include the following: Ac is acetyl; BrettPhos-Pd-G3 is [(2-di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (CAS Number 1470372-59-8); DCE is 1,2-dichloroethane; DCM is dichloromethane; DIPEA is *N,N*-diisopropylethylamine; DMF is *N,N*-dimethylformamide; Fmoc is fluorenylmethyloxycarbonyl; rt or r.t. is room temperature; RuPhos-Pd-G3 is (2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (CAS Number 1445085-77-7); STAB refers to sodium triacetoxyborohydride; TFA is trifluoroacetic acid; and THF is tetrahydrofuran.

[0099] Compounds of formula (I) may be synthesized as shown in the following schemes.

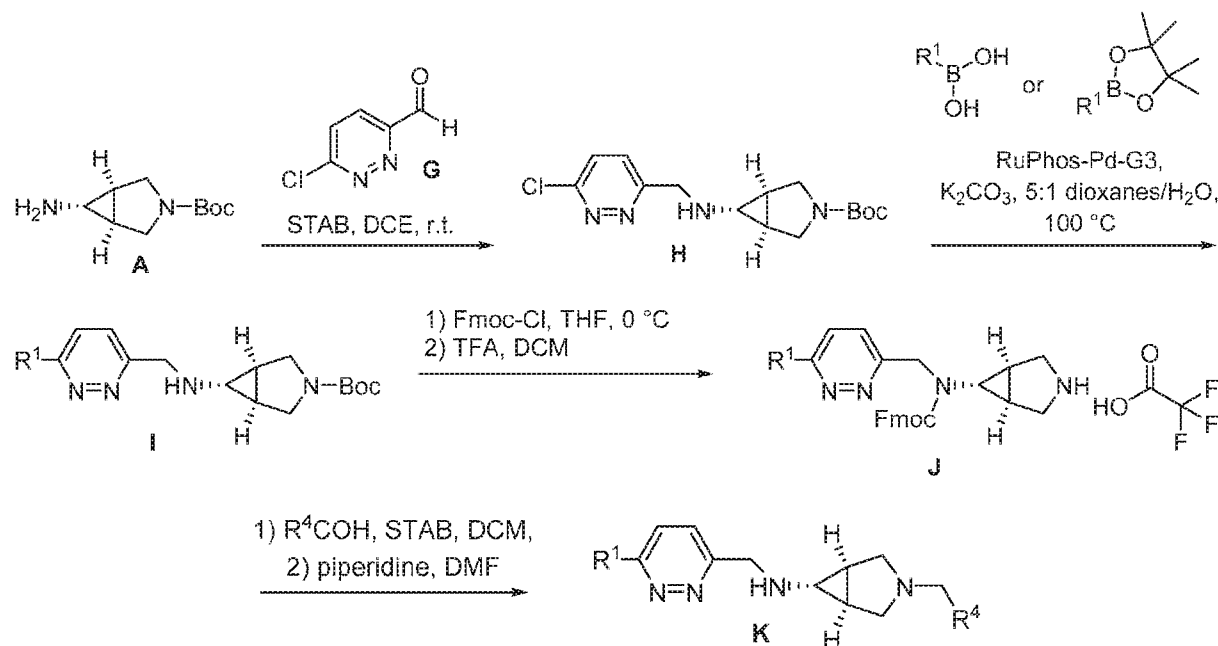
Scheme 1



[00100] As shown in Scheme 1, (1*R*,5*S*,6*S*)-*tert*-butyl 6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate (compound A, commercially available, CAS No. 273206-92-1) may be coupled with 3,6-dichloropyridazine (B) to generate compound C, which may be coupled with an appropriate

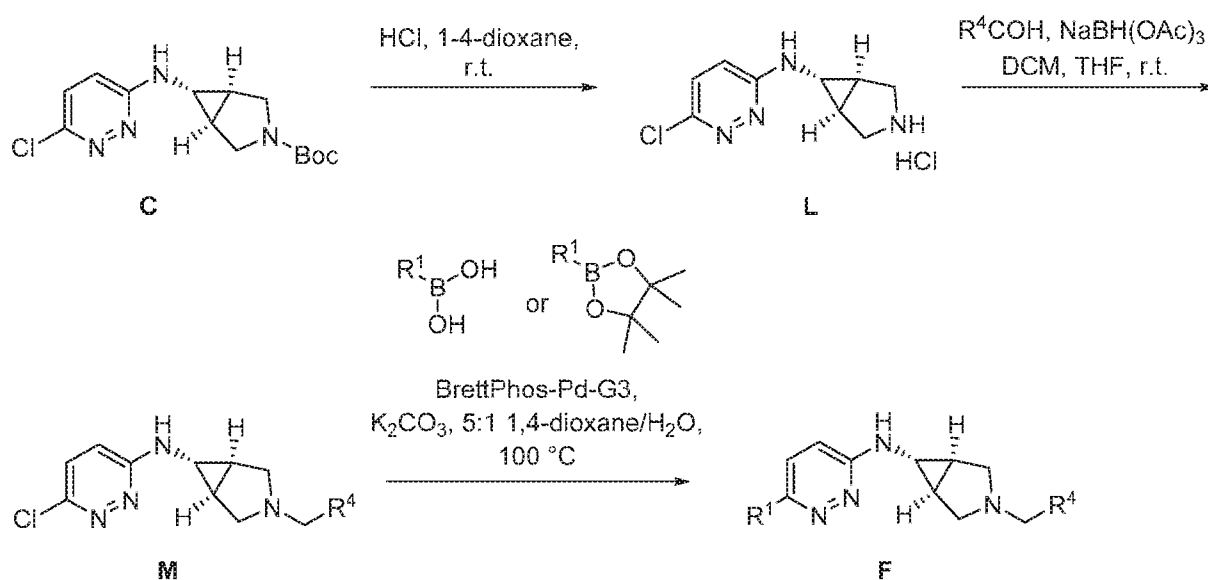
boronic acid or ester to form compound **D**. Deprotection of compound **D** can provide compound **E**, and reaction of compound **E** with a suitable aldehyde under reducing conditions may provide compound **F** (i.e. a compound of formula (Ia) wherein m is 0 and R^3 is H).

Scheme 2



[00101] As shown in Scheme 2, compound **A** may be coupled with 6-chloro-3-pyridinecarboxaldehyde to generate compound **H**, which may be coupled with an appropriate boronic acid or ester to form compound **I**. Protection of the amine using Fmoc-Cl may generate compound **J**, which can be reacted with a suitable aldehyde under reducing conditions and then deprotected to form compound **K** (i.e. a compound of formula (Ia) wherein m is 1 and R^3 is H).

Scheme 3



[00102] As shown in Scheme 3, the compound of formula **C** may be deprotected under acidic conditions to provide amine **L**, which may in turn be reacted with an aldehyde under reductive amination conditions to provide compound **M**. Compound **M** may be reacted with suitable boronic acids or esters under Suzuki-type conditions to provide compounds of formula **F**.

[00103] 2-Bromo-5-chloropyrazine, 3-bromo-6-fluoropyridine, and 2-chloro-thiazoles may replace 3,6-dichloropyridazine in the methods of Schemes 1 and 3 to prepare additional compounds where ring A in formula (I) is pyrazine, pyridine, or optionally substituted thiazole. Reaction conditions (e.g., time, temperature, solvent) and co-reactants (e.g., bases) may be modified as needed to promote the nucleophilic aromatic substitution reaction.

[00104] The compounds and intermediates may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for instance in "Vogel's Textbook of Practical Organic Chemistry," 5th edition (1989), by Furniss, Hannaford, Smith, and Tatchell, pub. Longman Scientific & Technical, Essex CM20 2JE, England.

[00105] A disclosed compound may have at least one basic nitrogen whereby the compound can be treated with an acid to form a desired salt. For example, a compound may be reacted with an acid at or above room temperature to provide the desired salt, which is deposited, and collected by filtration after cooling. Examples of acids suitable for the reaction include, but are not limited to tartaric acid, lactic acid, succinic acid, as well as mandelic, atrolactic, methanesulfonic, ethanesulfonic, toluenesulfonic, naphthalenesulfonic, benzenesulfonic, carbonic, fumaric, maleic, gluconic, acetic, propionic, salicylic, hydrochloric, hydrobromic, phosphoric, sulfuric, citric, hydroxybutyric, camphorsulfonic, malic, phenylacetic, aspartic, or glutamic acid, and the like.

[00106] Reaction conditions and reaction times for each individual step can vary depending on the particular reactants employed and substituents present in the reactants used. Specific procedures are provided in the Examples section. Reactions can be worked up in the conventional manner, e.g. by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or can be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature. Starting materials, if not commercially available, can be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above described schemes or the procedures described in the synthetic examples section.

[00107] Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that cannot be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method are included in the scope of the invention. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which can be found in PGM Wuts and TW Greene, in Greene's book titled Protective Groups in Organic Synthesis (4th ed.), John Wiley & Sons, NY (2006), which is incorporated herein by reference in its entirety. Synthesis of the compounds of the invention can be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

[00108] When an optically active form of a disclosed compound is required, it can be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

[00109] Similarly, when a pure geometric isomer of a compound is required, it can be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

[00110] It can be appreciated that the synthetic schemes and specific examples as described are illustrative and are not to be read as limiting the scope of the invention as it is defined in the appended claims. All alternatives, modifications, and equivalents of the synthetic methods and specific examples are included within the scope of the claims.

c. Muscarinic Acetylcholine Receptor M₄ Activity

[00111] M₄ is the most highly expressed mAChR subtype in the striatum and its expression is similar in rodents and primates. Due to a lack of selective M₄ antagonists, mechanistic understanding of the role of M₄ has been guided by biochemical and genetic studies, as well as the use of highly selective M₄ positive allosteric modulators (PAMs). Highly selective M₄ PAMs induce robust decreases in behavioral responses to psychomotor stimulants that act by increasing striatal DA levels. Furthermore, genetic deletion of M₄ increases exploratory locomotor activity, potentiates locomotor responses to amphetamine and other stimulants, and eliminates effects of M₄ PAMs on locomotor activity and these effects are also observed with selective deletion of M₄ from striatal spiny projection neurons that express the D1 subtype of DA receptor (D1-SPNs). In vivo microdialysis studies reveal that administration of M₄ PAMs reduces amphetamine-induced DA release in the dorsal and ventral striatum and fMRI studies show that M₄ PAMs reverse amphetamine-induced increases in cerebral blood flow (CBV) in striatum and other basal ganglia nuclei. More recently, fast-scanning cyclic voltammetry (FSCV) and genetic studies, demonstrated that M₄ PAMs act, at least in part, by inhibition of DA release from presynaptic DA terminals in the striatum through release of an endocannabinoid from striatal spiny projection neurons (SPNs) and activation of CB2 cannabinoid receptors on DA terminals.

[00112] M₄ is heavily expressed in a subset of SPNs that also express the D₁ subtype of DA receptor (D₁DR), which form the direct pathway (D1-SPNs) sending inhibitory projections to the substantia nigra pars reticulata (SNr). Interestingly, D₁DRs activate a unique GTP-binding protein in D1-SPNs, termed G_{o1f} that couples D₁Rs to activation of adenylyl cyclase, formation of cAMP, and activation of protein kinase A (PKA). This signaling pathway is critical for many of the behavioral actions of DA-mediated activation of motor activity. Interestingly, M₄ couples to G_{α_{1o}} G proteins, which inhibit adenylyl cyclase and have the potential to directly counteract inhibit D₁ receptor signaling and effects on motor function. These studies raise the possibility that, in addition to inhibition of DA release, M₄ PAMs may directly inhibit D₁R-mediated signaling in D1-SPNs by direct inhibition of cAMP formation and this could also contribute to the powerful inhibitory effect of selective M₄ activation of DA signaling in the basal ganglia. Consistent with this, M₄ PAMs inhibit locomotor-stimulating effects of a direct acting D₁ agonist. Furthermore, a series of pharmacological, genetic, and molecular/cellular studies reveal that this response is mediated by inhibition of D₁DR signaling in D1-SPNs. Thus, the primary action of M₄ PAMs on D₁DR signaling is not in the striatum, but on GABAergic terminals of D₁-SPNs in the SNr, where activation of D₁DRs induces a robust increase in GABA release. This challenges the widespread view that cholinergic regulation of striatal function is almost exclusively mediated through ACh released from tonically active, striatal cholinergic interneurons (ChIs) and raises the possibility that cholinergic innervation of the SNr from cholinergic projections from the pedunculopontine nucleus may also play a critical role in regulating motor activity and other functions of the basal ganglia direct pathway. Together, these data suggest that in addition to inhibiting DA release, M₄ activation also acts postsynaptically in D₁-expressing SPNs to inhibit motor function.

