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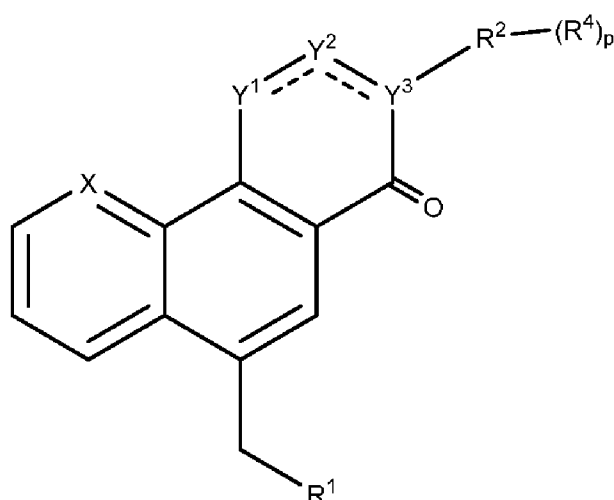
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[Continued on next page]

(54) Title: M1 RECEPTOR POSITIVE ALLOSTERIC MODULATORS AND METHODS OF USE THEREOF



(57) Abstract: The present invention is directed to compounds of general formula (I) or pharmaceutically acceptable salts thereof, which are M1 receptor positive allosteric modulators and that are useful in the treatment of diseases in which the M1 receptor is involved, such as Alzheimer's disease, schizophrenia, pain or sleep disorders. The invention is also directed to pharmaceutical compositions comprising the compounds, or pharmaceutically acceptable salts thereof, and to the use of the compounds and compositions in the treatment of diseases mediated by the M1 receptor.

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- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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TITLE OF THE INVENTION

M1 RECEPTOR POSITIVE ALLOSTERIC MODULATORS AND METHODS OF USE
THEREOF

5 FIELD OF THE INVENTION

The invention is directed to compounds which are muscarinic M1 receptor positive allosteric modulators, and hence are useful in the treatment of Alzheimer's Disease and other diseases mediated by the muscarinic M1 receptor. In particular, the invention is directed to such compounds, their salts, pharmaceutical compositions comprising them and their use in therapy of
10 the human body.

BACKGROUND OF THE INVENTION

Alzheimer's Disease is a common neurodegenerative disease affecting the elderly, resulting in progressive memory impairment, loss of language and visuospatial skills, and
15 behavior deficits. Characteristics of the disease include degeneration of cholinergic neurons in the cerebral cortex, hippocampus, basal forebrain, and other regions of the brain, neurofibrillary tangles, and accumulation of the amyloid β peptide ($A\beta$). $A\beta$ is a 39-43 amino acid produced in the brain by processing of the beta-amyloid precursor protein (APP) by the beta-amyloid protein cleaving enzyme ("beta secretase" or "BACE") and gamma-secretase. The processing leads to
20 accumulation of $A\beta$ in the brain.

Cholinergic neurotransmission involves the binding of acetylcholine either to the nicotinic acetylcholine receptor (nAChR) or to the muscarinic acetylcholine receptor (mAChR). It has been hypothesized that cholinergic hypofunction contributes to the cognitive deficits of patients suffering from Alzheimer's Disease. Consequently, acetyl cholinesterase inhibitors,
25 which inhibit acetylcholine hydrolysis, have been approved in the United States for use in the treatment of the cognitive impairments of Alzheimer's Disease patients. While acetyl cholinesterase inhibitors have provided some cognitive enhancement in Alzheimer's Disease patients, the therapy has not been shown to change the underlying disease pathology.

A second potential pharmacotherapeutic target to counteract cholinergic hypofunction is
30 the activation of muscarinic receptors. Muscarinic receptors are prevalent throughout the body. Five distinct muscarinic receptors (M1-M5) have been identified in mammals. In the central nervous system, muscarinic receptors are involved in cognitive, behavior, sensory, motor and autonomic functions.

The muscarinic M1 receptor, which is prevalent in the cerebral cortex, hippocampus and striatum, has been found to have a major role in cognitive processing and is believed to have a role in the pathophysiology of Alzheimer's Disease. See Eglen et al, *TRENDS in Pharmacological Sciences*, 2001, 22:8, 409-414.

5 In addition, unlike acetyl cholinesterase inhibitors, which are known to provide only symptomatic treatment, M1 agonists also have the potential to treat the underlying disease mechanism of Alzheimer's Disease. The cholinergic hypothesis of Alzheimer's Disease is linked to both β -amyloid and hyperphosphorylated tau protein. Formation of β -amyloid may impair the coupling of the muscarinic receptor with G-proteins. Stimulation of the M1
10 muscarinic receptor has been shown to increase formation of the neuroprotective α APPs fragment, thereby preventing the formation of the A β peptide. Thus, M1 agonists may alter APP processing and enhance α APPs secretion. See Fisher, *Jpn J Pharmacol*, 2000, 84:101-112.

However, M1 ligands which have been developed and studied for Alzheimer's Disease have produced side effects common to other muscarinic receptor ligands, such as sweating,
15 nausea and diarrhea. See Spalding et al, *Mol Pharmacol*, 2002, 61:6, 1297-1302. See also WO2005056552, WO2005030188 and WO2007067489.

The muscarinic receptors are known to contain one or more allosteric sites, which may alter the affinity with which muscarinic ligands bind to the primary binding or orthosteric sites. See, e.g., S. Lazareno et al, *Mol Pharmacol*, 2002, 62:6, 1491-1505; S.
20 Lazareno et al, *Mol Pharmacol*, 2000, 58, 194-207.

Thus the compounds of the invention, which are muscarinic M1 receptor positive allosteric modulators, are believed to be useful in the treatment of Alzheimer's Disease and other diseases mediated by the muscarinic M1 receptor.

25 SUMMARY OF THE INVENTION

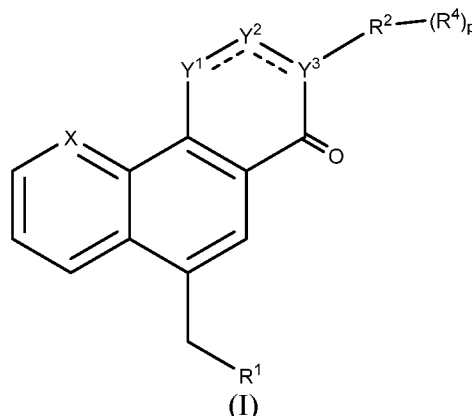
The present invention is directed to novel compounds of generic formula (I) described below, or a pharmaceutically acceptable salt thereof, which is useful as an M1 receptor positive allosteric modulator. Unless otherwise defined, compounds of the invention are compounds of formula (I), formula (Ia) and /or formula (Ib).

30 The invention is further directed to methods of treating a patient (preferably a human) for diseases or disorders in which the M1 receptor is involved, such as Alzheimer's disease, cognitive impairment, schizophrenia, pain disorders and sleep disorders, by administering to the patient a therapeutically effective amount of a compound of the instant invention, or a

pharmaceutically acceptable salt thereof. The invention is also directed to pharmaceutical compositions which include an effective amount of a compound of the instant invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, and the use of the compounds and pharmaceutical compositions of the invention in the treatment of such diseases.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the invention is directed to compounds of formula (I)



or pharmaceutically acceptable salts thereof, wherein

----- represents an optional double bond, provided that there is only one double bond in the ring;

X is selected from the group consisting of CR^a and N;

Y^1 and Y^2 are independently selected from the group consisting of $\text{C}(\text{R}^b)_n$ and $\text{N}(\text{R}^b)_m$;

Y^3 is selected from the group consisting of $\text{C}(\text{R}^a)_q$ and N;

Provided at least one of Y^1 and Y^3 is a nitrogen substitution;

R, R^a and R^b are independently selected from the group consisting of H and C_{1-6} alkyl;

R^1 is selected from the group consisting of aryl, heteroaryl and heterocyclyl, wherein the aryl, heteroaryl and heterocyclyl are optionally substituted with one to three substituents selected from R^5 ;

R^2 is heterocyclyl or C_{3-8} cycloalkyl;

R^4 is independently selected from the group consisting of OR, halo, C_{1-6} alkyl, heteroaryl and heterocyclyl, wherein the alkyl, heteroaryl and heterocyclyl group is optionally substituted with one to three substituents selected from OR, halo, C_{1-6} alkyl, heteroaryl or heterocyclyl;

R^5 is independently selected from the group consisting of CN, halo, C_{1-6} alkyl, OR, SR, NR^2 , aryl, heteroaryl, and heterocyclyl, wherein the alkyl, aryl, heteroaryl or heterocyclyl groups are optionally substituted with one to three substituents selected from R^6 ;

R^6 is independently selected from the group consisting of C_{1-6} alkyl, OR, CN, halo, SR, NR^2 , heteroaryl and aryl;

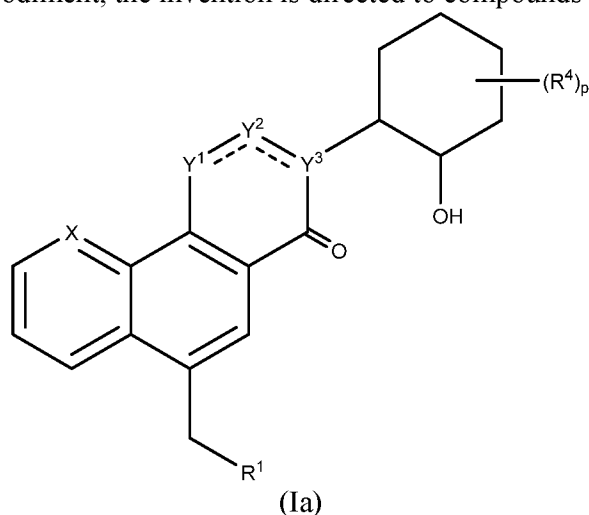
m is independently 0 or 1;

n is independently 1 or 2;

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

q is 0 or 1.