[00113] Consistent with a prominent role of M₄ as the primary mAChR subtype involved in regulating motor function, multiple reports indicate that the locomotor-activating effects of the mAChR antagonist scopolamine are dramatically reduced in M₄ knockout mice, but not the other four mAChR subtypes (M_{1-3,5}). Furthermore, haloperidol-induced catalepsy, a model of parkinsonian motor disability, is reduced in M₄ knockout mice as compared to wild-type controls. Evaluation of the anti-parkinsonian effects of scopolamine, by assessing effects of this compound on catalepsy induced by the DA receptor antagonist haloperidol, display robust catalepsy that was completely reversed by scopolamine in WT mice. The reversal by

scopolamine was uncommonly robust and more pronounced than we observe with agents targeting a number of other targets being evaluated for potential antiparkinsonian effects, including metabotropic glutamate (mGlu) receptors mGlu₄ or mGlu₅, A₂A adenosine receptors, and NMDA receptors. Importantly, scopolamine was ineffective in reducing catalepsy in M₄ KO mice, suggesting that the anti-cataleptic effect of scopolamine requires actions on mAChR M₄. Taken together with the extensive studies of M₄ modulation of basal ganglia and motor function, these studies provide compelling evidence that M₄ is the dominant mAChR subtype involved in the antiparkinsonian effects of non-selective mAChR antagonists and provide support for discovery and development of selective M₄ antagonists for treatment of neurodegenerative disease such as PD, dystonia, tardive dyskinesia and other movement disorders.

[00114] Despite advances in mAChR research, there is still a scarcity of compounds that are potent, efficacious and selective antagonists of the M₄ mAChR. Highly selective M₄ antagonists represent a new therapeutic approach for the treatment of neurodegenerative diseases including PD, dystonia, tardive dyskinesia and other movement disorders and may offer the clinical benefit of scopolamine, without the adverse effects mediated by *pan*-mAChR inhibition.

[00115] In some embodiments, the disclosed compounds are antagonists of mAChR M₄. Such activity can be demonstrated by methodology known in the art. For example, antagonism of mAChR M₄ activity can be determined by measurement of calcium flux in response to agonist, e.g. acetylcholine, in cells loaded with a Ca²⁺-sensitive fluorescent dye (e.g., Fluo-4) and co-expression of a chimeric or promiscuous G protein. In some embodiments, the calcium flux can be measured as an increase in fluorescent static ratio. In some embodiments, antagonist activity can be analyzed as a concentration-dependent increase in the EC₈₀ acetylcholine response (i.e. the response of mAChR M₄ at a concentration of acetylcholine that yields 80% of the maximal response).

[00116] In some embodiments, the disclosed compounds antagonize mAChR M₄ as a decrease in calcium fluorescence in mAChR M₄-transfected CHO-K1 cells in the presence of the compound, compared to the response of equivalent CHO-K1 cells in the absence of the compound. In some embodiments, a disclosed compound antagonizes the mAChR M₄ response with an IC₅₀ of less than about 10 μM, less than about 5 μM, less than about 1 μM, less than about 500 nM, of less than about 100 nM, or less than about 50 nM. In some embodiments, the mAChR M₄-transfected CHO-K1 cells are transfected with human mAChR M₄. In some

embodiments, the mAChR M₄-transfected CHO-K1 cells are transfected with rat mAChR M₄. In some embodiments, the mAChR M₄-transfected CHO-K1 cells are transfected with mAChR M₄ from dog or cynomolgus monkey.

[00117] The disclosed compounds may antagonize mAChR M₄ response in mAChR M₄-transfected CHO-K1 cells with an IC₅₀ less than the IC₅₀ for one or more of mAChR M₁, M₂, M₃ or M₅-transfected CHO-K1 cells. That is, a disclosed compound can have selectivity for the mAChR M₄ receptor vis-à-vis one or more of the mAChR M₁, M₂, M₃ or M₅ receptors. For example, in some embodiments, a disclosed compound can antagonize mAChR M₄ response with an IC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₁. In some embodiments, a disclosed compound can antagonize mAChR M₄ response with an IC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₂. In some embodiments, a disclosed compound can antagonize mAChR M₄ response with an IC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₃. In some embodiments, a disclosed compound can antagonize mAChR M₄ response with an IC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₅. In some embodiments, a disclosed compound can antagonize mAChR M₄ response with an IC₅₀ of 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less than that for the M₂-M₅ receptors, of about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for the mAChR M₁, M₂, M₃, or M₅ receptors.

[00118] The disclosed compounds may antagonize mAChR M₄ response in M₄-transfected CHO-K1 cells with an IC₅₀ of less than about 10 μM and exhibit a selectivity for the M₄ receptor vis-à-vis one or more of the mAChR M₁, M₂, M₃, or M₅ receptors. For example, in some embodiments, the compound can have an IC₅₀ of less than about 10 μM, of less than about 5 μM, of less than about 1 μM, of less than about 500 nM, of less than about 100 nM, or of less than

about 50 nM; and the compound can also antagonize mAChR M₄ response with an IC₅₀ of about 5-fold less, 10-fold less, 20-fold less, 30-fold less, 50-fold less, 100-fold less, 200-fold less, 300-fold less, 400-fold less, or greater than about 500-fold less than that for mAChR M₁. In some embodiments, the compound can have an IC₅₀ of less than about 10 μM, of less than about 5 μM, of less than about 1 μM, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also antagonize mAChR M₄ response with an IC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₂. In some embodiments, the compound can have an IC₅₀ of less than about 10 μM, of less than about 5 μM, of less than about 1 μM, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also antagonize mAChR M₄ response with an IC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₃. In some embodiments, the compound can have an IC₅₀ of less than about 10 μM, of less than about 5 μM, of less than about 1 μM, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also antagonize mAChR M₄ response with an IC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₅. In some embodiments, the compound can have an IC₅₀ of less than about 10 μM, of less than about 5 μM, of less than about 1 μM, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also antagonize mAChR M₄ response with IC₅₀ of 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less than that for the M₂-M₅ receptors, of about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, M₂, M₃, or M₅ receptors, or greater than about 500-fold less than that for the mAChR M₁, M₂, M₃, or M₅ receptors.

[00119] In vivo efficacy for disclosed compounds in models that predict antiparkinsonian activity can be measured in a number of preclinical rat models. For example, disclosed compounds may reverse deficits in motor function induced by the dopamine receptor antagonist in mice or rats. Also, these compounds may reverse deficits in motor function that are observed with other manipulations that reduce dopaminergic signaling, such as selective lesions of

dopamine neurons. In addition, it is possible that these compounds will have efficacy in animal models of dystonia and may increase attention, cognitive function, and measures of motivation in animal models.

3. Pharmaceutical Compositions and Formulations

[00120] The disclosed compounds may be incorporated into pharmaceutical compositions suitable for administration to a subject (such as a patient, which may be a human or non-human). The disclosed compounds may also be provided as formulations, such as spray-dried dispersion formulations.

[00121] The pharmaceutical compositions and formulations may include a “therapeutically effective amount” or a “prophylactically effective amount” of the agent. A “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the composition may be determined by a person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of a compound of the invention (e.g., a compound of formula (I)) are outweighed by the therapeutically beneficial effects. A “prophylactically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[00122] For example, a therapeutically effective amount of a compound of formula (I), may be about 1 mg/kg to about 1000 mg/kg, about 5 mg/kg to about 950 mg/kg, about 10 mg/kg to about 900 mg/kg, about 15 mg/kg to about 850 mg/kg, about 20 mg/kg to about 800 mg/kg, about 25 mg/kg to about 750 mg/kg, about 30 mg/kg to about 700 mg/kg, about 35 mg/kg to about 650 mg/kg, about 40 mg/kg to about 600 mg/kg, about 45 mg/kg to about 550 mg/kg, about 50 mg/kg to about 500 mg/kg, about 55 mg/kg to about 450 mg/kg, about 60 mg/kg to about 400 mg/kg, about 65 mg/kg to about 350 mg/kg, about 70 mg/kg to about 300 mg/kg, about 75 mg/kg to about 250 mg/kg, about 80 mg/kg to about 200 mg/kg, about 85 mg/kg to about 150 mg/kg, and about 90 mg/kg to about 100 mg/kg.

[00123] The pharmaceutical compositions and formulations may include pharmaceutically acceptable carriers. The term “pharmaceutically acceptable carrier,” as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such as propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00124] Thus, the compounds and their physiologically acceptable salts may be formulated for administration by, for example, solid dosing, eye drop, in a topical oil-based formulation, injection, inhalation (either through the mouth or the nose), implants, or oral, buccal, parenteral, or rectal administration. Techniques and formulations may generally be found in “Remington's Pharmaceutical Sciences,” (Meade Publishing Co., Easton, Pa.). Therapeutic compositions must typically be sterile and stable under the conditions of manufacture and storage.

[00125] The route by which the disclosed compounds are administered and the form of the composition will dictate the type of carrier to be used. The composition may be in a variety of forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, implants, or parenteral) or topical administration (e.g., dermal, pulmonary, nasal, aural, ocular, liposome delivery systems, or iontophoresis).

[00126] Carriers for systemic administration typically include at least one of diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, antioxidants, preservatives,

glidants, solvents, suspending agents, wetting agents, surfactants, combinations thereof, and others. All carriers are optional in the compositions.

[00127] Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of diluent(s) in a systemic or topical composition is typically about 50 to about 90%.

[00128] Suitable lubricants include silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma. The amount of lubricant(s) in a systemic or topical composition is typically about 5 to about 10%.

[00129] Suitable binders include polyvinyl pyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, microcrystalline cellulose, and sodium carboxymethylcellulose. The amount of binder(s) in a systemic composition is typically about 5 to about 50%.

[00130] Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of disintegrant(s) in a systemic or topical composition is typically about 0.1 to about 10%.

[00131] Suitable colorants include a colorant such as an FD&C dye. When used, the amount of colorant in a systemic or topical composition is typically about 0.005 to about 0.1%.

[00132] Suitable flavors include menthol, peppermint, and fruit flavors. The amount of flavor(s), when used, in a systemic or topical composition is typically about 0.1 to about 1.0%.

[00133] Suitable sweeteners include aspartame and saccharin. The amount of sweetener(s) in a systemic or topical composition is typically about 0.001 to about 1%.

[00134] Suitable antioxidants include butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of antioxidant(s) in a systemic or topical composition is typically about 0.1 to about 5%.

[00135] Suitable preservatives include benzalkonium chloride, methyl paraben and sodium benzoate. The amount of preservative(s) in a systemic or topical composition is typically about 0.01 to about 5%.

[00136] Suitable glidants include silicon dioxide. The amount of glidant(s) in a systemic or topical composition is typically about 1 to about 5%.

[00137] Suitable solvents include water, isotonic saline, ethyl oleate, glycerine, hydroxylated castor oils, alcohols such as ethanol, and phosphate buffer solutions. The amount of solvent(s) in a systemic or topical composition is typically from about 0 to about 100%.

[00138] Suitable suspending agents include AVICEL RC-591 (from FMC Corporation of Philadelphia, PA) and sodium alginate. The amount of suspending agent(s) in a systemic or topical composition is typically about 1 to about 8%.

[00139] Suitable surfactants include lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS from Atlas Powder Company of Wilmington, Delaware. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp.587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The amount of surfactant(s) in the systemic or topical composition is typically about 0.1% to about 5%.

[00140] Although the amounts of components in the systemic compositions may vary depending on the type of systemic composition prepared, in general, systemic compositions include 0.01% to 50% of an active compound (e.g., a compound of formula (I)) and 50% to 99.99% of one or more carriers. Compositions for parenteral administration typically include 0.1% to 10% of actives and 90% to 99.9% of a carrier including a diluent and a solvent.

[00141] Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms include a safe and effective amount, usually at least about 5%, and more particularly from about 25% to about 50% of actives. The oral dosage compositions include about 50% to about 95% of carriers, and more particularly, from about 50% to about 75%.

[00142] Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically include an active component, and a carrier comprising ingredients selected from diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, glidants, and combinations thereof. Specific diluents include calcium carbonate, sodium carbonate, mannitol, lactose and cellulose. Specific binders include starch, gelatin, and sucrose. Specific disintegrants include alginic acid and croscarmellose. Specific lubricants include magnesium stearate, stearic acid, and talc. Specific colorants are the FD&C dyes, which

can be added for appearance. Chewable tablets preferably contain sweeteners such as aspartame and saccharin, or flavors such as menthol, peppermint, fruit flavors, or a combination thereof.

[00143] Capsules (including implants, time release and sustained release formulations) typically include an active compound (e.g., a compound of formula (I)), and a carrier including one or more diluents disclosed above in a capsule comprising gelatin. Granules typically comprise a disclosed compound, and preferably glidants such as silicon dioxide to improve flow characteristics. Implants can be of the biodegradable or the non-biodegradable type.

[00144] The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this invention.

[00145] Solid compositions may be coated by conventional methods, typically with pH or time-dependent coatings, such that a disclosed compound is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically include one or more components selected from the group consisting of cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, EUDRAGIT® coatings (available from Evonik Industries of Essen, Germany), waxes and shellac.

[00146] Compositions for oral administration can have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically include a disclosed compound and a carrier, namely, a carrier selected from diluents, colorants, flavors, sweeteners, preservatives, solvents, suspending agents, and surfactants. Peroral liquid compositions preferably include one or more ingredients selected from colorants, flavors, and sweeteners.

[00147] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically include one or more of soluble filler substances such as diluents including sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Such compositions may further include lubricants, colorants, flavors, sweeteners, antioxidants, and glidants.

[00148] The disclosed compounds can be topically administered. Topical compositions that can be applied locally to the skin may be in any form including solids, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions include: a disclosed compound (e.g., a compound of formula (I)), and a carrier. The carrier of the topical composition preferably aids penetration of the compounds into the skin. The carrier may further include one or more optional components.

[00149] The amount of the carrier employed in conjunction with a disclosed compound is sufficient to provide a practical quantity of composition for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

[00150] A carrier may include a single ingredient or a combination of two or more ingredients. In the topical compositions, the carrier includes a topical carrier. Suitable topical carriers include one or more ingredients selected from phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, symmetrical alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, dimethyl isosorbide, castor oil, combinations thereof, and the like. More particularly, carriers for skin applications include propylene glycol, dimethyl isosorbide, and water, and even more particularly, phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, and symmetrical alcohols.

[00151] The carrier of a topical composition may further include one or more ingredients selected from emollients, propellants, solvents, humectants, thickeners, powders, fragrances, pigments, and preservatives, all of which are optional.

[00152] Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols,

petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, and combinations thereof. Specific emollients for skin include stearyl alcohol and polydimethylsiloxane. The amount of emollient(s) in a skin-based topical composition is typically about 5% to about 95%.

[00153] Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof. The amount of propellant(s) in a topical composition is typically about 0% to about 95%.

[00154] Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Specific solvents include ethyl alcohol and homotopic alcohols. The amount of solvent(s) in a topical composition is typically about 0% to about 95%.

[00155] Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Specific humectants include glycerin. The amount of humectant(s) in a topical composition is typically 0% to 95%.

[00156] The amount of thickener(s) in a topical composition is typically about 0% to about 95%.

[00157] Suitable powders include beta-cyclodextrins, hydroxypropyl cyclodextrins, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically-modified magnesium aluminum silicate, organically-modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof. The amount of powder(s) in a topical composition is typically 0% to 95%.

[00158] The amount of fragrance in a topical composition is typically about 0% to about 0.5%, particularly, about 0.001% to about 0.1%.

[00159] Suitable pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of a topical pharmaceutical composition.

[00160] The pharmaceutical composition or formulation may antagonize mAChR M₄ with an IC₅₀ of less than about 10 μ M, less than about 5 μ M, less than about 1 μ M, less than about 500 nM, or less than about 100 nM. The pharmaceutical composition or formulation may antagonize

mAChR M4 with an IC₅₀ of between about 10 μM and about 1 nM, about 1 μM and about 1 nM, about 100 nM and about 1 nM, or between about 10 nM and about 1 nM.

a. Spray-Dried Dispersion Formulations

[00161] The disclosed compounds may be formulated as a spray-dried dispersion (SDD). An SDD is a single-phase, amorphous molecular dispersion of a drug in a polymer matrix. It is a solid solution with the compound molecularly “dissolved” in a solid matrix. SDDs are obtained by dissolving drug and a polymer in an organic solvent and then spray-drying the solution. The use of spray drying for pharmaceutical applications can result in amorphous dispersions with increased solubility of Biopharmaceutics Classification System (BCS) class II (high permeability, low solubility) and class IV (low permeability, low solubility) drugs. Formulation and process conditions are selected so that the solvent quickly evaporates from the droplets, thus allowing insufficient time for phase separation or crystallization. SDDs have demonstrated long-term stability and manufacturability. For example, shelf lives of more than 2 years have been demonstrated with SDDs. Advantages of SDDs include, but are not limited to, enhanced oral bioavailability of poorly water-soluble compounds, delivery using traditional solid dosage forms (e.g., tablets and capsules), a reproducible, controllable and scalable manufacturing process and broad applicability to structurally diverse insoluble compounds with a wide range of physical properties.

[00162] Thus, in one embodiment, the disclosure may provide a spray-dried dispersion formulation comprising a compound of formula (I).

4. Methods of Use

[00163] The disclosed compounds, pharmaceutical compositions and formulations may be used in methods for treatment of disorders, such as neurological and/or psychiatric disorders, associated with muscarinic acetylcholine receptor dysfunction. The disclosed compounds and pharmaceutical compositions may also be used in methods for decreasing muscarinic acetylcholine receptor activity in a mammal. The methods further include cotherapeutic methods for improving treatment outcomes. In the methods of use described herein, additional therapeutic agent(s) may be administered simultaneously or sequentially with the disclosed compounds and compositions.

a. Treating disorders

[00164] The disclosed compounds, pharmaceutical compositions and formulations may be used in methods for treating, preventing, ameliorating, controlling, reducing, or reducing the risk of a variety of disorders, or symptoms of the disorders, in which a patient would benefit from antagonism of mAChR M₄. In some embodiments, the disorder may be a neurodegenerative disorder, a movement disorder, or a brain disorder. The methods may comprise administering to a subject in need of such treatment a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

[00165] Disorders in which a patient would benefit from antagonism of mAChR M₄ may include neurodegenerative disorders and movement disorders. For example, exemplary disorders may include Parkinson's disease, drug-induced Parkinsonism, dystonia, Tourette's syndrome, dyskinesias (e.g., tardive dyskinesia or levodopa-induced dyskinesia), schizophrenia, cognitive deficits associated with schizophrenia, excessive daytime sleepiness (e.g., narcolepsy), attention deficit hyperactivity disorder (ADHD), Huntington's disease, chorea (e.g., chorea associated with Huntington's disease), cerebral palsy, and progressive supranuclear palsy.

[00166] In some embodiments, the disclosure provides a method for treating motor symptoms in a subject having Parkinson's disease, comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In some embodiments, the motor symptoms are selected from bradykinesia, tremor, rigidity, gait dysfunction, and postural instability. The method may treat the motor symptoms, control the motor symptoms, and/or reduce the motor symptoms in the subject.

[00167] In some embodiments, the disclosure provides a method for treating motor symptoms in a subject having dystonia, comprising administering to the subject a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. The method may treat the motor

symptoms, control the motor symptoms, and/or reduce the motor symptoms in the subject. For example, treatment may reduce muscle contractions or spasms in a subject having dystonia.

[00168] In some embodiments, the disclosure provides a method for treating motor symptoms in a subject having tardive dyskinesia, comprising administering to the subject a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. The method may treat the motor symptoms, control the motor symptoms, and/or reduce the motor symptoms in the subject. For example, treatment may reduce involuntary movements in a subject having tardive dyskinesia.

[00169] In some embodiments, the disclosure provides a method of preventing or delaying tardive dyskinesia in a subject at risk of developing tardive dyskinesia, comprising administering to the subject a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. For example, the subject may be a subject being treated with a neuroleptic medication (e.g., a typical antipsychotic or an atypical antipsychotic), a dopamine antagonist, or an antiemetic.

[00170] In some embodiments, the disclosure provides a method of treating catalepsy in a subject suffering from schizophrenia, comprising administering to the subject a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. For example, the subject suffering from schizophrenia may have catalepsy induced by a neuroleptic agent (e.g., a typical antipsychotic or an atypical antipsychotic).

[00171] In some embodiments, the disclosure provides a method of treating a brain disorder characterized by altered dopamine and cholinergic signaling that could benefit from antagonism of mAChR M₄, comprising administering to the subject a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. For example, the treatment may increase motivation or

goal-directed behavior in patients suffering from disorders characterized by reduced motivation for goal-directed behavior, such as schizophrenia and other brain disorders.

[00172] In some embodiments, the disclosure provides a method for increasing wakefulness and/or reducing excessive daytime sleepiness in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is a subject suffering from narcolepsy.

[00173] In some embodiments, the disclosure provides a method of increasing attention in a subject (e.g., a subject suffering from an attention deficit disorder such as ADHD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

[00174] In some embodiments, the disclosure provides a method for treating motor symptoms in a subject having a drug-induced movement disorder, comprising administering the subject a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In some embodiments, the drug-induced movement disorder is selected from drug-induced parkinsonism, tardive dyskinesia, tardive dystonia, akathisia, myoclonus, and tremor. The method may treat the motor symptoms, control the motor symptoms, and/or reduce the motor symptoms in the subject.

[00175] The compounds and compositions may be further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein. The compounds and compositions may be further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions, in combination with other agents.

[00176] In the treatment of conditions such as those that would benefit from antagonism of mAChR M₄, an appropriate dosage level may be about 0.01 to 500 mg per kg patient body weight per day, which can be administered in single or multiple doses. The dosage level may be about 0.1 to about 250 mg/kg per day, or about 0.5 to about 100 mg/kg per day. A suitable

dosage level can be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage can be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, or 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosage regimen can be adjusted to provide the optimal therapeutic response. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[00177] Thus, in some embodiments, the disclosure relates to a method for antagonizing the mAChR M₄ receptor in at least one cell, comprising the step of contacting the at least one cell with at least one disclosed compound or at least one product of a disclosed method in an amount effective to antagonize mAChR M₄ in the at least one cell. In some embodiments, the cell is mammalian, for example, human. In some embodiments, the cell has been isolated from a subject prior to the contacting step. In some embodiments, contacting is via administration to a subject.

[00178] In some embodiments, the invention relates to a method for antagonizing the mAChR M₄ receptor in a subject, comprising the step of administering to the subject at least one disclosed compound or at least one product of a disclosed method in a dosage and amount effective to antagonize the mAChR M₄ receptor in the subject. In some embodiments, the subject is mammalian, for example, human. In some embodiments, the mammal has been diagnosed with a need for mAChR M₄ antagonism prior to the administering step. In some embodiments, the mammal has been diagnosed with a need for mAChR M₄ antagonism prior to the administering step. In some embodiments, the method further comprises the step of identifying a subject in need of mAChR M₄ antagonism.

b. Antagonism of the Muscarinic Acetylcholine Receptor

[00179] In some embodiments, the disclosure relates to a method for antagonizing mAChR M₄ in a mammal, comprising the step of administering to the mammal an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising at least one disclosed compound or pharmaceutically acceptable salt thereof.

[00180] In some embodiments, antagonism of the muscarinic acetylcholine receptor decreases muscarinic acetylcholine receptor activity.

[00181] In some embodiments, the compound administered antagonizes mAChR M₄ with an IC₅₀ of less than about 10 μM, less than about 5 μM, less than about 1 μM, less than about 500 nM, or less than about 100 nM. In some embodiments, the compound administered antagonizes mAChR M₄ with an IC₅₀ of between about 10 μM and about 1 nM, about 1 μM and about 1 nM, about 100 nM and about 1 nM, or about 10 nM and about 1 nM.

[00182] In some embodiments, the mammal is a human. In some embodiments, the mammal has been diagnosed with a need for reduction of muscarinic acetylcholine receptor activity prior to the administering step. In some embodiments, the method further comprises the step of identifying a mammal in need of reducing muscarinic acetylcholine receptor activity. In some embodiments, the antagonism of the muscarinic acetylcholine receptor treats a disorder associated with muscarinic acetylcholine receptor activity in the mammal. In some embodiments, the muscarinic acetylcholine receptor is mAChR M₄.

[00183] In some embodiments, antagonism of the muscarinic acetylcholine receptor in a mammal is associated with the treatment of a disorder associated with a muscarinic receptor dysfunction, such as a disorder disclosed herein. In some embodiments, the muscarinic receptor is mAChR M₄.

[00184] In some embodiments, the disclosure provides a method for antagonizing the muscarinic acetylcholine receptor in a cell, comprising the step of contacting the cell with an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof. In some embodiments, the cell is mammalian (e.g., human). In some embodiments, the cell has been isolated from a mammal prior to the contacting step. In some embodiments, contacting is via administration to a mammal.

c. Cotherapeutic methods

[00185] The present disclosure is further directed to administration of a mAChR M₄ antagonist, such as a selective mAChR M₄ antagonist, for improving treatment outcomes. That is, in some embodiments, the disclosure relates to a cotherapeutic method comprising a step of administering to a mammal an effective amount and dosage of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[00186] In some embodiments, administration improves treatment outcomes in the context of cognitive or behavioral therapy. Administration in connection with cognitive or behavioral therapy can be continuous or intermittent. Administration need not be simultaneous with therapy and can be before, during, and/or after therapy. For example, cognitive or behavioral therapy can be provided within 1, 2, 3, 4, 5, 6, 7 days before or after administration of the compound. As a further example, cognitive or behavioral therapy can be provided within 1, 2, 3, or 4 weeks before or after administration of the compound. As a still further example, cognitive or behavioral therapy can be provided before or after administration within a period of time of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 half-lives of the administered compound.

[00187] In some embodiments, administration may improve treatment outcomes in the context of physical or occupational therapy. Administration in connection with physical or occupational therapy can be continuous or intermittent. Administration need not be simultaneous with therapy and can be before, during, and/or after therapy. For example, physical or occupational therapy can be provided within 1, 2, 3, 4, 5, 6, 7 days before or after administration of the compound. As a further example, physical or occupational therapy can be provided within 1, 2, 3, or 4 weeks before or after administration of the compound. As a still further example, physical or occupational therapy can be provided before or after administration within a period of time of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 half-lives of the administered compound.

[00188] It is understood that the disclosed cotherapeutic methods can be used in connection with the disclosed compounds, compositions, kits, and uses.

d. Combination Therapies

[00189] In the methods of use described herein, additional therapeutic agent(s) may be administered simultaneously or sequentially with the disclosed compounds and compositions. Sequential administration includes administration before or after the disclosed compounds and compositions. In some embodiments, the additional therapeutic agent or agents may be

administered in the same composition as the disclosed compounds. In other embodiments, there may be an interval of time between administration of the additional therapeutic agent and the disclosed compounds. In some embodiments, administration of an additional therapeutic agent with a disclosed compound may allow lower doses of the other therapeutic agents and/or administration at less frequent intervals. When used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula (I). The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds.