In a second embodiment, the invention is directed to compounds of formula (Ia)



or pharmaceutically acceptable salts thereof, wherein

----- represents an optional double bond, provided that there is only one double bond in the ring;

X is selected from the group consisting of CR^a and N;

5

Y¹ and Y² are independently selected from the group consisting of C(R^b)_n and N(R^b)_m;

Y³ is selected from the group consisting of C(R^a)_q and N;

Provided at least one of Y¹ and Y³ is a nitrogen substitution;

10

R, R^a and R^b are independently selected from the group consisting of H and C₁₋₆ alkyl;

R¹ is selected from the group consisting of C₆₋₁₀ aryl, 6-membered monocyclic heteroaryl, 9- to 10-membered fused bicyclic heteroaryl, 6-membered monocyclic heterocycl, and 8- to 11-

15

bicyclic heterocycl, wherein each of the aryl, heteroaryl and heterocycl are optionally substituted with one to three substituents selected from R⁵;

R⁵ is independently selected from the group consisting of H, CN, halo, C₁₋₆ alkyl, -OR, -SR, aryl and, heteroaryl, wherein the alkyl, aryl and heteroaryl groups are optionally substituted with one to three substituents selected from R⁶;

20

R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, OR, CN, SR, halo, heteroaryl, and aryl;

25

m is independently 0 or 1;

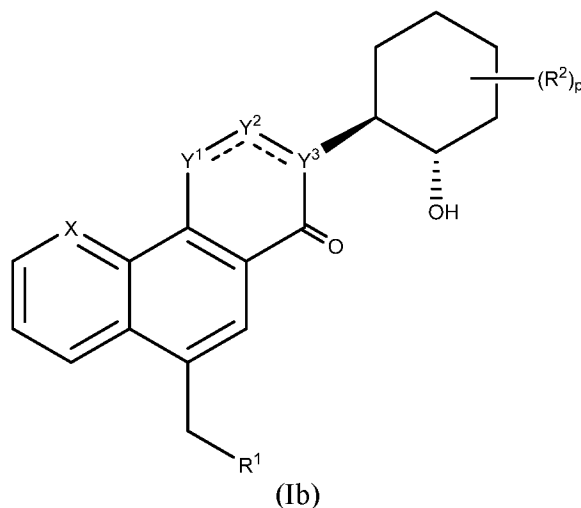
n is independently 1 or 2;

p is 0, 1 or 2; and

q is 0 or 1.

30

In a further embodiment, the invention is directed to compounds of formula (Ib)



or pharmaceutically acceptable salts thereof, wherein

5 represents an optional double bond, provided there is only one double bond in the ring;

X is CH or N;

Y¹ is C(R^b)_n;

10

Y² is C(R^b)_n or N(R^b)_m;

Y³ is N;

15

p is 0 or 1;

and all substituents are as previously defined above.

In a further embodiment, the invention is directed to compounds of formulae (I),

20

(Ia) or (Ib), wherein

R¹ is selected from the group consisting of pyridinyl, piperidinyl, isoquinoline, quinolone, and piperazinyl, wherein the pyridinyl, piperidinyl, isoquinoline, quinolone, and piperazinyl is optionally substituted with one to three substituents selected from R⁵;

25

and all substituents are as previously defined above.

In one embodiment of the compounds of formula (I), (Ia) or (Ib), X is N.

In another embodiment of the compounds of formula (I), (Ia) or (Ib), X is CR^a.

5 In one embodiment of the compounds of formula (I), (Ia) or (Ib), Y¹ is C(R^b)_n, Y² is C(R^b)_n, Y³ is N.

In one embodiment of the compounds of formula (I), (Ia) or (Ib), Y¹ is C(R^b)_n, Y² is N(R^b)_m, Y³ is N.

10 In one embodiment of the compounds of formula (I), (Ia) or (Ib), Y¹ is N(R^b)_m, Y² is C(R^b)_n, Y³ is C(R^a)_q.

In another embodiment of the compounds of formula (I), (Ia) or (Ib), R^a and R^b are both hydrogen or one of R^a and R^b is hydrogen and the other is methyl.

15 In another embodiment of the compounds of formula (I), (Ia) or (Ib), R¹ is optionally substituted C₆₋₁₀ aryl. A subembodiment of this invention is realized when R¹ is optionally substituted phenyl.

In another embodiment of the compounds of formula (I), (Ia) or (Ib), R¹ is optionally substituted 6-membered monocyclic heterocyclyl. A subembodiment of this invention is realized when R¹ is optionally substituted piperidiny1 or optionally substituted piperazinyl.

20 In another embodiment of the compounds of formula (I), (Ia) or (Ib), R¹ is optionally substituted 8- to 11-membered fused bicyclic heterocyclic.

In another embodiment of the compounds of formula (I), (Ia) or (Ib), R¹ is optionally substituted 6-membered fused bicyclic heteroaryl. A subembodiment of this invention is realized when R¹ is optionally substituted pyridyl.

25 In another embodiment of the compounds of formula (I), (Ia) or (Ib), R¹ is optionally substituted 9- to 10-membered fused bicyclic heteroaryl. A subembodiment of this invention is realized when R¹ is optionally substituted isoquinoline or optionally substituted quinoline.

30 In another embodiment of the compounds of formula (I), (Ia) or (Ib), R¹ is selected from the group consisting of pyridinyl, piperidinyl and piperazinyl, wherein the pyridinyl, piperidinyl, and piperazinyl is optionally substituted with one to three substituents selected from R⁵.

In another embodiment of the compounds of formula (I), (Ia) or (Ib), R⁵ is

selected from the group consisting of CN, halo, C₁₋₆ alkyl, OR, SR, heteroaryl and aryl.

In another embodiment of the compounds of formula (I), (Ia) or (Ib), R⁴ is OR, halo and C₁₋₆ alkyl. In a subembodiment, R⁴ is OR.

In yet another embodiment the invention is directed to methods of treating a patient (preferably a human) for diseases in which the M1 receptor is involved, such as Alzheimer's Disease, cognitive impairment, schizophrenia, pain disorders and sleep disorders, by administering to the patient a therapeutically effective amount of a compound of the instant invention.

The invention is also directed to the use of a compound of the invention for treating diseases or disorders in which the M1 receptor is involved, such as Alzheimer's disease, cognitive impairment, schizophrenia, pain disorders and sleep disorders.

The invention is also directed to medicaments or pharmaceutical compositions for treating diseases or disorders in which the M1 receptor is involved, such as Alzheimer's disease, cognitive impairment, schizophrenia, pain disorders and sleep disorders, which comprise a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention is further directed to a method for the manufacture of a medicament or a composition for treating diseases or disorders in which the M1 receptor is involved, such as Alzheimer's disease, cognitive impairment, schizophrenia, pain disorders and sleep disorders, comprising combining a compound of the invention with one or more pharmaceutically acceptable carriers.

Specific examples of the compounds of the instant invention are:

(±)-*trans*-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)benzo[f]phthalazin-4(3*H*)-one;

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)benzo[f] phthalazin-4(3*H*)-one;

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)benzo[f]phthalazin-4(3*H*)-one;

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)benzo[f]phthalazin-4(3*H*)-one;

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-(methylthio)pyridin-3-yl)methyl)benzo[f]phthalazin-4(3*H*)-one;

(±)-*trans*-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[*f*]phthalazin-4(1*H*)-one;
 3-(2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinolin-4(1*H*)-one;
 1-((8-((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)-4-
 5 (pyridin-2-yl)piperidine-4-carbonitrile;
 6-(4-((8-((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)piperazin-1-yl)nicotinonitrile;
 1-((8-((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)-4-phenylpiperidine-4-carbonitrile;
 10 5-((4-fluoropiperidin-1-yl)methyl)-8-((1*S*,2*S*)-2-hydroxycyclohexyl)-1,8-phenanthrolin-7(8*H*)-one;
 4-fluoro-1-((8-((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)piperidine-4-carbonitrile;
 5-((4,4-difluoropiperidin-1-yl)methyl)-8-((1*S*,2*S*)-2-hydroxycyclohexyl)-1,8-phenanthrolin-
 15 7(8*H*)-one;
 or pharmaceutically acceptable salts thereof.

The invention is also directed to methods of treating a patient (preferably a human) for diseases or disorders in which the M1 receptor is involved, such as Alzheimer's Disease, cognitive impairment, schizophrenia, pain disorders and sleep disorders, by administering to the
 20 patient a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

The invention is also directed to the use of a compound of the invention, for treating a disease or disorder in which the M1 receptor is involved, such as Alzheimer's Disease, cognitive impairment, schizophrenia, pain disorders and sleep disorders, by administering to the patient a
 25 compound of the instant invention, or a pharmaceutically acceptable salt thereof.

The invention is also directed to medicaments or, pharmaceutical compositions for the treatment of diseases or disorders in a patient (preferably a human) in which the M1 receptor is involved, such as Alzheimer's Disease, cognitive impairment, schizophrenia, pain disorders, and sleep disorders, which comprise a compound of the invention or a pharmaceutically acceptable
 30 salt thereof, and a pharmaceutically acceptable carrier.

The invention is also directed to a method for the manufacture of a medicament or a pharmaceutical composition for treating diseases in which M1 receptor is involved, such as Alzheimer's Disease, cognitive impairment, schizophrenia, pain disorders, and sleep disorders,

comprising combining a compound of the invention, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.

When any variable (e.g. heteroaryl, heterocyclyl, R^a, R⁵ etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" encompasses groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, and alkynyl and means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, and heptyl. "Alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. Preferably, alkenyl is C₂-C₆ alkenyl. Preferred alkynyl are C₂-C₆ alkynyl.