[00190] The disclosed compounds can be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the aforementioned diseases, disorders and conditions for which the compound or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) can be administered by a route and in an amount commonly used therefor, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound may be used. However, the combination therapy can also be administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound can be more efficacious than either as a single agent. Thus, when used in combination with one or more other active ingredients, the disclosed compounds and the other active ingredients can be used in lower doses than when each is used singly.

[00191] The pharmaceutical compositions and methods of the present invention can further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

[00192] The above combinations include combinations of a disclosed compound not only with one other active compound, but also with two or more other active compounds. Likewise, disclosed compounds can be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for

which disclosed compounds are useful. Such other drugs can be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to a disclosed compound is preferred. Accordingly, the pharmaceutical compositions include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

[00193] The weight ratio of a disclosed compound to the second active ingredient can be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of a disclosed compound to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[00194] In such combinations a disclosed compound and other active agents can be administered separately or in conjunction. In addition, the administration of one element can be prior to, concurrent to, or subsequent to the administration of other agent(s).

[00195] Accordingly, the disclosed compounds can be used alone or in combination with other agents which are known to be beneficial in the subject indications or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the disclosed compounds. The subject compound and the other agent can be coadministered, either in concomitant therapy or in a fixed combination.

[00196] In some embodiments, the compound can be employed in combination with any other agent that is used to treat a disorder described herein, such as a standard of care therapy for a disorder that would benefit from mAChR M₄ antagonism, such as a disorder described herein. For example, in some embodiments, the compound can be employed in combination with a Parkinsonian drug (e.g., L-DOPA, or carbidopa/levodopa) an mGlu₄ positive allosteric modulator, an mGlu₈ negative allosteric modulator, an A_{2A} inhibitor, a T-type calcium channel antagonist, a VMAT2 inhibitor, a muscle relaxant (e.g., baclofen), an anticholinergic agent, an antiemetic, a typical or atypical neuroleptic agent (e.g., risperidone, ziprasidone, haloperidol,

pimozide, fluphenazine), an antihypertensive agent (e.g., clonidine or guanfacine), a tricyclic antidepressant (e.g., amitriptyline, butriptyline, clomipramine, desipramine, dosulepin, doxepin, imipramine, iprindole, lofepramine, nortriptyline, protriptyline, or trimipramine) an agent that increases extracellular dopamine levels (e.g., amphetamine, methylphenidate, or lisdexamfetamine), an agent for treating excessive daytime sleepiness (e.g., sodium oxybate or a wakefulness-promoting agent such as armodafinil or modafinil), and a norepinephrine reuptake inhibitor (including selective NRIs, e.g., atomoxetine, and non-selective NRIs, e.g., bupropion).

e. Modes of Administration

[00197] Methods of treatment may include any number of modes of administering a disclosed composition. Modes of administration may include tablets, pills, dragees, hard and soft gel capsules, granules, pellets, aqueous, lipid, oily or other solutions, emulsions such as oil-in-water emulsions, liposomes, aqueous or oily suspensions, syrups, elixirs, solid emulsions, solid dispersions or dispersible powders. For the preparation of pharmaceutical compositions for oral administration, the agent may be admixed with commonly known and used adjuvants and excipients such as for example, gum arabic, talcum, starch, sugars (such as, e.g., mannitolose, methyl cellulose, lactose), gelatin, surface-active agents, magnesium stearate, aqueous or non-aqueous solvents, paraffin derivatives, cross-linking agents, dispersants, emulsifiers, lubricants, conserving agents, flavoring agents (e.g., ethereal oils), solubility enhancers (e.g., benzyl benzoate or benzyl alcohol) or bioavailability enhancers (e.g. Gelucire™). In the pharmaceutical composition, the agent may also be dispersed in a microparticle, e.g. a nanoparticulate composition.

[00198] For parenteral administration, the agent can be dissolved or suspended in a physiologically acceptable diluent, such as, e.g., water, buffer, oils with or without solubilizers, surface-active agents, dispersants or emulsifiers. As oils for example and without limitation, olive oil, peanut oil, cottonseed oil, soybean oil, castor oil and sesame oil may be used. More generally spoken, for parenteral administration, the agent can be in the form of an aqueous, lipid, oily or other kind of solution or suspension or even administered in the form of liposomes or nano-suspensions.

[00199] The term “parenterally,” as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

5. Kits

[00200] In one aspect, the disclosure provides a kit comprising at least one disclosed compound or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising at least one disclosed compound or a pharmaceutically acceptable salt thereof and one or more of:

- (a) at least one agent known to increase mAChR M₄ activity;
- (b) at least one agent known to decrease mAChR M₄ activity;
- (c) at least one agent known to treat a disorder associated with mAChR M₄, such as a disorder described herein; and
- (d) instructions for administering the compound.

[00201] In some embodiments, the at least one disclosed compound and the at least one agent are co-formulated. In some embodiments, the at least one disclosed compound and the at least one agent are co-packaged. The kits can also comprise compounds and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising a disclosed compound and/or product and another component for delivery to a patient.

[00202] That the disclosed kits can be employed in connection with disclosed methods of use.

[00203] The kits may further comprise information, instructions, or both that use of the kit will provide treatment for medical conditions in mammals (particularly humans). The information and instructions may be in the form of words, pictures, or both, and the like. In addition or in the alternative, the kit may include the compound, a composition, or both; and information, instructions, or both, regarding methods of application of compound, or of composition, preferably with the benefit of treating or preventing medical conditions in mammals (e.g., humans).

[00204] The compounds and processes of the invention will be better understood by reference to the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

6. Examples

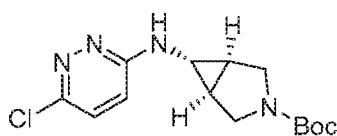
[00205] All NMR spectra were recorded on a 400 MHz AMX Bruker NMR spectrometer. ¹H chemical shifts are reported in δ values in ppm downfield with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, bs =

broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, ABq = AB quartet), coupling constant, integration. Reversed-phase LCMS analysis was performed using an Agilent 1200 system comprised of a binary pump with degasser, high-performance autosampler, thermostatted column compartment, C18 column, diode-array detector (DAD) and an Agilent 6150 MSD with the following parameters. The gradient conditions were 5% to 95% acetonitrile with the aqueous phase 0.1% TFA in water over 1.4 minutes. Samples were separated on a Waters Acquity UPLC BEH C18 column (1.7 μ m, 1.0 x 50 mm) at 0.5 mL/min, with column and solvent temperatures maintained at 55 °C. The DAD was set to scan from 190 to 300 nm, and the signals used were 220 nm and 254 nm (both with a band width of 4nm). The MS detector was configured with an electrospray ionization source, and the low-resolution mass spectra were acquired by scanning from 140 to 700 AMU with a step size of 0.2 AMU at 0.13 cycles/second, and peak width of 0.008 minutes. The drying gas flow was set to 13 liters per minute at 300 °C and the nebulizer pressure was set to 30 psi. The capillary needle voltage was set at 3000 V, and the fragmentor voltage was set at 100V. Data acquisition was performed with Agilent Chemstation and Analytical Studio Reviewer software.

[00206] Abbreviations used in the examples that follow include the following: BrettPhos-Pd-G3 is [(2-di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (CAS Number 1470372-59-8); DCE is 1,2-dichloroethane; DCM is dichloromethane; DIPEA is *N,N*-diisopropylethylamine; DMF is *N,N*-dimethylformamide; DMSO is dimethyl sulfoxide; EtOAc is ethyl acetate; eq. is equivalent(s); Fmoc is fluorenylmethyloxycarbonyl; h is hour(s); IPA is isopropyl alcohol; MeOH is methanol; min is minute(s); n-BuOH is n-butyl alcohol; rt or r.t. is room temperature; RuPhos-Pd-G3 is (2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (CAS Number 1445085-77-7); TFA is trifluoroacetic acid; and THF is tetrahydrofuran.

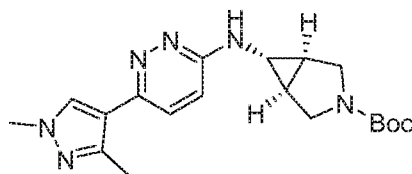
Example 1. (1*R*,5*S*,6*s*)-3-(3,3-dimethylbutyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine (Compound 1)

Tert-butyl (1*R*,5*S*,6*s*)-6-[(6-chloropyridazin-3-yl)amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate



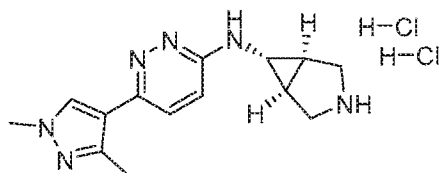
[00207] (1*R*,5*S*,6*S*)-Tert-butyl 6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate (CAS No. 273206-92-1) (250 mg, 1.26 mmol, 1.0 eq.) was dissolved in *n*-BuOH (6.3 mL, 0.2 M). DIPEA (0.66 mL, 3.78 mmol, 3.0 eq.) was added followed by 3,6-dichloropyridazine (564 mg, 3.78 mmol, 3.0 eq.). The reaction mixture was stirred at 100 °C overnight, after which time the reaction was cooled to r.t., and diluted with DCM and sat. soln. NaHCO₃. The aqueous layer was extracted with IPA/CHCl₃ (1:3, 3x). The combined extracts were dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (0-40% EtOAc/hexanes then 40-80% EtOAc/DCM) to provide the title compound as a yellow viscous oil (150 mg, 38%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.51 (s, 1H), 7.43 (d, *J* = 9.3 Hz, 1H), 6.97 (d, *J* = 9.4 Hz, 1H), 3.56 (d, *J* = 10.8 Hz, 2H), 2.41-3.55 (m, 2H), 2.34-2.30 (m, 1H), 1.73-1.66 (m, 2H), 1.39 (s, 9H); ES-MS [M+H]⁺ = [M+H]⁺ - tButyl = 255.3.

Tert-butyl (1*R*,5*S*,6*S*)-6-[[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate



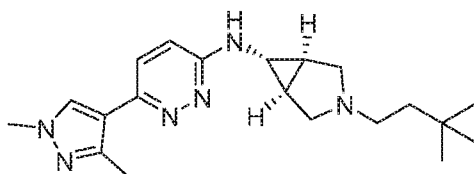
[00208] Tert-butyl (1*R*,5*S*,6*S*)-6-[(6-chloropyridazin-3-yl)amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate (150 mg, 0.48 mmol, 1.0 eq.), 1,3-dimethylpyrazole-4-boronic acid pinacol ester (182 mg, 0.821 mmol, 1.7 eq.), K₂CO₃ (203 mg, 1.45 mmol, 3.0 eq.) and BrettPhos-Pd-G3 (22 mg, 0.024 mmol, 0.05 eq.) were charged into a reaction vial. A degassed mixture of 5:1 (v/v) 1,4-dioxane/H₂O (3.1 mL) was added. The resulting suspension was stirred at 100 °C for 1 hour. After cooling to r.t., the reaction mixture was filtered through a pad of Celite which was washed thoroughly with EtOAc. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (0-70% EtOAc/hexanes then 0-75% MeOH/DCM/NH₄OH (10:89:1) in DCM) to give the title compound as a pale yellow oil (85 mg, 47%). ES-MS [M+H]⁺ = 371.3.

(1*R*,5*S*,6*S*)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine dihydrochloride



[00209] *Tert*-butyl (1R,5S,6s)-6-[[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate (85 mg, 0.229 mmol, 1.0 eq.) was dissolved in 1,4-dioxane (2.0 mL). 4M HCl in 1,4-dioxane solution (1.0 mL, 4.0 mmol, 17.4 eq.) was added dropwise. After stirring 2 hours at r.t., solvents were removed under reduced pressure. The crude material was azeotroped with toluene (3x) to provide the title compound as an off white powder which was used without further purification as the HCl salt. ES-MS $[M+H]^+ = 271.4$.

(1R,5S,6s)-3-(3,3-dimethylbutyl)-N-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine (Compound 1)



1

[00210] (1R,5S,6s)-N-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine dihydrochloride (18 mg, 0.052 mmol, 1.0 eq.) was suspended in DCE (1.0 mL) and acetic acid (0.1 mL). 3,3-dimethylbutyraldehyde (26.3 μ L, 0.262 mmol, 5.0 eq.) was added. The mixture was stirred at 50 $^{\circ}$ C for 1 h and sodium triacetoxyborohydride (55.5 mg, 0.262 mmol, 5.0 eq.) was added. The resulting solution was stirred at rt for 16 h, after which time the reaction mixture was quenched with sat. soln. NaHCO_3 , and extracted with chloroform/IPA (3:1, v/v). The combined extracts were filtered through a phase separator and concentrated. The crude residue was purified by reverse phase HPLC to give the title compound as a pale yellow powder (3.0 mg, 16%). $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.47 (d, $J = 9.2$ Hz, 1H), 6.96 (d, $J = 2.7$ Hz, 1H), 6.84 (d, $J = 9.3$ Hz, 1H), 3.79 (s, 3H), 3.13 (d, $J = 8.7$ Hz, 1H), 2.79-2.76 (m, 1H), 2.39 (s, 3H), 2.37-2.35 (m, 1H), 2.29 (d, $J = 8.3$ Hz, 2H), 1.53-1.49 (m, 2H), 1.35-1.31 (m, 2H), 0.88 (s, 9H); ES-MS $[M+H]^+ = 355.5$.