The term "cycloalkyl" refers to a saturated hydrocarbon containing one ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "C₁₋₆" includes alkyls containing 6, 5, 4, 3, 2, or 1 carbon atoms

The term "alkoxy" as used herein, alone or in combination, includes an alkyl group connected to the oxy connecting atom. The term "alkoxy" also includes alkyl ether groups, where the term 'alkyl' is defined above, and 'ether' means two alkyl groups with an oxygen atom between them. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, methoxymethane (also referred to as 'dimethyl ether'), and methoxyethane (also referred to as 'ethyl methyl ether').

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, or biphenyl.

The term heterocycle, heterocyclyl, or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation

of a stable structure. The term heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnoliny, dihydrobenzofuryl, dihydrobenzothienyl, 5 dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazoliny, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoquinoliny, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholiny, naphthyridiny, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdiny, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, 10 pyrrolidinyl, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, tetrahydrofuryl, tetrahydroisoquinoliny, tetrahydroquinoliny, thiamorpholiny, thiamorpholiny sulfoxide, thiazolyl, thiazoliny, thienofuryl, thienothienyl, thienyl and triazolyl.

The term "heteroaryl", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 9- to 10-membered fused bicyclic heteroaryl which contains 15 an aromatic ring, any ring of which may be saturated, such as piperidinyl, partially saturated, or unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic 20 rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heteroaryl groups include, but are not limited to, benzimidazole, benzisothiazole, benzisoxazole, benzofuran, benzothiazole, benzothiophene, benzotriazole, benzoxazole, carboline, cinnoline, furan, furazan, imidazole, indazole, indole, indolizine, isoquinoline, isothiazole, isoxazole, 25 naphthyridine, oxadiazole, oxazole, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and N-oxides thereof.

In certain other embodiments, the heterocyclic group is fused to an aryl or heteroaryl group. Examples of such fused heterocycles include, without limitation, 30 tetrahydroquinoliny and dihydrobenzofuranyl.

The term "heteroatom" means O, S or N, selected on an independent basis.

A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example,

substituted phenyls include 2-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2,4-difluoro-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4-dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes (-CH₂-) substituted with oxygen to form carbonyl (-CO-).

- 5 Unless otherwise stated, as employed herein, when a moiety (e.g., cycloalkyl, aryl, alkyl, heteroaryl, heterocyclyl, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (e.g., an annular -CH- substituted with oxo is -C(O)-), nitro,
- 10 halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:
- 15 (a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino, and
(b) C₁-C₆ alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C₁-C₈ alkyl, SO₂CF₃, CF₃, SO₂Me, C₁-C₈ alkenyl, C₁-C₈ alkoxy, C₁-C₈ alkoxy-carbonyl, aryloxy-carbonyl, C₂-C₈ acyl, C₂-C₈ acylamino, C₁-C₈ alkylthio, arylalkylthio, arylthio, C₁-C₈alkylsulfinyl,
- 20 arylalkylsulfinyl, arylsulfinyl, C₁-C₈ alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C₀-C₆ N-alkylcarbamoyl, C₂-C₁₅ *N,N* dialkylcarbamoyl, C₃-C₇ cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C₃-C₇ heterocycle, or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more
- 25 moieties listed in (a), above.

"Halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "mammal" "mammalian" or "mammals" includes humans, as well as animals, such as dogs, cats, horses, pigs and cattle.

30 All patents, patent applications and publications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety and are deemed representative of the prevailing state of the art.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise. Thus, for example,

reference to "a primer" includes two or more such primers, reference to "an amino acid" includes more than one such amino acid, and the like.

The compounds of the invention may have one or more asymmetric centers. Compounds with asymmetric centers give rise to enantiomers (optical isomers), diastereomers

5 (configurational isomers) or both, and it is intended that all of the possible enantiomers and diastereomers in mixtures and as pure or partially purified compounds are included within the scope of this invention. The present invention is meant to encompass all such isomeric forms of the compounds of invention.

10 Formula (I) and Formula (Ia) are shown above without a definite stereochemistry. The present invention includes all stereoisomers of formulae (I), (Ia) and (Ib) , and pharmaceutically acceptable salts thereof.

The independent syntheses of the enantiomerically or diastereomerically enriched compounds, or their chromatographic separations, may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry
15 may be determined by the x-ray crystallography of crystalline products or crystalline intermediates that are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers or diastereomers are isolated. The separation can be carried out by methods well
20 known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the
25 added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods using chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer or diastereomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known
30 configuration by methods well known in the art.

In the compounds of the instant invention, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic

mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of the instant invention. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds of the instant invention can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

The compounds of the invention may be prepared according to the reaction Schemes included herein, in which variables are as defined before or are derived, using readily available starting materials, from reagents and conventional synthetic procedures. It is also possible to use variants which are themselves known to those of ordinary skill in organic synthesis art, but are not mentioned in greater detail.

The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of the invention.

During any of the synthetic sequences it may be necessary or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973, and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1999. The protecting groups may be removed at a convenient sequent stage using methods known from the art.

Specific embodiments of the compounds of the invention, and methods of making them, are described in the Examples herein.

As used herein, the term "muscarinic M1 receptor" refers to one of the five subtypes of the muscarinic acetylcholine receptor, which is from the superfamily of G-protein coupled receptors. The family of muscarinic receptors is described, for example, in *Pharmacol Ther*, 1993, 58:319-379; *Eur J Pharmacol*, 1996, 295:93-102, and *Mol Pharmacol*, 2002, 61:1297-1302. The muscarinic receptors are known to contain one or more allosteric sites, which may alter the affinity with which muscarinic ligands bind to the primary binding or orthosteric sites. See, e.g., S. Lazareno et al, *Mol Pharmacol*, 2002, 62:6, 1491-1505.

As used herein, the terms "positive allosteric modulator" and "allosteric potentiator" are used interchangeably, and refer to a ligand which interacts with an allosteric site of a receptor to activate the primary binding site. The compounds of the invention are positive allosteric modulators of the muscarinic M1 receptor. For example, a modulator or
5 potentiator may directly or indirectly augment the response produced by the endogenous ligand (such as acetylcholine or xanomeline) at the orthosteric site of the muscarinic M1 receptor in an animal, in particular, a human.

The actions of ligands at allosteric receptor sites may also be understood according to the "allosteric ternary complex model," as known by those skilled in the art. The allosteric
10 ternary complex model is described with respect to the family of muscarinic receptors in Birdsall et al, *Life Sciences*, 2001, 68:2517-2524. For a general description of the role of allosteric binding sites, see Christopoulos, *Nature Reviews: Drug Discovery*, 2002, 1:198-210.

It is believed that the compounds of the invention bind to an allosteric binding site
15 that is distinct from the orthosteric acetylcholine site of the muscarinic M1 receptor, thereby augmenting the response produced by the endogenous ligand acetylcholine at the orthosteric site of the M1 receptor. It is also believed that the compounds of the invention bind to an allosteric site which is distinct from the xanomeline site of the muscarinic M1 receptor, thereby augmenting the response produced by the endogenous ligand xanomeline at the
20 orthosteric site of the M1 receptor.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. The compounds of the invention may be mono, di or tris salts, depending on the number of acid functionalities present in the free base form of the compound.
25 Free bases and salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like.

Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases
30 include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine,

glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

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

Suitable pharmaceutically acceptable salts include ammonium, sodium, potassium, hydrochloride, hydrobromide and fumarate.

The present invention is directed to the use of the compounds of formulae (I), (Ia) and (Ib) disclosed herein as M1 allosteric modulators in a patient or subject such as a mammal in need of such activity, comprising the administration of an effective amount of the compound. In addition to humans, a variety of other mammals can be treated according to the method of the present invention.

The compounds of the present invention may have utility in treating or ameliorating Alzheimer's disease. The compounds may also be useful in treating or ameliorating other diseases mediated by the muscarinic M1 receptor, such as schizophrenia, sleep disorders, pain disorders (including acute pain, inflammatory pain and neuropathic pain) and cognitive disorders (including mild cognitive impairment). Other conditions that may be treated by the compounds of the invention include Parkinson's Disease, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, urinary incontinence, glaucoma, schizophrenia, Trisomy 21 (Down Syndrome), cerebral amyloid angiopathy, degenerative dementia, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), Creutzfeld-Jakob disease, prion disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, head trauma, stroke, pancreatitis, inclusion body myositis, other peripheral amyloidoses, diabetes, autism and atherosclerosis.

In preferred embodiments, the compounds of the invention may be useful in treating Alzheimer's Disease, cognitive disorders, schizophrenia, pain disorders and sleep disorders. For example, the compounds may be useful for the prevention of dementia of the Alzheimer's type, as well as for the treatment of early stage, intermediate stage or late stage dementia of the Alzheimer's type.

Potential schizophrenia conditions or disorders for which the compounds of the invention may be useful include one or more of the following conditions or diseases: schizophrenia or psychosis including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance-induced or drug-induced (phencyclidine, ketamine and other dissociative anaesthetics, amphetamine and other psychostimulants and cocaine) psychosis, psychotic disorder, psychosis associated with affective disorders, brief reactive psychosis, schizoaffective psychosis, "schizophrenia-spectrum" disorders such as schizoid or schizotypal personality disorders, or illness associated with psychosis (such as major depression, manic depressive (bipolar) disorder, Alzheimer's disease and post-traumatic stress syndrome), including both the positive and the negative symptoms of schizophrenia and other psychoses; cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, multi-infarct dementia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnesic disorders or age related cognitive decline. Thus, in another specific embodiment, the compounds of the present invention may be useful as a method for treating schizophrenia or psychosis comprising administering to a patient in need thereof an effective amount of a compound of the present invention. At present, the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes paranoid, disorganized, catatonic or undifferentiated schizophrenia and substance-induced psychotic disorder. As used herein, the term "schizophrenia or psychosis" includes treatment of those mental disorders as described in DSM-IV-TR. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term "schizophrenia or psychosis" is intended to include like disorders that are described in other diagnostic sources.

Potential sleep conditions or disorders for which the compounds of the invention may be useful include enhancing sleep quality; improving sleep quality; augmenting sleep maintenance; increasing the value which is calculated from the time that a subject sleeps divided by the time that a subject is attempting to sleep; decreasing sleep latency or onset (the time it takes to fall asleep); decreasing difficulties in falling asleep; increasing sleep continuity; decreasing the

number of awakenings during sleep; decreasing nocturnal arousals; decreasing the time spent awake following the initial onset of sleep; increasing the total amount of sleep; reducing the fragmentation of sleep; altering the timing, frequency or duration of REM sleep bouts; altering the timing, frequency or duration of slow wave (i.e. stages 3 or 4) sleep bouts; increasing the amount and percentage of stage 2 sleep; promoting slow wave sleep; enhancing EEG-delta activity during sleep; increasing daytime alertness; reducing daytime drowsiness; treating or reducing excessive daytime sleepiness; insomnia; hypersomnia; narcolepsy; interrupted sleep; sleep apnea; wakefulness; nocturnal myoclonus; REM sleep interruptions; jet-lag; shift workers' sleep disturbances; dyssomnias; night terror; insomnias associated with depression, emotional/mood disorders, as well as sleep walking and enuresis, and sleep disorders which accompany aging; Alzheimer's sundowning; conditions associated with circadian rhythmicity as well as mental and physical disorders associated with travel across time zones and with rotating shift-work schedules; conditions due to drugs which cause reductions in REM sleep as a side effect; syndromes which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep; and conditions which result from a diminished quality of sleep.

Pain disorders for which the compounds of the invention may be useful include neuropathic pain (such as postherpetic neuralgia, nerve injury, the "dynias", e.g., vulvodinia, phantom limb pain, root avulsions, painful diabetic neuropathy, painful traumatic mononeuropathy, painful polyneuropathy); central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system); postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, stump pain); bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia); perioperative pain (general surgery, gynecological), chronic pain, dysmenorrhea, as well as pain associated with angina, and inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno- synovitis and gout), headache, migraine and cluster headache, headache, primary hyperalgesia, secondary hyperalgesia, primary allodynia, secondary allodynia, or other pain caused by central sensitization.

Compounds of the invention may also be used to treat or prevent dyskinesias. Furthermore, compounds of the invention may be used to decrease tolerance and/or dependence to opioid treatment of pain, and for treatment of withdrawal syndrome of e.g., alcohol, opioids, and cocaine.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment of diseases or conditions for which the compounds of the present invention have utility, where the combination of the drugs together are safer or more effective than either drug alone. Additionally, the compounds of the present invention may be used in combination with one or more other drugs that treat, prevent, control, ameliorate, or reduce the risk of side effects or toxicity of the compounds of the present invention. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with the compounds of the present invention. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to the compounds of the present invention. The combinations may be administered as part of a unit dosage form combination product, or as a kit or treatment protocol wherein one or more additional drugs are administered in separate dosage forms as part of a treatment regimen.

Examples of combinations of the compounds of the present invention include combinations with anti-Alzheimer's Disease agents, for example beta-secretase inhibitors; alpha 7 nicotinic agonists, such as ABT089, SSR180711 and MEM63908; ADAM 10 ligands or activators; gamma-secretase inhibitors, such as LY450139 and TAK 070; gamma secretase modulators; tau phosphorylation inhibitors; glycine transport inhibitors; LXR β agonists; ApoE4 conformational modulators; NR2B antagonists; androgen receptor modulators; blockers of A β oligomer formation; 5-HT4 agonists, such as PRX-03140; 5-HT6 antagonists, such as GSK 742467, SGS-518, FK-962, SL-65.0155, SRA-333 and xaliproden; 5-HT1a antagonists, such as lecozotan; p25/CDK5 inhibitors; NK1/NK3 receptor antagonists; COX-2 inhibitors; HMG-CoA reductase inhibitors; NSAIDs including ibuprofen; vitamin E; anti-amyloid antibodies (including anti-amyloid humanized monoclonal antibodies), such as bapineuzumab, ACC001, CAD106, AZD3102, H12A11V1; anti-inflammatory compounds such as (R)-flurbiprofen, nitroflurbiprofen, ND-1251, VP-025, HT-0712 and EHT-202; PPAR gamma agonists, such as pioglitazone and rosiglitazone; CB-1 receptor antagonists or CB-1 receptor inverse agonists, such as AVE1625; antibiotics such as doxycycline and rifampin; N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine, neramexane and EVT101; cholinesterase inhibitors such as galantamine, rivastigmine, donepezil, tacrine, phenserine, ladostigil and ABT-089; growth hormone secretagogues such as ibutamoren, ibutamoren mesylate, and capromorelin; histamine H₃ receptor antagonists such as ABT-834, ABT 829, GSK 189254 and CEP16795; AMPA agonists or AMPA modulators, such as CX-717, LY 451395, LY404187 and S-18986;

PDE IV inhibitors, including MEM1414, HT0712 and AVE8112; GABA_A inverse agonists; GSK3 β inhibitors, including AZD1080, SAR502250 and CEP16805; neuronal nicotinic agonists; selective M1 agonists; HDAC inhibitors; and microtubule affinity regulating kinase (MARK) ligands; or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the compounds of the present invention.

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

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

receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alantemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole. It will be appreciated that the dopamine agonist may be in the form of a pharmaceutically acceptable salt, for example, alantemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, 5 naxagolide hydrochloride and pergolide mesylate.

In another embodiment, the subject compound may be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, 10 fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone. It will be appreciated that the neuroleptic agents when used in combination with the 15 subject compound may be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine, 20 haloperidol, pimozide and risperidone are commonly used in a non-salt form. Thus, the subject compound may be employed in combination with acetophenazine, alantemol, aripiprazole, amisuiptide, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, 25 pergolide, perphenazine, pimozide, pramipexole, quetiapine, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene, trifluoperazine or ziprasidone.

Examples of combinations of the compounds include combinations with agents for the treatment of pain, for example non-steroidal anti-inflammatory agents, such as aspirin, diclofenac, duflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, 30 naproxen, oxaprozin, piroxicam, sulindac and tolmetin; COX-2 inhibitors, such as celecoxib, rofecoxib, valdecoxib, 406381 and 644784; CB-2 agonists, such as 842166 and SAB378; VR-1 antagonists, such as AMG517, 705498, 782443, PAC20030, V114380 and A425619; bradykinin B 1 receptor antagonists, such as SSR240612 and NVPSAA164; sodium channel blockers and

antagonists, such as VX409 and SPI860; nitric oxide synthase (NOS) inhibitors (including iNOS and nNOS inhibitors), such as SD6010 and 274150; glycine site antagonists, including lacosamide; neuronal nicotinic agonists, such as ABT 894; NMDA antagonists, such as AZD4282; potassium channel openers; AMPA/kainate receptor antagonists; calcium channel
 5 blockers, such as ziconotide and NMED160; GABA-A receptor IO modulators (e.g., a GABA-A receptor agonist); matrix metalloprotease (MMP) inhibitors; thrombolytic agents; opioid analgesics such as codeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene; neutrophil inhibitory factor (NIF); pramipexole, ropinirole; anticholinergics; amantadine; monoamine oxidase B15 ("MAO-
 10 B") inhibitors; 5HT receptor agonists or antagonists; mGlu5 antagonists, such as AZD9272; alpha agonists, such as AGNXX/YY; neuronal nicotinic agonists, such as ABT894; NMDA receptor agonists or antagonists, such as AZD4282; NK1 antagonists; selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), such as duloxetine; tricyclic antidepressant drugs, norepinephrine modulators;
 15 lithium; valproate; gabapentin; pregabalin; rizatriptan; zolmitriptan; naratriptan and sumatriptan.

The compounds of the present invention may be administered in combination with compounds useful for enhancing sleep quality and preventing and treating sleep disorders and sleep disturbances, including e.g., sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, antihistamines, benzodiazepines, barbiturates, cyclopyrrolones, orexin antagonists, alpha-
 20 1 antagonists, GABA agonists, 5HT-2 antagonists including 5HT-2A antagonists and 5HT-2A/2C antagonists, histamine antagonists including histamine H3 antagonists, histamine H3 inverse agonists, imidazopyridines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, other orexin antagonists, orexin agonists, prokineticin agonists and antagonists, pyrazolopyrimidines, T-type calcium channel antagonists, triazolopyridines, and the
 25 like, such as: adinazolam, allobarbitol, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, armodafinil, APD-125, bentazepam, benzocetamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capromorelin, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, conazepam, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone,
 30 divalproex, diphenhydramine, doxepin, EMD-281014, eplivanserin, estazolam, eszopiclone, ethchlorinol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, gaboxadol, glutethimide, halazepam, hydroxyzine, ibutamoren, imipramine, indiplon, lithium, lorazepam, lormetazepam, LY-156735, maprotiline, MDL-100907,

meclqualone, melatonin, mephobarbital, meprobamate, methaqualone, methypylon, midaflur, midazolam, modafinil, nefazodone, NGD-2-73, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, ramelteon, reclazepam, roletamide, secobarbital, sertraline, suproclone, TAK-375, temazepam, thioridazine, tiagabine, tracazolate, tranlycypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zopiclone, zolpidem, and salts thereof, and combinations thereof, and the like, or the compound of the present invention may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

The subject or patient to whom the compounds of the present invention is administered is generally a human being, male or female, in whom M1 allosteric modulation is is desired, but may also encompass other mammals, such as dogs, cats, mice, rats, cattle, horses, sheep, rabbits, monkeys, chimpanzees or other apes or primates, for which treatment of the above noted disorders is desired.

The term "composition" as used herein is intended to encompass a product comprising specified ingredients in predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the

pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1 mg to about 500 mg of the active ingredient and each cachet or capsule preferably containing from about 0.1 mg to about 500 mg of the active ingredient.

Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Other pharmaceutical compositions include aqueous suspensions, which contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. In addition, oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Oily suspensions may also contain various excipients. The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions, which may also contain excipients such as sweetening and flavoring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension, or in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can also be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art.

By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment in a form that can be introduced into that individual's body in a therapeutically useful form and therapeutically useful amount, including, but not limited to: oral dosage forms, such as tablets, capsules, syrups, suspensions, and the like; injectable dosage forms, such as IV, IM, or IP, and the like; transdermal dosage forms, including creams, jellies, powders, or patches; buccal dosage forms; inhalation powders, sprays, suspensions, and the like; and rectal suppositories.

The terms “effective amount” or “therapeutically effective amount” means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

5 As used herein, the term "treatment" or "treating" means any administration of a compound of the present invention and includes (1) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or (2) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased
10 (i.e., reversing the pathology and/or symptomatology).

 The compositions containing compounds of the present invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. The term “unit dosage form” is taken to mean a single dose wherein all active and inactive ingredients are combined in a suitable system, such that the patient or person
15 administering the drug to the patient can open a single container or package with the entire dose contained therein, and does not have to mix any components together from two or more containers or packages. Typical examples of unit dosage forms are tablets or capsules for oral administration, single dose vials for injection, or suppositories for rectal administration. This list of unit dosage forms is not intended to be limiting in any way, but merely to represent typical
20 examples of unit dosage forms.

 The compositions containing compounds of the present invention may conveniently be presented as a kit, whereby two or more components, which may be active or inactive ingredients, carriers, diluents, and the like, are provided with instructions for preparation of the actual dosage form by the patient or person administering the drug to the patient. Such kits may
25 be provided with all necessary materials and ingredients contained therein, or they may contain instructions for using or making materials or components that must be obtained independently by the patient or person administering the drug to the patient.

 When treating or ameliorating a disorder or disease for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 mg to about 100 mg per
30 kg of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. The total daily dosage is from about 1.0 mg to about 2000 mg, preferably from about 0.1 mg to about 20 mg per kg of body weight. In the case of a

70 kg adult human, the total daily dose will generally be from about 7 mg to about 1,400 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

5 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.005 mg to about 2.5 g of active agent, compounded with an appropriate and convenient amount of carrier material. Unit dosage forms will generally
10 contain between from about 0.005 mg to about 1000 mg of the active ingredient, typically 0.005, 0.01 mg, 0.05 mg, 0.25 mg, 1 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg, administered once, twice or three times a day.

 It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the
15 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.

 The following abbreviations are used throughout the text:

20	Ac:	acetyl
	aq:	aqueous
	Ar:	aryl
	Bn:	benzyl
	Boc:	<i>tert</i> -butoxycarbonyl
25	<i>t</i> -Bu:	<i>tert</i> -butyl
	CHO:	Chinese Hamster Ovary
	ClZn:	Chlorozinc
	DMAP:	4-dimethylaminopyridine
	DMEM:	Dulbecco's Modified Eagle Medium (High Glucose)
30	DMF:	dimethylformamide
	DMSO:	dimethylsulfoxide
	Et:	ethyl
	FBS:	fetal bovine serum

	HPLC:	high performance liquid chromatography
	LRMS:	low resolution mass spectrometry
	Me:	methyl
	Ms:	mesyl
5	MS:	mass spectrometry
	NBS:	N-bromosuccinimide
	NMO:	<i>N</i> -methyl morpholine <i>N</i> -oxide
	NMR:	Nuclear Magnetic Resonance
	Ph:	phenyl
10	rt:	room temperature
	THF:	tetrahydrofuran

Several methods for preparing the compounds of this invention are illustrated in the schemes and examples herein. Starting materials are made according to procedures known in the art or as illustrated herein. The following examples are provided so that the invention might be more fully understood. The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of the invention.

Starting materials useful for the preparation of the compounds in the present invention are known in the art, or may be prepared using chemical methodologies known to those skilled in the art or as illustrated herein.

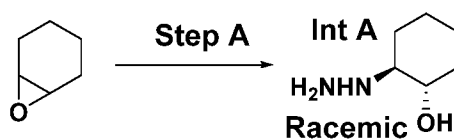
All reactions were stirred (mechanically, stir bar/stir plate, or shaken) and conducted under an inert atmosphere of nitrogen or argon unless specifically stated otherwise and all solvents were anhydrous unless otherwise specified. The progress of reactions was determined by either analytical thin layer chromatography (TLC) performed with E. Merck (EMD Millipore, Billerica MA) pre-coated TLC plates, silica gel 60E-254, layer thickness 0.25 mm or liquid chromatography-mass spectrum (LC-MS). Mass analysis was performed on an Agilent 1200Series coupled with Agilent 6130 Quadrupole LC\MS with ES+APCI (positive/negative) mode. High performance liquid chromatography (HPLC) was conducted on an Agilent 1200 series HPLC on ATLANTIS dC18(250x4.6m -5 11) column with gradient 10:90-100 v/vCH₃CN/H₂O + v 0.1 % TFA in water; flow rate 1.0 mL/min, UV wavelength 215nm).

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Flash chromatography was performed by Biotage-Isolera™ Flash chromatography instrument on Biotage® SNAP KP-Sil pre-packed with 50 µm silica particles with a surface area of 500 m²/g.

¹H-NMR spectra were obtained on a 400 BRUKER Avance[®] Spectrometer in CDCl₃ or CD₃OD or other solvents as indicated and chemical shifts are reported as δ using the solvent peak as reference and coupling constants are reported in hertz (Hz).

5

SYNTHESIS OF INTERMEDIATE A:



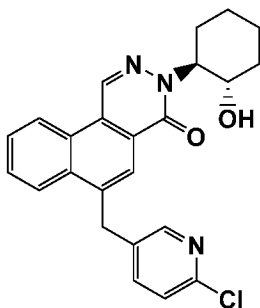
A solution of 7-oxabicyclo[4.1.0]heptane (5.0 g, 51 mmol) in hydrazine hydrate (12.7 g, 255 mmol) was heated to 100°C for 3 hours. The mixture was cooled to room temperature and concentrated in vacuo. Methanol was added, the volatiles were removed under reduced pressure, and the residue was washed twice with toluene. The organic extract was concentrated in vacuo and the residue washed with diethyl ether and then dried to provide (±)-*trans*-2-hydrazinylcyclohexanol that gave a proton NMR spectra consistent with theory and a mass ion [ES⁺] of 131.2 for [M + H]⁺.

10

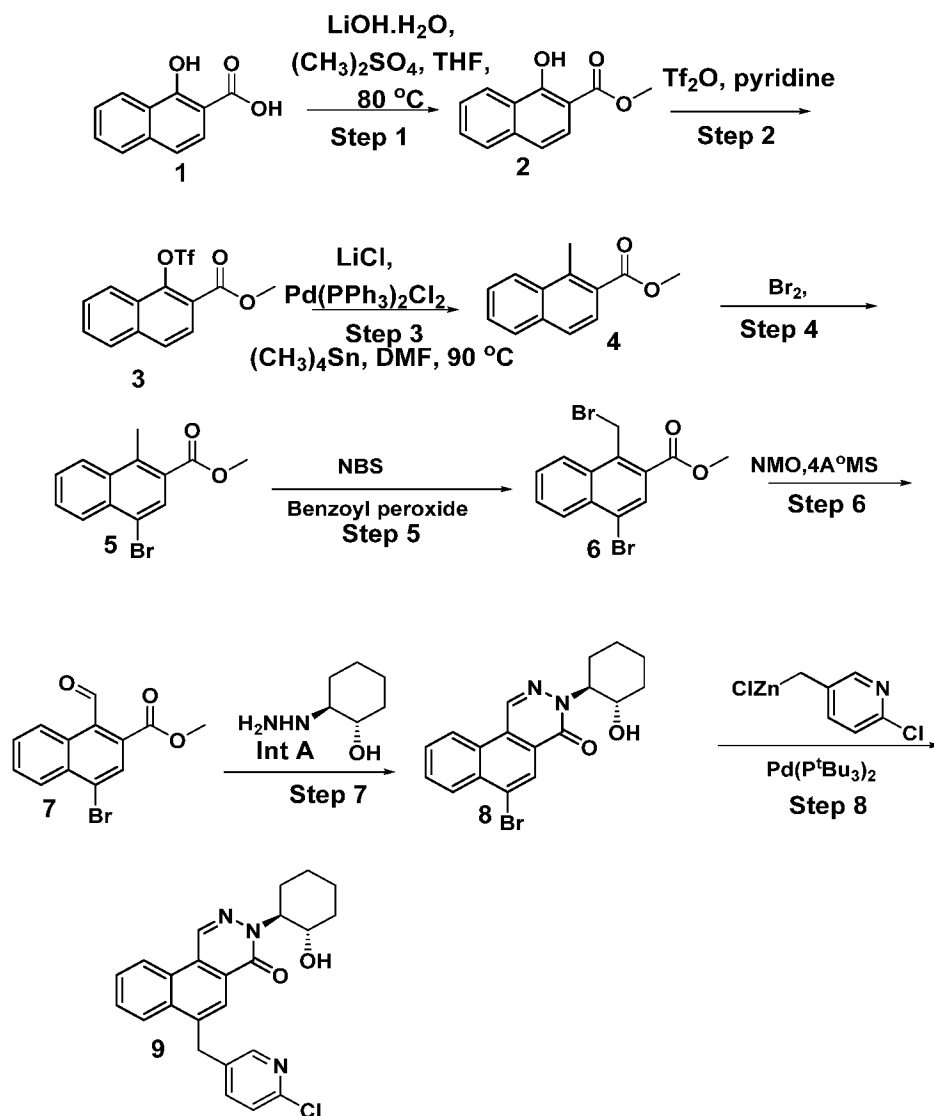
EXAMPLE 1

15

(±)-*trans*-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)benzo[*f*]phthalazin-4(3*H*)-one



Scheme 1

**Step 1: Synthesis of methyl 1-hydroxy-2-naphthoate, compound 2**

To a stirred solution of 1-hydroxy-2-naphthoic acid (5.0 g, 27 mmol) in THF (25 mL) at room temperature was added lithium hydroxide monohydrate (1.1 g, 27 mmol). The mixture was stirred for 30 minutes, after which dimethyl sulfate (2.54 mL, 26.6 mmol) was added. The mixture was then refluxed for 3 hours, cooled to ambient temperature and concentrated in vacuo. The residue was diluted with saturated aqueous NaHCO_3 and extracted with diethyl ether. The organic extracts were dried with sodium sulfate, filtered and concentrated in vacuo, providing the titled compound.