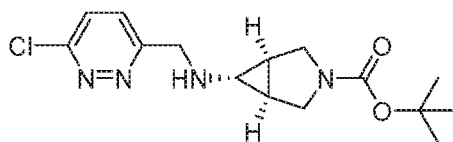
[00211] The compounds shown in Table 1 were prepared similarly to Compound 1, with appropriate starting materials.

Table 1

Cpd. No.	Name	Structure	ES-MS [M+1] ⁺
2	(1R,5S,6s)-3-(5-bicyclo[2.2.1]hept-2-enylmethyl)-N-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine		377.4
3	(1R,5S,6s)-N-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-(2,3,3-trimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine		369.4

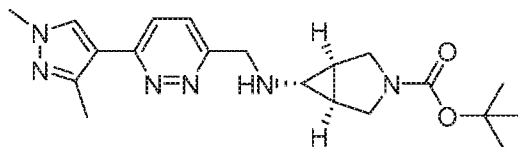
Example 2. (1R,5S,6s)-N-(((6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridazin-3-yl)methyl)-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine (Compound 4)

Tert-butyl (1R,5S,6s)-6-(((6-chloropyridazin-3-yl)methyl)amino)-3-azabicyclo[3.1.0]hexane-3-carboxylate



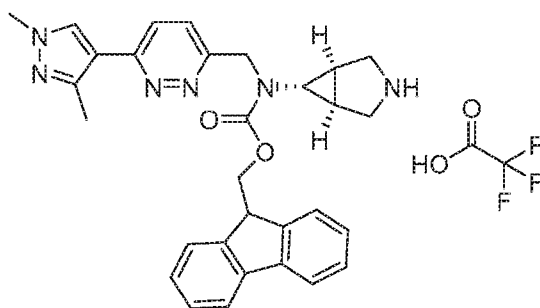
[00212] 6-chloro-3-pyridazinecarboxaldehyde (300 mg, 2.10 mmol) was dissolved in DCE (10 mL) and tert-butyl (1R,5S,6s)-6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate (626 mg, 3.16 mmol) was added. The resulting solution was stirred at r.t. for 30 min, after which time sodium triacetoxyborohydride (669 mg, 3.16 mmol) was added. The resulting mixture was stirred at r.t. overnight, after which time the reaction was quenched with sat. NaHCO₃, and the aqueous layer was extracted with DCM and 3:1 chloroform/IPA. The collected organic extracts were filtered through a phase separator and concentrated, and crude residue was purified by RP-HPLC. Fractions containing product were extracted with 3:1 chloroform/IPA, and combined organic extracts were dried with Na₂SO₄. Solvents were filtered and removed to give the title compound as a slightly yellow oil (251 mg, 37%). ¹H-NMR (400 MHz, CDCl₃) δ 7.50 – 7.25 (m, 2H), 4.17 – 4.08 (m, 2H), 3.52 (d, *J* = 10.9 Hz, 1H), 3.44 (d, *J* = 10.9 Hz, 1H), 3.37 – 3.29 (m, 2H), 2.01 (t, *J* = 2.1 Hz, 1H), 1.60 – 1.54 (m, 2H), 1.42 (s, 9H). ES-MS [M+H]⁺ = 225.4 (-BOC).

Tert-butyl (1R,5S,6s)-6-(((6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridazin-3-yl)methyl)amino)-3-azabicyclo[3.1.0]hexane-3-carboxylate



[00213] *Tert*-butyl (1*R*,5*S*,6*S*)-6-(((6-chloropyridazin-3-yl)methyl)amino)-3-azabicyclo[3.1.0]hexane-3-carboxylate (91 mg, 0.28 mmol), 1,3-dimethylpyrazole-4-boronic acid pinacol ester (75 mg, 0.34 mmol), K₂CO₃ (118 mg, 0.84 mmol) and RuPhos-Pd-G3 (23 mg, 0.028 mmol) were combined in a sealed vial which was placed under an inert atmosphere. 1,4-dioxanes/H₂O solution (5:1, 2 mL, degassed) was then added via syringe, and the resulting solution was heated to 100 °C for 2 h, after which time the reaction was cooled to r.t. and diluted with sat. NaHCO₃ and DCM. The aqueous layer was extracted with DCM (2x), and organic extracts were filtered through a phase separator and concentrated, and crude residue was purified by RP-HPLC. Fractions containing product were extracted with 3:1 chloroform/IPA, and the combined organic extracts were filtered through a phase separator and concentrate to give the title compound as a colorless oil (56 mg, 52%). ¹H-NMR (400 MHz, CDCl₃) δ 7.92 (s, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 4.16 – 4.06 (m, 2H), 3.91 (s, 3H), 3.53 (d, *J* = 10.9 Hz, 1H), 3.45 (d, *J* = 10.8 Hz, 1H), 3.38 – 3.30 (m, 2H), 2.57 (s, 3H), 2.03 (t, *J* = 2.1 Hz, 1H), 1.61 – 1.56 (m, 2H), 1.41 (s, 9H). ES-MS [M+H]⁺ = 385.4.

(9*H*-Fluoren-9-yl)methyl ((1*R*,5*S*,6*S*)-3-azabicyclo[3.1.0]hexan-6-yl)((6-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridazin-3-yl)methyl)carbamate 2,2,2-trifluoroacetate

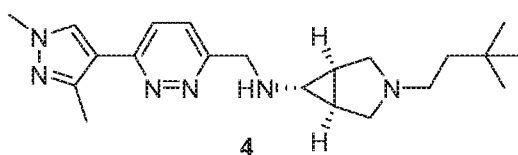


[00214] *Tert*-butyl (1*R*,5*S*,6*S*)-6-(((6-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridazin-3-yl)methyl)amino)-3-azabicyclo[3.1.0]hexane-3-carboxylate (55 mg, 0.14 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. DIPEA (0.032 mL, 0.19 mmol) and Fmoc-Cl (41 mg, 0.16 mmol) were then added sequentially, and the resulting solution was stirred at 0 °C for 1.5 h, after which time the reaction was quenched with H₂O, and the aqueous layer was extracted with DCM. The combined organic extracts were filtered through a phase separator and concentrated,

and the resulting yellow foam was dried under vacuum and used directly without further purification. ES-MS $[M+H]^+ = 607.3$.

[00215] The residue was dissolved in DCM (2 mL) and TFA (0.5 mL) was added dropwise. The resulting solution was stirred at r.t. for 30 min, after which time solvents were removed under reduced pressure to give the title compound as a yellow oil which was dried under vacuum and used directly without further purification (89 mg, 100%). ES-MS $[M+H]^+ = 507.4$.

(1*R*,5*S*,6*s*)-*N*-((6-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridazin-3-yl)methyl)-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine (Compound 4)



[00216] (9*H*-Fluoren-9-yl)methyl ((1*R*,5*S*,6*s*)-3-azabicyclo[3.1.0]hexan-6-yl)((6-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridazin-3-yl)methyl)carbamate 2,2,2-trifluoroacetate (29.6 mg, 0.048 mmol) was dissolved in DCM (1 mL) and 3,3-dimethylbutyraldehyde (23.8 mg, 0.24 mmol) was added, followed by sodium triacetoxyborohydride (50.5 mg, 0.24 mmol). The resulting solution was stirred at r.t. for 1.5 h, after which time the reaction was quenched with H₂O, and extracted with DCM and 3:1 chloroform/IPA. The organic extracts were filtered through a phase separator and concentrated, and the residue was taken up in a 20% solution of piperidine in DMF (v/v, 1 mL), and stirred for 20 min, after which time the crude residue was purified directly by RP-HPLC. Fractions containing product were basified with saturated NaHCO₃, and extracted with 3:1 chloroform/IPA. The combined organic extracts were filtered through a phase separator and concentrated to give the title compound as a white solid (4.9 mg, 28%). ¹H-NMR (400 MHz, CDCl₃) δ 7.90 (s, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 4.09 (s, 2H), 3.91 (s, 3H), 3.03 (d, *J* = 8.9 Hz, 2H), 2.56 (s, 3H), 2.49 – 2.47 (m, 1H), 2.36 – 2.30 (m, 4H), 1.46 – 1.44 (m, 2H), 1.32 – 1.28 (m, 2H), 0.85 (s, 9H). ES-MS $[M+H]^+ = 369.5$.

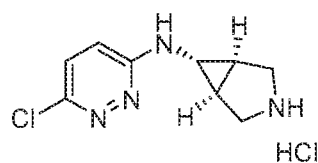
[00217] The compounds shown in Table 2 were prepared similarly to Compound 4, with appropriate starting materials.

Table 2

Cpd. No.	Name	Structure	ES-MS $[M+1]^+$
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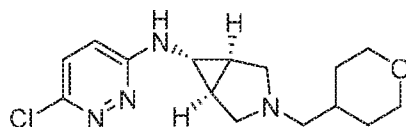
Cpd. No.	Name	Structure	ES-MS [M+1] ⁺
5	(1 <i>R</i> ,5 <i>S</i> ,6 <i>s</i>)- <i>N</i> -((6-(2-chloro-5-fluorophenyl)pyridazin-3-yl)methyl)-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine		403.4
6	(1 <i>R</i> ,5 <i>S</i> ,6 <i>s</i>)- <i>N</i> -((6-(2-chloro-5-fluorophenyl)pyridazin-3-yl)methyl)-3-(cyclohexylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		415.4
7	(1 <i>R</i> ,5 <i>S</i> ,6 <i>s</i>)-3-(cyclohexylmethyl)- <i>N</i> -((6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-amine		381.5

[00218] **Example 3. (1*R*,5*S*,6*s*)-*N*-((6-(2-chlorophenyl)pyridazin-3-yl)-3-((tetrahydro-2*H*-pyran-4-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-amine**



[00219] **(1*R*,5*S*,6*s*)-*N*-((6-chloropyridazin-3-yl)-3-azabicyclo[3.1.0]hexan-6-amine**

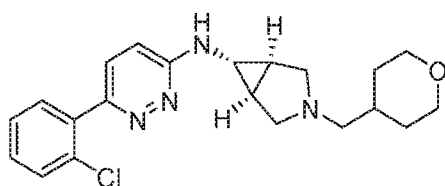
hydrochloride. tert-butyl (1*R*,5*S*,6*s*)-6-((6-chloropyridazin-3-yl)amino)-3-azabicyclo[3.1.0]hexane-3-carboxylate (409 mg, 1.32 mmol) was dissolved in 1,4-dioxane (8 mL) and MeOH (3 mL), and a solution of 4M HCl in dioxanes (4 mL) was added dropwise. The resulting cloudy solution was stirred at r.t. for 2 h, after which time solvents were concentrated under reduced pressure, and the resulting white solid was dried under vacuum and used directly without further purification (325 mg, 100%). ES-MS [M+H]⁺ = 211.4.



[00220] **(1*R*,5*S*,6*s*)-*N*-((6-chloropyridazin-3-yl)-3-((tetrahydro-2*H*-pyran-4-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-amine.**

(1*R*,5*S*,6*s*)-*N*-((6-chloropyridazin-3-yl)-3-azabicyclo[3.1.0]hexan-6-amine hydrochloride (325 mg, 1.32 mmol) was suspended in DCM (4

mL) and THF (4 mL) and 4-oxanaldehyde (451 mg, 3.95 mmol) was added, followed by sodium triacetoxyborohydride (837 mg, 3.95 mmol). The resulting solution was stirred at r.t. for 1 h, after which time the reaction mixture was quenched with saturated NaHCO₃, and extracted with DCM and 3:1 chloroform/IPA (v/v). The combined organic extracts were filtered through a phase separator, and concentrated under reduced pressure. The crude residue was purified by RP-HPLC (2-32% MeCN in 0.1% TFA aqueous solution over 20 min). Fractions containing product were basified with saturated NaHCO₃, and extracted with 3:1 chloroform/IPA. The combined organic extracts were dried with MgSO₄, and solvents were filtered and concentrated under reduced pressure to give the title compound as a white solid (288 mg, 71%). ¹H-NMR (400 MHz, CDCl₃) δ 7.21 (d, *J* = 9.3 Hz, 1H), 6.91 (d, *J* = 9.3 Hz, 1H), 6.06 (br, 1H), 3.92 (dd, *J* = 11.1, 3.6 Hz, 2H), 3.34 (td, *J* = 12.0, 1.7 Hz, 2H), 3.13 (d, *J* = 8.8 Hz, 2H), 2.78 (s, 1H), 2.39 (d, *J* = 8.1 Hz, 2H), 2.26 (d, *J* = 6.7 Hz, 2H), 1.62 – 1.59 (m, 5H), 1.23 – 1.13 (m, 2H). ES-MS [M+H]⁺ = 309.5.