Step 2: Synthesis of methyl 1-(((trifluoromethyl)sulfonyl)oxy)-2-naphthoate, compound 3

To a stirred solution of methyl 1-hydroxy-2-naphthoate (500 mg, 2.47 mmol) in pyridine (3.5 mL) at -5°C, was added triflic anhydride (1.25 mL, 7.42 mmol). The reaction mixture was warmed to room temperature and stirred for 1 hour. The mixture was cooled, diluted with ice-cold water (25 mL) and extracted with ethyl acetate. The combined organic layers were washed
5 with water and brine, dried with sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10-20 % ethyl acetate in petroleum ether) to obtain the titled compound.

Step 3: Synthesis of methyl 1-methyl-2-naphthoate, compound 4

10 To a stirred solution of methyl 1-(((trifluoromethyl)sulfonyl)oxy)-2-naphthoate (200 mg, 0.598 mmol) in DMF (1.4 mL) at room temperature was added lithium chloride (126 mg, 2.98 mmol), bis(triphenylphosphine)palladium(II) dichloride (21.0 mg, 0.030 mmol) followed by tetramethyltin (235 mg, 1.32 mmol). The resultant solution was heated to 110°C for 3 hours, cooled to room temperature, diluted with cold water and extracted with ethyl acetate. The
15 combined organic layers were washed with cold water, dried with sodium sulfate, filtered and the filtrate was concentrated under reduced. The residue was purified by silica gel column chromatography (0 - 3% ethyl acetate in petroleum ether) to provide the titled compound.

Step 4: Synthesis of methyl 4-bromo-1-methyl-2-naphthoate, compound 5

20 To a solution of methyl 1-methyl-2-naphthoate (500 mg, 2.49 mmol) in acetic acid (7 mL) was added a solution of bromine (0.129 mL, 2.50 mmol) in acetic acid (3 mL). The mixture was heated to 90°C for 4 hours, cooled to room temperature, poured into water and extracted with dichloromethane (10 mL). The organic layer was washed with aqueous sodium bicarbonate (saturated), water, and brine. The filtrate was dried with sodium sulfate, filtered, and the filtrate
25 was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-3 % ethyl acetate in petroleum ether) to provide the titled compound.

Step 5: Synthesis of methyl 4-bromo-1-(bromomethyl)-2-naphthoate, compound 6

To a solution of methyl 4-bromo-1-methyl-2-naphthoate (450 mg, 1.61 mmol) in carbon tetrachloride (8 mL) was added *N*-Bromosuccinimide (430 mg, 2.42 mmol) and benzoyl peroxide (46.9 mg, 0.193 mmol). The mixture was refluxed for 3 hours, cooled to room
30 temperature, and diluted with ethyl acetate (10 mL). The organic layer was washed with water, aqueous saturated sodium bicarbonate, and brine. The organic layer was dried with sodium

sulfate, filtered and the filtrate was concentrated under reduced pressure. The mixture was purified by silica gel column chromatography (0-3% ethyl acetate in petroleum ether) to provide the titled compound.

5 **Step 6: Synthesis of methyl 4-bromo-1-formyl-2-naphthoate, compound 7**

To a stirred suspension of methyl 4-bromo-1-(bromomethyl)-2-naphthoate (2.50 g, 6.98 mmol) in acetonitrile (80 mL) was added 4-methylmorpholine 4-oxide (2.62 g, 22.3 mmol) and 4 Å molecular sieves (1.00 g). The mixture was stirred at room temperature for 1 hour, after which dichloromethane and water were added. The mixture was extracted with dichloromethane and
10 the combined organic layers were dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0-3 % ethyl acetate in petroleum ether) to provide the titled compound.

Step 7: Synthesis of (±)-trans-6-bromo-3-(2-hydroxycyclohexyl)benzo[f]phthalazin-4(3H)-one, compound 8

To a solution of methyl 4-bromo-1-formyl-2-naphthoate (1.0 g, 3.4 mmol) in THF (3 mL) at room temperature was added (±)-trans-2-hydrazinylcyclohexanol (0.66 g, 5.1 mmol) and triethylamine (1.4 mL, 10 mmol). The mixture was refluxed for 18 hours, cooled to room temperature, and concentrated in vacuo. The residue was purified by silica gel column
20 chromatography (25-30% ethyl acetate in petroleum ether) to provide the titled compound: mass ion [ES⁺] of 375.0 for [M + H]⁺.

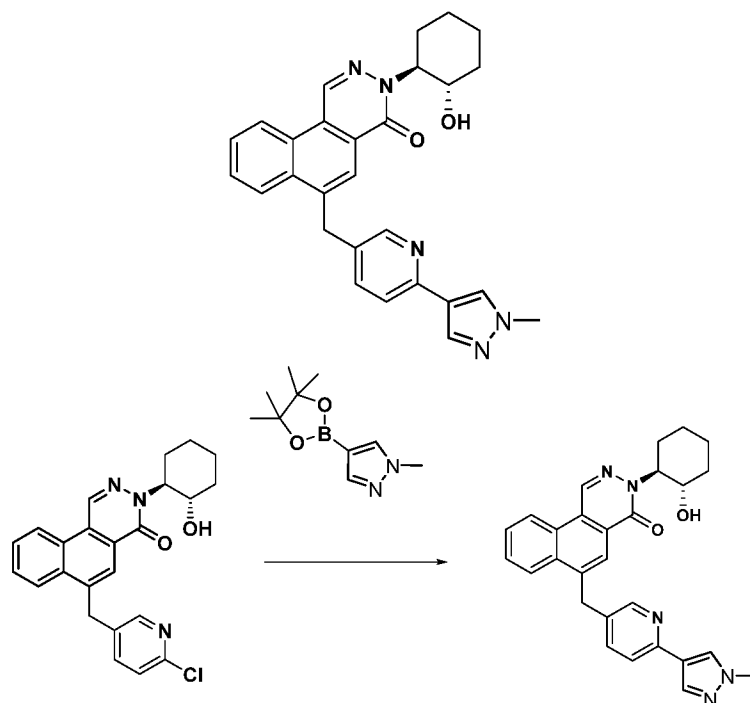
Step 8: Synthesis of (±)-trans-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)benzo [f]phthalazin-4(3H)-one, compound 8

To a solution of (±)-trans-6-bromo-3-(2-hydroxycyclohexyl)benzo[f]phthalazin-4(3H)-one (150 mg, 0.402 mmol) in THF (0.15 mL) at 0°C was added (2-chloro-5-pyridyl)methylzinc chloride (2.01 mL, 0.5M in THF, 1.00 mmol), followed by bis(tri-*tert*-butylphosphine)palladium(0) (6.16 mg, 0.012 mmol). The mixture was warmed to room temperature and stirred for 15 minutes. The mixture was cooled to 0°C, treated with water (10 mL), and then diluted with
30 dichloromethane and water. A solid precipitated, which was filtered through a bed of celite. The filtrate was washed with dichloromethane (2x 20 mL) and the combined organic layers were dried with sodium sulfate and concentrated in vacuo. The residue was purified silica gel column chromatography (80-90% ethyl acetate in petroleum ether) and the appropriate fractions were

further purified by preparative reverse phase HPLC (90:10 to 0:100; water containing 0.1% formic acid : acetonitrile containing 0.1% formic acid) to obtain the titled compound. ^1H NMR (400MHz, DMSO- d_6): δ . 9.34 (s, 1H), 8.94–8.92 (m, 1H), 8.44 (d, $J = 2.3$ Hz, 1H), 8.31–8.28 (m, 1H), 8.12 (s, 1H), 7.85–7.80 (m, 2H), 7.66 (dd, $J = 2.5, 8.2$ Hz, 1H), 7.41 (d, $J = 8.2$ Hz, 1H), 4.85–4.78 (m, 1H), 4.65 (s, 2H), 3.91–3.86 (m, 1H), 2.07–1.98 (m, 1H), 1.76–1.73 (m, 4H), 1.39–1.34 (m, 3H) ppm. LRMS calculated $(\text{M}+\text{H})^+$ $\text{C}_{24}\text{H}_{23}\text{ClN}_3\text{O}_2$ [calc'd 420.1, obs. 420.2].

EXAMPLE 2

($\pm$)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)benzo[*f*] phthalazin-4(3*H*)-one



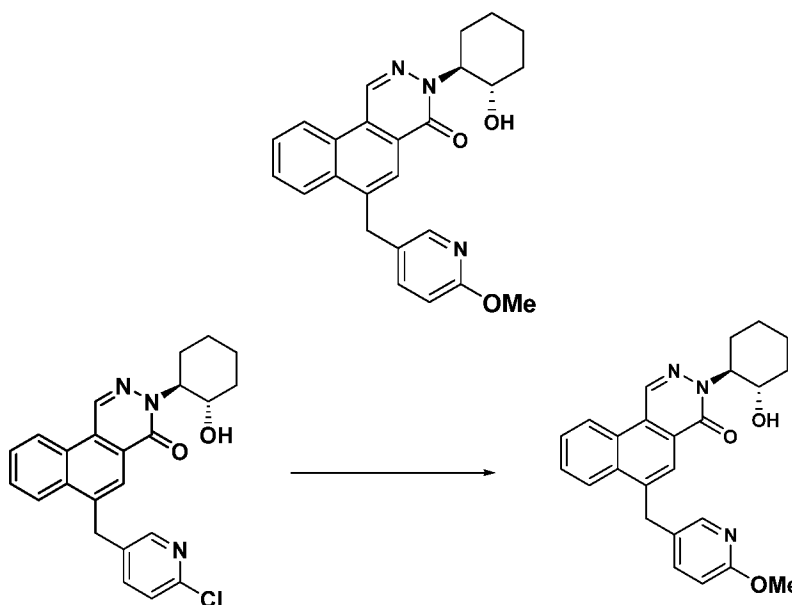
Scheme -2

To a stirred solution of racemic *trans* 6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)benzo[*f*]phthalazin-4(3*H*)-one (Example 1, 50 mg, 0.12 mmol) in 3:1 mixture of 1,4-dioxane (3 mL) : water (1 mL) under nitrogen at room temperature was added sodium carbonate (38 mg, 0.36 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (49 mg, 0.24 mmol). The mixture was sparged under nitrogen for 25 minutes and then treated with tetrakis(triphenylphosphine)palladium(0) (6.9 mg, 5.9 μmol). The mixture was sparged under nitrogen for an additional 5 minutes, the vessel was sealed, and then heated to 100°C for 16 hours. The mixture was cooled to room temperature and diluted with ethyl acetate

and the solution was washed with water and brine and then extracted with ethyl acetate. The combined organic layers were dried with sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (2-3% methanol in dichloromethane) to provide the titled compound. ^1H NMR (400MHz, DMSO-d_6): δ : 9.35 (s, 1H), 8.95–8.93 (m, 1H), 8.52 (s, 1H), 8.37–8.35 (m, 1H), 8.21 (s, 1H), 8.14 (s, 1H), 7.92 (s, 1H), 7.85–7.83 (m, 2H), 7.58–7.52 (m, 2H), 4.86–4.81 (m, 1H), 4.67–4.63 (m, 1H), 4.62 (s, 2H), 3.98–3.91 (m, 1H), 3.86 (s, 3H), 2.05–1.99 (m, 1H), 1.83–1.70 (m, 4H), 1.43–1.30 (m, 3H) ppm. LRMS calculated $(\text{M}+\text{H})^+$ $\text{C}_{28}\text{H}_{28}\text{N}_5\text{O}_2$ [calc'd 466.2, obs. 466.4].

EXAMPLE 3

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-(((6-methoxypyridin-3-yl)methyl)benzo[*f*]phthalazin-4(3*H*)-one



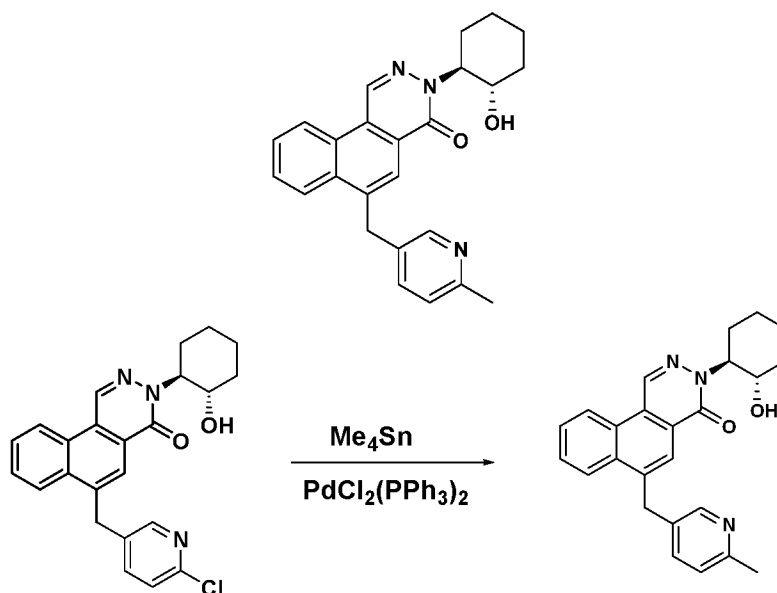
Scheme 3

To a stirred solution of racemic *trans* in (±)-*trans*-6-(((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)benzo[*f*]phthalazin-4(3*H*)-one (Example 1, 70 mg, 0.17 mmol) in MeOH (3 mL) under nitrogen at room temperature was added potassium hydroxide (14 mg, 0.25 mmol) and 5-(di-*tert*-butylphosphino)-1',3',5'-triphenyl-1,4'-bi-1*H*-pyrazole (1.7 mg, 3.33 μmol). The mixture was sparged under nitrogen for 25 minutes and was treated with tris(dibenzylideneacetone)dipalladium(0) (0.76 mg, 0.83 μmol). The mixture was again sparged under nitrogen for 5 minutes, the vessel sealed, and then heated to 80°C for 6 hours. The mixture was cooled to room temperature and diluted dichloromethane. The organic layer was

separated, washed with water and brine, and then dried with sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (2-3% methanol in dichloromethane) to provide the titled compound. ^1H NMR (400MHz, DMSO- d_6): δ . 9.35 (s, 1H), 8.94–8.92 (m, 1H), 8.38–8.35 (m, 1H), 8.19 (s, 1H), 8.08 (s, 1H), 7.86–7.83 (m, 2H), 7.56–7.53 (m, 1H), 6.75–6.73 (m, 1H), 4.87–4.81 (m, 1H), 4.66 (d, J = 4.9 Hz, 1H), 4.56 (s, 2H), 3.91–3.90 (m, 1H), 3.81 (s, 3H), 2.05–1.99 (m, 1H), 1.78–1.74 (m, 4H), 1.36–1.30 (m, 3H) ppm. LRMS calculated $(\text{M}+\text{H})^+$ $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_3$ [calc'd 416.2, obs. 416.4].

EXAMPLE 4

($\pm$)-*trans*-3-(2-hydroxycyclohexyl)-6-(((6-methylpyridin-3-yl)methyl)benzo[*f*]phthalazin-4(3*H*)-one



Scheme 4

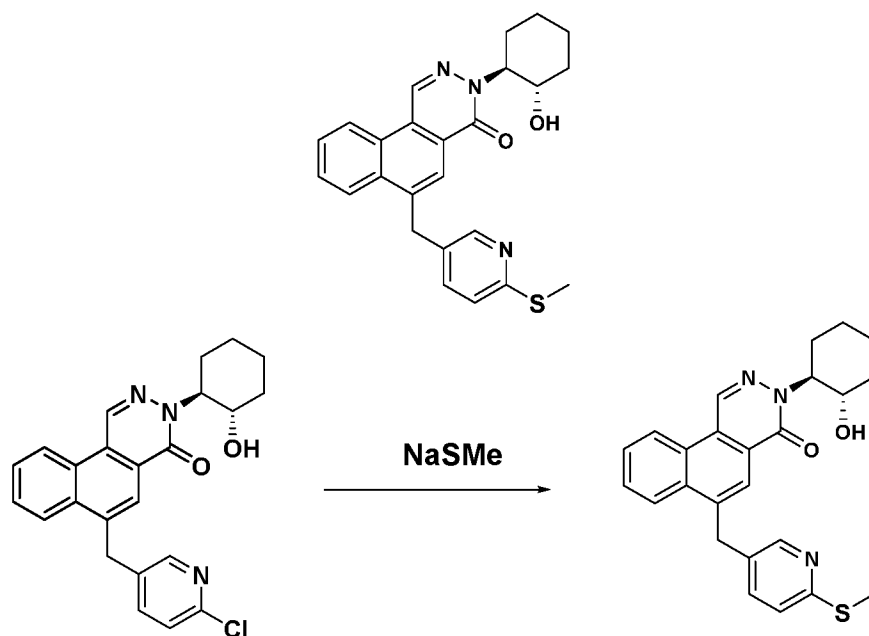
To a stirred solution of racemic *trans* ($\pm$)-*trans*-6-(((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)benzo[*f*]phthalazin-4(3*H*)-one (50 mg, 0.12 mmol) in DMF (2 mL) was added bis(triphenylphosphine)palladium(II) dichloride (84 mg, 0.12 mmol) followed by tetramethyltin (21 mg, 0.12 mmol) at room temperature under nitrogen. The mixture was heated to 110°C for 12 hours, cooled to room temperature, diluted with cold water and extracted with ethyl acetate. The combined organic layers were washed with cold water, dried with sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (0-3 % ethyl acetate in petroleum ether) to provide the titled compound. ^1H NMR (400MHz, DMSO- d_6): δ . 9.33 (s, 1H), 8.93–8.91 (m, 1H), 8.45 (d, J = 2.0 Hz, 1H), 8.32–8.30 (m, 1H), 8.10 (s, 1H), 7.85–7.79 (m, 1H), 7.48–7.45 (m, 1H), 7.14 (d, J = 7.9 Hz, 1H),

4.86–4.78 (m, 1H), 4.66 (d, $J = 5.2$ Hz, 1H), 4.58 (s, 2H), 3.92–3.86 (m, 1H), 2.39 (s, 3H), 2.00–1.98 (m, 1H), 1.76–1.73 (m, 4H), 1.39–1.34 (m, 3H) ppm. LRMS calculated $(M+H)^+$ $C_{25}H_{26}N_3O_2$ [calc'd 400.2, obs. 400.4].