[00221] (1R,5S,6s)-N-(6-(2-chlorophenyl)pyridazin-3-yl)-3-((tetrahydro-2H-pyran-4-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-amine. (1R,5S,6s)-N-(6-chloropyridazin-3-yl)-3-((tetrahydro-2H-pyran-4-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-amine (20.6 mg, 0.067 mmol), 2-chlorophenylboronic acid (15.6 mg, 0.10 mmol), potassium carbonate (28.1 mg, 0.20 mmol) and BrettPhos-Pd-G3 (6.1 mg, 0.007 mmol) were combined in a sealed vial, and 5:1 1,4-dioxane/H₂O (1 mL, degassed) was added via syringe. The resulting mixture was stirred under an inert atmosphere at 100 °C for 2 h, after which time the reaction mixture was cooled to r.t. and solvents were concentrated. The crude residue was taken up in DMSO, and additional solids were removed by syringe filtration. The crude residue was purified by RP-HPLC (5-35% MeCN in 0.1% TFA aqueous solution over 5 min). Fractions containing product were basified with saturated NaHCO₃, and extracted with 3:1 chloroform/IPA. The combined organic extracts were filtered through a phase separator and concentrated to give the title compound as a slightly orange solid (7.9 mg, 31%). ¹H-NMR (400 MHz, CDCl₃) δ 7.69 – 7.65 (m, 2H), 7.46 (dd, *J* =

7.2, 2.0 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.01 (d, $J = 9.2$ Hz, 1H), 5.97 (br, 1H), 3.95 (dd, $J = 11.4$, 3.3 Hz, 2H), 3.40 – 3.27 (m, 4H), 3.03 (br, 1H), 2.60 (br, 2H), 2.42 (d, $J = 4.8$ Hz, 2H), 1.75 – 1.66 (m, 4H), 1.30 – 1.20 (m, 3H). ES-MS $[M+H]^+ = 385.0$.

[00222] The compounds shown in Table 3 were prepared similarly to the compounds described above, with appropriate starting materials.

Table 3

Cpd. No.	Name	Structure	ES-MS $[M+1]^+$
8	(1R,5S,6s)-N-[6-(2-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		369
9	(1R,5S,6s)-N-[6-(3-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		369
10	(1R,5S,6s)-N-[6-(4-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		369
11	(1S,5R,6s)-N-[6-(2-chlorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		385
12	(1R,5S,6s)-N-[6-(2-chloro-5-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		403
13	(1R,5S,6s)-N-[6-(2-chloro-3-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		403
14	(1R,5S,6s)-N-[6-(2-chloro-4-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		403
15	(1R,5S,6s)-N-[6-(2-chloro-6-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		403

Cpd. No.	Name	Structure	ES-MS [M+1] ⁺
16	(1R,5S,6s)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		387
17	(1R,5S,6s)-N-[6-(6-quinolyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		402.2
18	(1R,5S,6s)-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		405
19	N-[4-[6-[(1R,5S,6s)-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-yl]amino]pyridazin-3-yl]phenyl]acetamide		408
20	(1R,5S,6s)-3-(tetrahydropyran-4-ylmethyl)-N-[6-[6-(trifluoromethyl)-3-pyridyl]pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine		420
21	(1R,5S,6s)-N-[6-(6-cyclopropyl-3-pyridyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		392
22	(1R,5S,6s)-N-[6-(2-chloro-5-fluorophenyl)pyridazin-3-yl]-3-[(3-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine		413
23	(1R,5S,6s)-N-[6-(2-chloro-5-fluorophenyl)pyridazin-3-yl]-3-[(4-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine		413
24	(1R,5S,6s)-N-[6-(2-chloro-5-fluorophenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		395.9

Cpd. No.	Name	Structure	ES-MS [M+1] ⁺
25	(1R,5S,6s)-3-(1,3-benzodioxol-5-ylmethyl)-N-[6-(2-chloro-5-fluorophenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine		438.9
26	(1R,5S,6s)-N-[6-(2-chloro-5-fluorophenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine		413
27	(1R,5S,6s)-N-[6-(2-chloro-5-fluorophenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine		389
28	(1R,5S,6s)-N-(6-phenylpyridazin-3-yl)-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		351.2
29	(1R,5S,6s)-N-[6-(2-naphthyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		401
30	(1R,5S,6s)-N-[6-(1,3-benzodioxol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		395
31	(1R,5S,6s)-N-[6-(2,3-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		387
32	(1R,5S,6s)-N-[6-(2,4-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		387

Cpd. No.	Name	Structure	ES-MS [M+1] ⁺
33	(1R,5S,6s)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(2-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine		397.4
34	(1R,5S,6s)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine		380.4
35	(1R,5S,6s)-3-(1,3-benzodioxol-5-ylmethyl)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine		423.4
36	(1R,5S,6s)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine		396.4
37	(1R,5S,6s)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine		373.4
38	(1R,5S,6s)-3-[(1,5-dimethylpyrazol-3-yl)methyl]-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine		415.4
39	(1R,5S,6s)-3-(3,3-dimethylbutyl)-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine		391.5

Biological Activity

A. Cell Lines Expressing Muscarinic Acetylcholine Receptors

[00223] Human M₄ cDNA, along with the chimeric G protein G_{q15}, were transfected into Chinese hamster ovary (CHO-K1) cells purchased from the American Type Culture Collection using Lipofectamine2000. M₄/G_{q15}/CHO cells were grown in Ham's F-12 medium containing 10% heat-inactivated fetal bovine serum (FBS), 20mM HEPES, 500 µg/mL G418 sulfate, and 200 µg/mL Hygromycin B.

B. Cell-Based Functional Assay of Muscarinic Acetylcholine Receptor Activity

[00224] For high throughput measurement of agonist-evoked increases in intracellular calcium, CHO-K1 cells stably expressing muscarinic receptors were plated in growth medium lacking G418 and hygromycin at 15,000 cells/20 µL/well in Greiner 384-well black-walled, tissue culture (TC)-treated, clear-bottom plates (VWR). Cells were incubated overnight at 37 °C and 5% CO₂. The next day, cells were washed using an ELX 405 (BioTek) with assay buffer; the final volume was then aspirated to 20 µL. Next, 20 µL of a 2.3 µM stock of Fluo-4/acetoxymethyl ester (Invitrogen, Carlsbad, CA), prepared as a 2.3 mM stock in DMSO and mixed in a 1:1 ratio with 10% (w/v) Pluronic F-127 and diluted in assay buffer, was added to the wells and the cell plates were incubated for 50 min at 37 °C and 5% CO₂. Dye was removed by washing with the ELX 405 and the final volume was aspirated to 20 µL. Compound master plates were formatted in a 10 point concentration-response curve (CRC) format (1:3 dilutions) in 100% DMSO with a starting concentration of 10 or 1 mM using a BRAVO liquid handler (Agilent). Test compound CRCs were then transferred to daughter plates (240 nL) using the Echo acoustic plate reformatter (Labcyte, Sunnyvale, CA) and then diluted into assay buffer (40 µL) to a 2× stock using a Thermo Fisher Combi (Thermo Fisher Scientific, Waltham, MA).

[00225] Calcium flux was measured using the Functional Drug Screening System (FDSS) 6000 or 7000 (Hamamatsu Corporation, Tokyo, Japan) as an increase in the fluorescent static ratio. Compounds were applied to cells (20 µL, 2X) using the automated system of the FDSS at 2 seconds into the protocol and the data were collected at 1 Hz. At 143 s, 10 µL of an EC₂₀ concentration of the muscarinic receptor agonist acetylcholine was added (5X), followed by the addition of 12 µL of an EC₈₀ concentration of acetylcholine at the 268 s time point (5X). Agonist activity was analyzed as a concentration-dependent increase in calcium mobilization upon compound addition. Positive allosteric modulator activity was analyzed as a concentration-

dependent increase in the EC₂₀ acetylcholine response. Antagonist activity was analyzed as a concentration-dependent decrease in the EC₈₀ acetylcholine response; for the purposes of the tables herein, an IC₅₀ (inhibitory concentration 50) was calculated as a concentration-dependent decrease of the response elicited by an EC₈₀ concentration of acetylcholine. Concentration-response curves were generated using a four-parameter logistical equation in XLFit curve fitting software (IDBS, Bridgewater, NJ) for Excel (Microsoft, Redmond, WA) or Prism (GraphPad Software, Inc., San Diego, CA) or the Dotmatics software platform (Dotmatics, Bishop's Stortford, UK).

[00226] The above described assay was also operated in a second mode where an appropriate fixed concentration of the present compounds were added to the cells after establishment of a fluorescence baseline for about 3 seconds, and the response in cells was measured. 140 s later, a full concentration-response range consisting of increasing concentrations of agonist was added and the calcium response (maximum-local minima response) was measured. The EC₅₀ values for the agonist in the presence or absence of test compound were determined by nonlinear curve fitting. A decrease in the EC₅₀ value of the agonist with increasing concentrations of the present compounds (a leftward shift of the agonist concentration-response curve) is an indication of the degree of muscarinic positive allosteric modulation at a given concentration of the present compound. An increase in the EC₅₀ value of the agonist with increasing concentrations of the present compounds (a rightward shift of the agonist concentration response curve) is an indication of the degree of muscarinic antagonism at a given concentration of the present compound. The second mode also indicates whether the present compounds also affect the maximum response of the muscarinic receptor to agonists.

C. Activity of Compounds in a mAChR M₄ Cell-Based Assay

[00227] Compounds were synthesized as described above. Activity (IC₅₀ and E_{min}) was determined in the mAChR M₄ cell-based functional assay as described above and the data are shown in Table 2. The compound numbers correspond to the compound numbers used in Examples 1 and 2 and Tables 1 and 2.

Table 4.

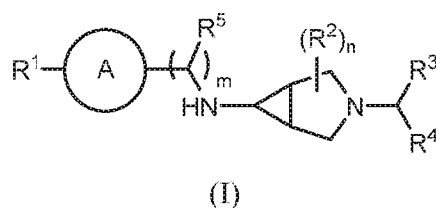
Cpd. No.	Human M ₄ IC ₅₀ (μM)	E _{min} (%) [*]
1	0.28	4.8

Cpd. No.	Human M ₄ IC ₅₀ (μM)	E _{min} (%)*
2	0.10	5.0
3	10.0	24.0
4	10.0	36.7
5	10.0	20.4
6	10.0	17.8
7	10.0	32.5
8	10.0	38
9	10.0	25
10	10.0	37
11	2.96	11
12	1.11	8
13	1.85	8
14	10.0	12
15	3.18	14
16	10.0	28
17	3.76	13
18	10.0	27
19	10.0	39
20	10.0	48
21	10.0	30
22	10.0	29
23	1.66	30
24	6.77	16
25	0.889	6
26	4.76	13
27	0.0255	4
28	10.0	28
29	10.0	15
30	10.0	16
31	10.0	27
32	10.0	40
33	10.0	39
34	10.0	46
35	10.0	36
36	10.0	38
37	0.255	4
38	>10.0	40
39	0.139	5

* %ACh maximum at 30 μM.

[00228] For reasons of completeness, various aspects of the invention are set out in the following numbered clauses:

[00229] Clause 1. A compound of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

A is a five- or six-membered heteroarylene having 1, 2 or 3 heteroatoms independently selected from N, O and S;

m is 0 or 1;

n is 1 or 2;

R¹ is selected from heteroaryl, aryl, heterocyclyl, and cycloalkyl;

each R² is independently selected from hydrogen, C₁-C₄ alkyl, halo, and -OR^a;

R³ is selected from hydrogen and C₁-C₄ alkyl;

R⁴ is selected from -(CR^bR^c)_p-Y, C₁-C₈ alkyl, and C₁-C₈ alkenyl;

R⁵ is selected from hydrogen, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkoxy;

Y' is selected from cycloalkyl, cycloalkenyl, heterocycle, aryl, and heteroaryl;

each R^a is independently selected from hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, and aryl;

each R^b is independently selected from hydrogen and C₁-C₄ alkyl;

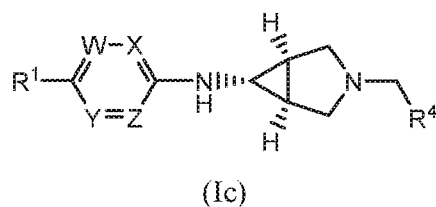
each R^c is independently selected from hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, and aryl;

and

p is 0, 1, 2, 3, or 4;

wherein each aryl, heteroaryl, heteroarylene, cycloalkyl, cycloalkenyl, and heterocycle is independently unsubstituted or substituted with 1, 2, or 3 substituents.

[00230] Clause 2. The compound of clause 1, or a pharmaceutically acceptable salt thereof, wherein the compound has formula (Ic)



wherein

the ring containing W, X, Y and Z is a 6-membered heteroaryl ring containing two or one nitrogen atoms and W, X, Y and Z are independently N or CH;

R¹ is a 5- to 10-membered aromatic ring system optionally containing 1-2 nitrogen atoms and optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C₁-C₄alkyl, C₁-C₄ haloalkyl, -NHCOR^e, and C₃-C₆cycloalkyl;

R^e is hydrogen or C₁-C₄ alkyl;

R⁴ is C₄-C₆ alkyl or -(CR^bR^c)_p-Y⁷;

each R^b is independently hydrogen or C₁-C₄ alkyl;

each R^c is independently hydrogen or C₁-C₄ alkyl;

p is 0, 1, 2, 3, or 4; and

Y⁷ is C₃-C₁₀ cycloalkyl; C₃-C₈ cycloalkenyl; aryl; a 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S; or a 5-, 6-, or 7-membered heterocycle having 1, 2, or 3 heteroatoms independently selected from N, O, and S;

wherein Y⁷ is unsubstituted or substituted with one or two substituents independently selected from halo and C₁-C₄ alkyl.

[00231] Clause 3. The compound of clause 1, or a pharmaceutically acceptable salt thereof, wherein ring A is unsubstituted.

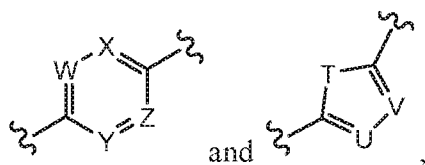
[00232] Clause 4. The compound of clause 1 or 3, or a pharmaceutically acceptable salt thereof, wherein each aryl, heteroaryl, heteroarylene, cycloalkyl, cycloalkenyl, and heterocycle is independently unsubstituted or substituted with 1, 2, or 3 substituents independently selected from C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ hydroxyalkyl, hydroxy, cyano, -NHCOR^e, and benzyl.

[00233] Clause 5. The compound of clause 4, or a pharmaceutically acceptable salt thereof, wherein R^e is hydrogen or C₁-C₄ alkyl.

[00234] Clause 6. The compound of clause 1 or 3, or a pharmaceutically acceptable salt thereof, wherein each aryl, heteroaryl, heteroarylene, cycloalkyl, cycloalkenyl, and heterocycle is independently unsubstituted or substituted with 1, 2, or 3 substituents independently selected from C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ hydroxyalkyl, hydroxy, cyano, -NHCOR^e, C₃-C₆cycloalkyl, and benzyl; and R^e is hydrogen or C₁-C₄ alkyl.

[00235] Clause 7. The compound of any of clauses 1 or 3-6, or a pharmaceutically acceptable salt thereof, wherein

A is selected from:



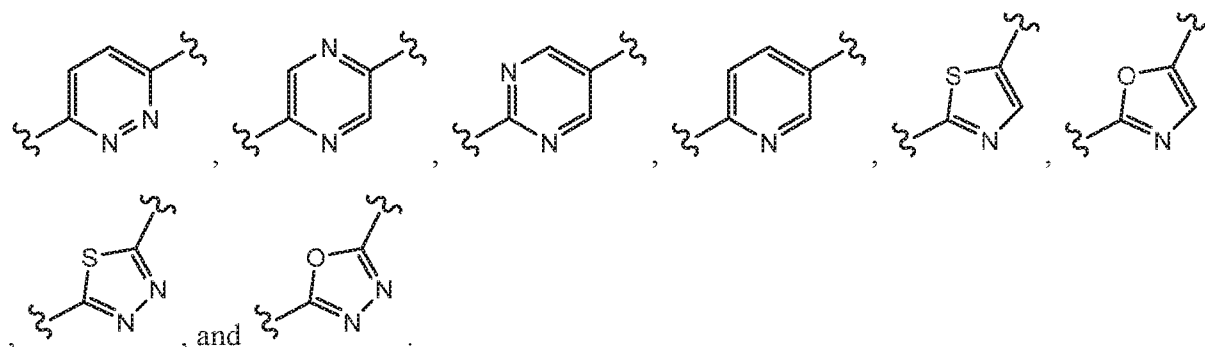
wherein:

T is selected from O, S and NH;

U, V, W, X, Y and Z are independently selected from N and CR^d, wherein at least one of W, X, Y, and Z is N, and at least one of U and V is N; and

each R^d is independently selected from hydrogen, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, and hydroxy.

[00236] Clause 8. The compound of clause 7, or a pharmaceutically acceptable salt thereof, wherein A is selected from:



[00237] Clause 9. The compound of any one of clauses 1 or 3-8, or a pharmaceutically acceptable salt thereof, wherein m is 0.

[00238] Clause 10. The compound of any one of clauses 1 or 3-8, or a pharmaceutically acceptable salt thereof, wherein m is 1; and R⁵ is hydrogen.

[00239] Clause 11. The compound of any one of clauses 1-10, or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from aryl and heteroaryl.

[00240] Clause 12. The compound of clause 11, or a pharmaceutically acceptable salt thereof, wherein R¹ is aryl optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C₁-C₄alkyl, C₁-C₄ haloalkyl, -NHCOR^e, and C₃-C₆cycloalkyl.

[00241] Clause 13. The compound of clause 12, or a pharmaceutically acceptable salt thereof, wherein the aryl at R¹ is a phenyl or a phenyl bonded to the parent molecular moiety and fused to a 5- or 6-membered heteroaryl, a 5- to 6-membered heterocycle containing 1-2 oxygen atoms, or a second phenyl.

[00242] Clause 14. The compound of clause 11, or a pharmaceutically acceptable salt thereof, wherein

R¹ is

a) phenyl,

b) a phenyl bonded to the parent molecular moiety and fused to a second ring selected from the group consisting of a 5- or 6-membered heteroaryl, a 5- to 6-membered heterocycle containing 1-2 oxygen atoms, and a second phenyl, or

c) a 5- or 6- membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S,

wherein R¹ is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, -NHCOR^e, and C₃-C₆cycloalkyl.

[00243] Clause 15. The compound of clause 14, or a pharmaceutically acceptable salt thereof, wherein R¹ is phenyl, quinolinyl, benzo[d][1,3]dioxolyl, indazolyl, pyrazolyl, or pyridinyl, wherein R¹ is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, -NHCOR^e, and C₃-C₆cycloalkyl.

[00244] Clause 16. The compound of clause 15, or a pharmaceutically acceptable salt thereof, wherein R¹ is phenyl, quinolin-6-yl, benzo[d][1,3]dioxol-5-yl, 2H-indazol-5-yl, 1H-pyrazol-4-yl, or pyridin-3-yl, wherein R¹ is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, -NHCOR^e, and C₃-C₆cycloalkyl.

[00245] Clause 17. The compound of clause 11, or a pharmaceutically acceptable salt thereof, wherein R¹ is phenyl or a 5- or 6- membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S,

wherein the phenyl or heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from halo, C₁-C₄ alkyl, and C₁-C₄ haloalkyl.

[00246] Clause 18. The compound of clause 11, or a pharmaceutically acceptable salt thereof, wherein

R¹ is phenyl, pyridinyl, or pyrazolyl,

wherein the phenyl, pyridinyl, or pyrazolyl is substituted with 1-2 substituents independently selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, -NHCOR^e, and C₃-C₆cycloalkyl.

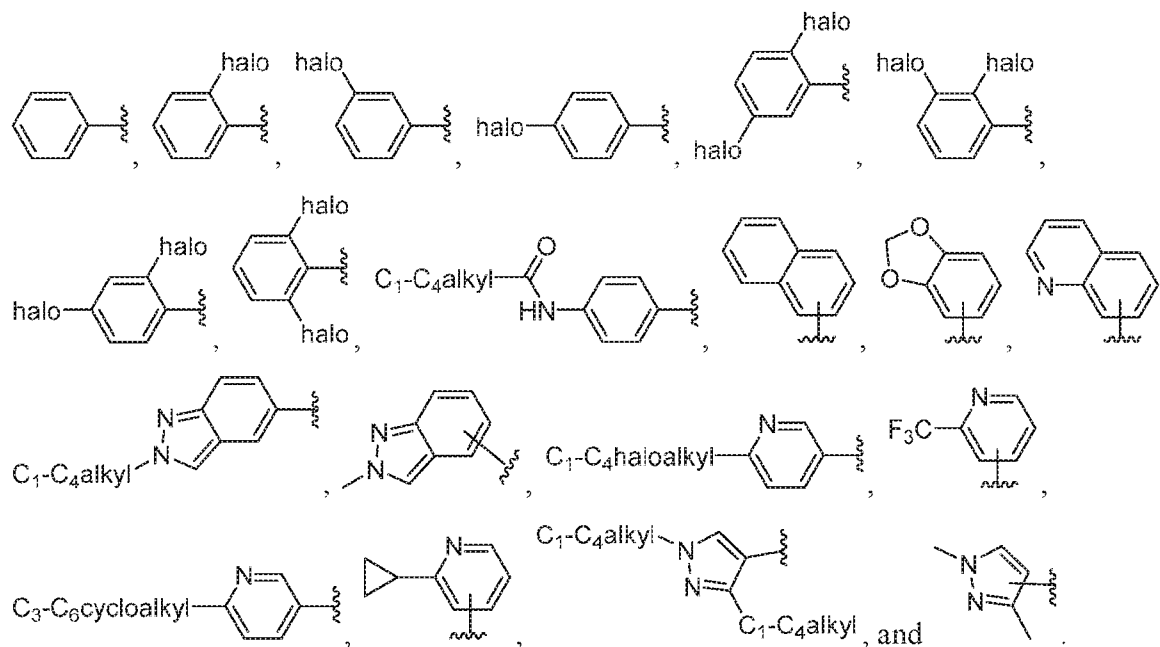
[00247] Clause 19. The compound of clause 17, or a pharmaceutically acceptable salt thereof, wherein

R¹ is phenyl or pyrazolyl,

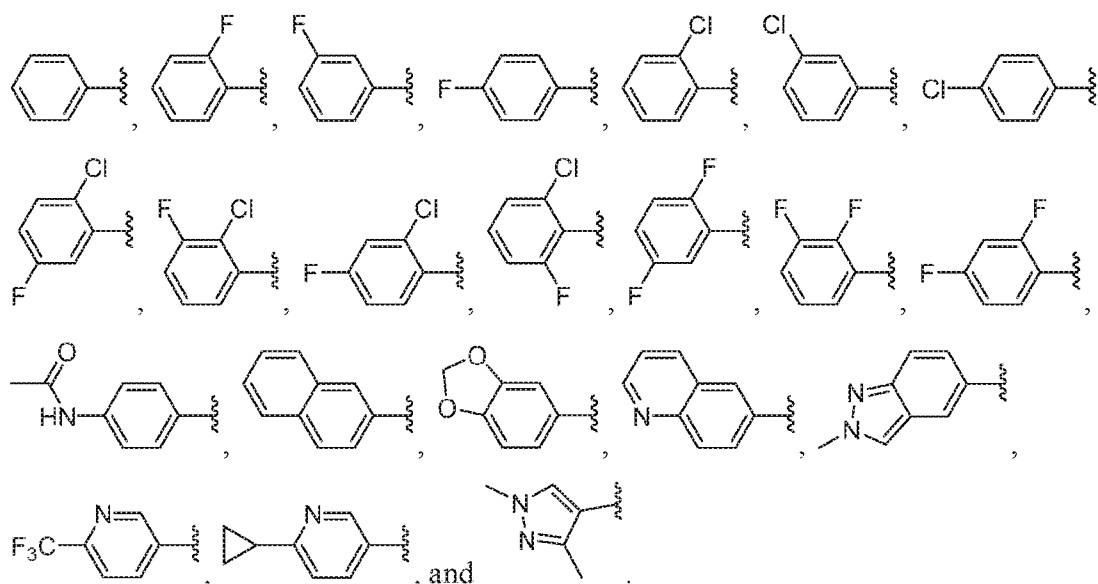
wherein the phenyl or pyrazolyl is substituted with two substituents independently selected from halo and C₁-C₄ alkyl.

[00248] Clause 20. The compound of any of clauses 11-16 or 18, or a pharmaceutically acceptable salt thereof, wherein R¹ is optionally substituted with 1-2 halogens, 1-2 C₁-C₄ alkyl, -NHCOR^e, C₁-C₄ haloalkyl, or C₃-C₆cycloalkyl.

[00249] Clause 21. The compound of clause 11, or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from the group consisting of:



[00250] Clause 22. The compound of clause 11, or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from the group consisting of:



[00251] Clause 23. The compound of any one of clauses 1 or 3-22, or a pharmaceutically acceptable salt thereof, wherein n is 1; and R^2 is hydrogen.

[00252] Clause 24. The compound of any one of clauses 1 or 3-23, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

[00253] Clause 25. The compound of any one of clauses 1-24, or a pharmaceutically acceptable salt thereof, wherein

R^4 is selected from C_4 - C_6 alkyl and $-(CR^bR^c)_p-Y'$;

each R^b is hydrogen;

each R^c is hydrogen;

p is 0, 1, 2, or 3; and

Y' is selected from: C_3 - C_{10} cycloalkyl; C_3 - C_8 cycloalkenyl; aryl; a 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S; and a 5-, 6-, or 7-membered heterocycle having 1, 2, or 3 heteroatoms independently selected from N, O, and S;

wherein Y' is unsubstituted or substituted with one or two substituents independently selected from halo and C_1 - C_4 alkyl.

[00254] Clause 26. The compound of any of clauses 1-25, or a pharmaceutically acceptable salt thereof, wherein

Y' is selected from: C_3 - C_{10} cycloalkyl; C_3 - C_8 cycloalkenyl; phenyl; a phenyl bonded to the parent molecular moiety and fused to a 5- to 6-membered heterocycle containing 1-2 oxygen

atoms; a 5- or 6-membered heteroaryl having 1, 2, or 3 nitrogen atoms; and a 5-, 6-, or 7-membered heterocycle containing 1 oxygen atom;

wherein Y' is unsubstituted or substituted with one or two substituents independently selected from halo and C₁-C₄ alkyl.

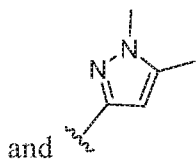
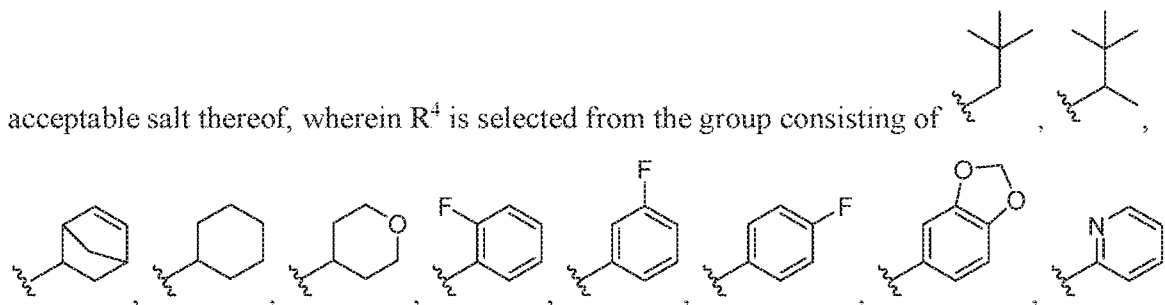
[00255] Clause 27. The compound of clause 26, or a pharmaceutically acceptable salt thereof, wherein

Y' is selected from: C₃-C₇ cycloalkyl; C₃-C₈ cycloalkenyl; phenyl; benzo[d][1,3]dioxolyl; pyridinyl, pyrazolyl, and tetrahydropyranyl;

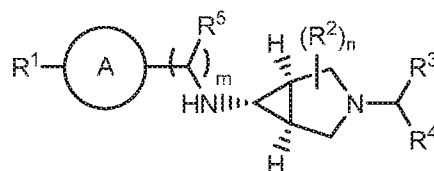
wherein Y' is unsubstituted or substituted with one or two substituents independently selected from halo and C₁-C₄ alkyl.

[00256] Clause 28. The compound of any of clauses 1-27, or a pharmaceutically

acceptable salt thereof, wherein R⁴ is selected from the group consisting of



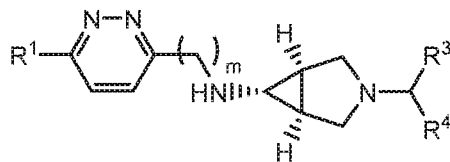
[00257] Clause 29. The compound of any of clauses 1 or 3-28, wherein the compound is a compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof.

[00258] Clause 30. The compound of any of clauses 1 or 3-29, wherein the compound is a compound of formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof.

[00259] Clause 31. The compound of clause 1, wherein the compound is selected from:

(1*S*,5*R*,6*s*)-3-(3,3-dimethylbutyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*,6*s*)-3-(5-bicyclo[2.2.1]hept-2-enylmethyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*,6*s*)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-(2,3,3-trimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-((6-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridazin-3-yl)methyl)-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-((6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl)methyl)-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-*N*-((6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl)methyl)-3-(cyclohexylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-3-(cyclohexylmethyl)-*N*-((6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*)-*N*-[6-(2-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*)-*N*-[6-(3-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*)-*N*-[6-(4-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*)-*N*-[6-(2-chlorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*)-*N*-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-3-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-4-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-6-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(6-quinolyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

N-[4-[6-[(1S,5R)-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-yl]amino]pyridazin-3-yl]phenyl]acetamide;

(1S,5R)-3-(tetrahydropyran-4-ylmethyl)-N-[6-[6-(trifluoromethyl)-3-pyridyl]pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(6-cyclopropyl-3-pyridyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(3-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(4-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-3-(1,3-benzodioxol-5-ylmethyl)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-(6-phenylpyridazin-3-yl)-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-naphthyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(1,3-benzodioxol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,3-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,4-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(2-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-3-(1,3-benzodioxol-5-ylmethyl)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-3-[(1,5-dimethylpyrazol-3-yl)methyl]-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine; and

(1S,5R)-3-(3,3-dimethylbutyl)-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine,

or a pharmaceutically acceptable salt thereof.

[00260] Clause 32. The compound of any one of clauses 1-31, wherein the compound is isotopically labeled.

[00261] Clause 33. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any one of clauses 1-32, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[00262] Clause 34. A method for antagonizing mAChR M₄ in a subject, comprising administering to the subject a therapeutically effective amount the compound of any one of clauses 1-32 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of clause 33.

[00263] Clause 35. A method for treating a disorder in a subject, wherein the subject would benefit from antagonism of mAChR M₄, comprising administering to the mammal a therapeutically effective amount the compound of any one of clauses 1-32, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of clause 33.

[00264] Clause 36. The method of clause 35, wherein the disorder is a movement disorder.

[00265] Clause 37. The method of clause 35, wherein the disorder is selected from Parkinson's disease, drug-induced Parkinsonism, dystonia, Tourette's syndrome, dyskinesias, schizophrenia, cognitive deficits associated with schizophrenia, excessive daytime sleepiness, attention deficit hyperactivity disorder (ADHD), Huntington's disease, chorea, cerebral palsy, and progressive supranuclear pals.

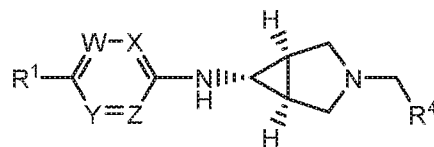
[00266] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents.

[00267] Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, compositions, formulations, or methods of use of the invention, may be made without departing from the spirit and scope thereof.

CLAIMS

What is claimed is:

1. A compound of formula (Ic), or a pharmaceutically acceptable salt thereof,



(Ic)

wherein

the ring containing W, X, Y and Z is a 6-membered heteroaryl ring containing two or one nitrogen atoms and W, X, Y and Z are independently N or CH;

R¹ is a 5- to 10-membered aromatic ring system optionally containing 1-2 nitrogen atoms and optionally substituted with 1-3 substituents independently selected from the group consisting of halogen, C₁-C₄alkyl, C₁-C₄ haloalkyl, -NHCOR^e, and C₃-C₆cycloalkyl;

R^e is hydrogen or C₁-C₄ alkyl;

R⁴ is C₄-C₆ alkyl or -(CR^bR^c)_p-Y⁷;

each R^b is independently hydrogen or C₁-C₄ alkyl;

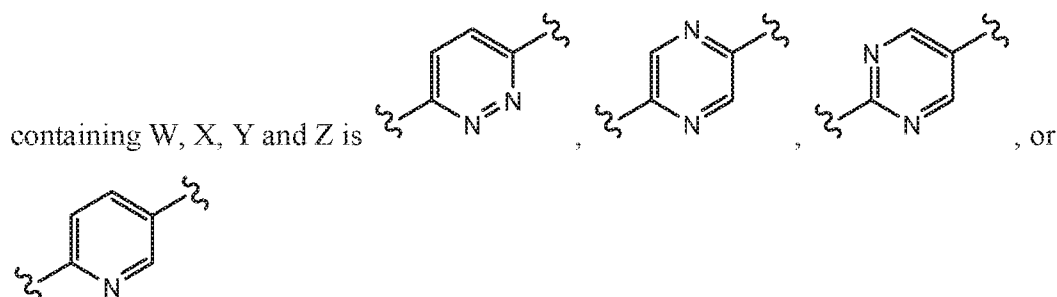
each R^c is independently hydrogen or C₁-C₄ alkyl;

p is 0, 1, 2, 3, or 4; and

Y⁷ is C₃-C₁₀ cycloalkyl; C₃-C₈ cycloalkenyl; aryl; a 5- or 6-membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S; or a 5-, 6-, or 7-membered heterocycle having 1, 2, or 3 heteroatoms independently selected from N, O, and S;

wherein Y⁷ is unsubstituted or substituted with one or two substituents independently selected from halo and C₁-C₄ alkyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the ring



3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is

a) phenyl,

b) a phenyl bonded to the parent molecular moiety and fused to a second ring selected from the group consisting of a 5- or 6-membered heteroaryl, a 5- to 6-membered heterocycle containing 1-2 oxygen atoms, and a second phenyl, or

c) a 5- or 6- membered heteroaryl having 1, 2, or 3 heteroatoms independently selected from N, O, and S,

wherein R^1 is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, $-NHCOR^e$, and C_3 - C_6 cycloalkyl.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl, quinolinyl, benzo[d][1,3]dioxolyl, indazolyl, pyrazolyl, or pyridinyl, wherein R^1 is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, $-NHCOR^e$, and C_3 - C_6 cycloalkyl.

5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl, quinolin-6-yl, benzo[d][1,3]dioxol-5-yl, 2H-indazol-5-yl, 1H-pyrazol-4-yl, or pyridin-3-yl, wherein R^1 is optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, $-NHCOR^e$, and C_3 - C_6 cycloalkyl.

6. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^1 is

Y' is C₃-C₁₀ cycloalkyl; C₃-C₈ cycloalkenyl; phenyl; a phenyl bonded to the parent molecular moiety and fused to a 5- to 6-membered heterocycle containing 1-2 oxygen atoms; a 5- or 6-membered heteroaryl having 1, 2, or 3 nitrogen atoms; or a 5-, 6-, or 7-membered heterocycle containing 1 oxygen atom;

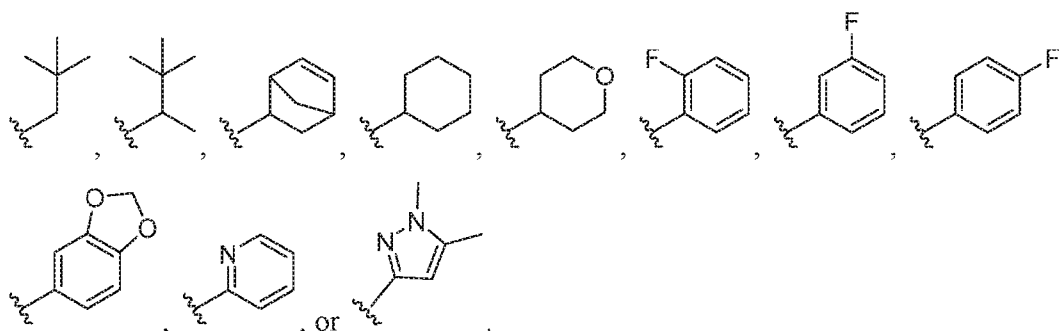
wherein Y' is unsubstituted or substituted with one or two substituents independently selected from halo and C₁-C₄ alkyl.

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein

Y' is C₃-C₇ cycloalkyl; C₃-C₈ cycloalkenyl; phenyl; benzo[d][1,3]dioxolyl; pyridinyl, pyrazolyl, or tetrahydropyranyl;

wherein Y' is unsubstituted or substituted with one or two substituents independently selected from halo and C₁-C₄ alkyl.

11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein R⁴ is



12. The compound of claim 1, selected from the group consisting of:

(1*S*,5*R*,6*s*)-3-(3,3-dimethylbutyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*,6*s*)-3-(5-bicyclo[2.2.1]hept-2-enylmethyl)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*,6*s*)-*N*-[6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl]-3-(2,3,3-trimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*R*,5*S*,6*s*)-3-(cyclohexylmethyl)-*N*-((6-(1,3-dimethylpyrazol-4-yl)pyridazin-3-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1*S*,5*R*)-*N*-[6-(2-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(3-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(4-fluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chlorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-

3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-3-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-

3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-4-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-

3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-6-fluoro-phenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-

3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(6-quinolyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-

azabicyclo[3.1.0]hexan-6-amine;

N-[4-[6-[[[(1S,5R)-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-yl]amino]pyridazin-3-yl]phenyl]acetamide;

(1S,5R)-3-(tetrahydropyran-4-ylmethyl)-N-[6-[6-(trifluoromethyl)-3-pyridyl]pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(6-cyclopropyl-3-pyridyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(3-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(4-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-3-(1,3-benzodioxol-5-ylmethyl)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-chloro-5-fluoro-phenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-(6-phenylpyridazin-3-yl)-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2-naphthyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(1,3-benzodioxol-5-yl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,3-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,4-difluorophenyl)pyridazin-3-yl]-3-(tetrahydropyran-4-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(2-fluorophenyl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(2-pyridylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-3-(1,3-benzodioxol-5-ylmethyl)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-[(1,5-dimethylpyrazol-3-yl)methyl]-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-N-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3-(3,3-dimethylbutyl)-3-azabicyclo[3.1.0]hexan-6-amine;

(1S,5R)-3-[(1,5-dimethylpyrazol-3-yl)methyl]-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexan-6-amine; and

(1S,5R)-3-(3,3-dimethylbutyl)-N-[6-(2-methylindazol-5-yl)pyridazin-3-yl]-3-

azabicyclo[3.1.0]hexan-6-amine,

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1 or 2, wherein the compound is isotopically labeled.
14. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
15. A method for antagonizing mAChR M₄ in a subject, comprising administering to the subject a therapeutically effective amount of the compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof.
16. A method for treating a disorder in a subject, wherein the subject would benefit from antagonism of mAChR M₄, comprising administering to the mammal a therapeutically effective amount of the compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof.
17. The method of claim 16, wherein the disorder is a movement disorder.
18. The method of claim 16, wherein the disorder is selected from Parkinson's disease, drug-induced Parkinsonism, dystonia, Tourette's syndrome, dyskinesias, schizophrenia, cognitive deficits associated with schizophrenia, excessive daytime sleepiness, attention deficit hyperactivity disorder (ADHD), Huntington's disease, chorea, cerebral palsy, and progressive supranuclear palsy.