5

EXAMPLE 5

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-(methylthio)pyridin-3-yl)methyl)benzo[*f*]phthalazin-4(3*H*)-one



Scheme 5

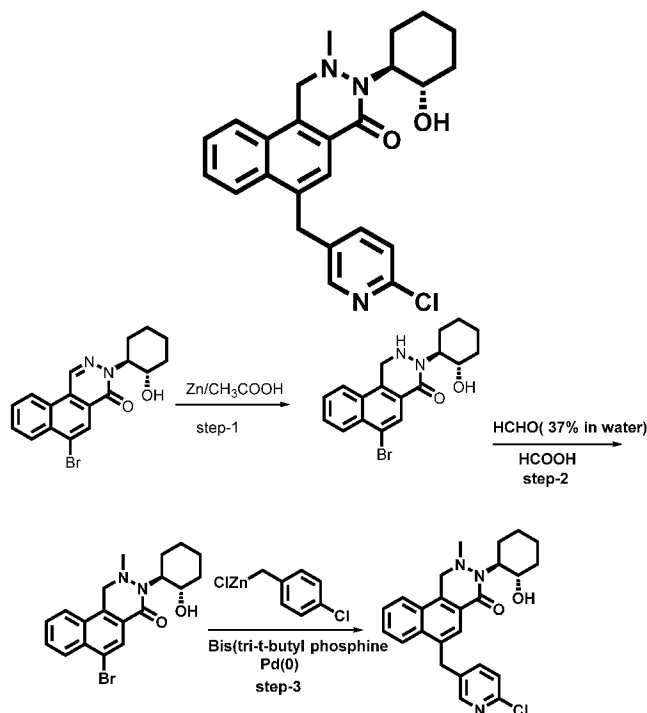
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To a vial containing solution of (±)-*trans*-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)benzo[*f*]phthalazin-4(3*H*)-one (Example 1, 25 mg, 0.060 mmol) in *N*-methyl-2-pyrrolidinone (1.5 mL) was added sodium thiomethoxide (21 mg, 0.30 mmol) at room temperature. The mixture was irradiated at 90°C for 15 minutes in a microwave reactor. The mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine and then dried with sodium sulphate and concentrated in vacuo. The residue was purified by silica gel column chromatography (50% ethyl acetate in petroleum ether) to provide the title compound. 1H NMR (400MHz, DMSO- d_6): δ . 9.35 (s, 1H), 8.95–8.92 (m, 1H), 8.47–8.46 (m, 1H), 8.35–8.32 (m, 1H), 8.11 (s, 1H), 7.86–7.81 (m, 2H), 7.47 (dd, $J = 2.4, 8.2$ Hz, 1H), 7.20 (d, $J = 8.4$ Hz, 1H), 4.85–4.80 (m, 1H), 4.67 (d, $J = 5.2$ Hz, 1H), 4.59 (s, 2H), 3.93–3.88 (m, 1H), 2.45 (s, 3H), 2.02–1.99 (m, 1H), 1.80–1.73 (m, 4H), 1.41–1.30 (m, 3H) ppm. LRMS calculated $(M+H)^+$ $C_{25}H_{26}N_3O_2S$ [calc'd 432.2, obs. 432.2].

20

EXAMPLE 6

(±)-*trans*-6-(((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[*f*]phthalazin-4(1*H*)-one



Scheme 6

Step 1: Preparation of 6-bromo-3-(2-hydroxycyclohexyl)-2,3-dihydrobenzo[*f*]phthalazin-4(1*H*)-one

- 10 To a stirred solution of 6-bromo-3-(2-hydroxycyclohexyl)benzo[*f*]phthalazin-4(3*H*)-one (Compound 8, scheme 1; 400 mg, 1.07 mmol) in acetic acid (12 mL) and water (1.5 mL) at room temperature, was added zinc (1.20 g, 18.3 mmol). The mixture was heated at 120°C for 1 hour, cooled to room temperature, and concentrated in vacuo. The residue was partitioned between aqueous saturated sodium bicarbonate and ethyl acetate. The organic extract was washed with
- 15 water and brine, dried with sodium sulfate, and concentrated in vacuo to provide the titled compound.

Step 2: Preparation of 6-bromo-3-(2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[*f*]phthalazin-4(1*H*)-one

- 20 Formaldehyde (37% in water, 4.50 mL, 0.266 mmol) and formic acid (8.00 mL, 209 mmol) were added to a flask containing 6-bromo-3-(2-hydroxycyclohexyl)-2,3-dihydrobenzo[*f*]phthalazin-

4(1*H*)-one (100 mg, 0.266 mmol). The mixture was heated at 100°C for 16 hours, cooled to room temperature, and treated with aqueous saturated sodium bicarbonate and then extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried with sodium sulfate, and concentrated in vacuo to provide the titled compound.

5

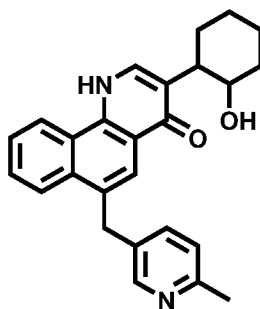
Step 3: Preparation of (±)-*trans*-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[*f*]phthalazin-4(1*H*)-one

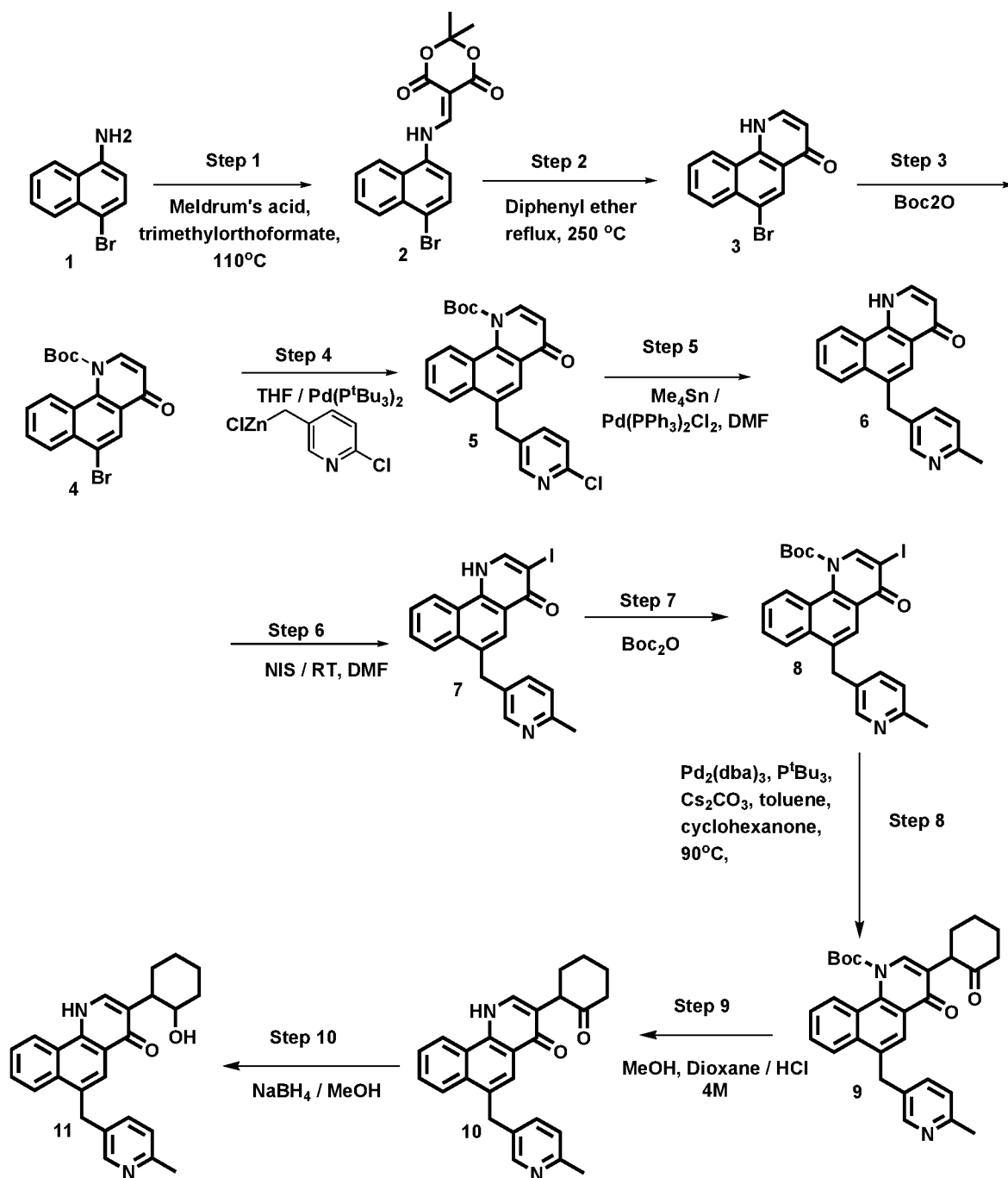
To a stirred solution of (±)-*trans*-6-bromo-3-(2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[*f*]phthalazin-4(1*H*)-one (70 mg, 0.18 mmol) in THF (5 mL) at 0°C was added (2-chloro-5-pyridyl)methylzinc chloride solution (0.90 mL, 0.45 mmol, 0.5M in THF), followed by bis(tri-*tert*-butylphosphine)palladium(0) (2.8 mg, 0.0054 mmol). The mixture was stirred at 0°C for 1 hour and then treated with ice water. The mixture was extracted with ethyl acetate and the combined organic extracts were washed with water and brine, dried with sodium sulfate and concentrated in vacuo. The residue was purified by preparative reverse phase HPLC (90:10 to 15 0:100; water containing 0.1% formic acid : acetonitrile containing 0.1% formic acid) to provide the titled compound. ¹H NMR (400MHz, CD₃OD): δ. 8.31 (d, *J* = 2.0 Hz, 1H), 8.13–8.09 (m, 2H), 7.89 (s, 1H), 7.66–7.61 (m, 3H), 7.37–7.33 (m, 1H), 4.88–4.80 (m, 1H), 4.67–4.60 (m, 1H), 4.56–4.55 (m, 2H), 4.30–4.24 (m, 1H), 3.92–3.87 (m, 1H), 2.65–2.63 (m, 3H), 2.13–2.10 (m, 1H), 1.89–1.80 (m, 4H), 1.44–1.39 (m, 3H) ppm. LRMS calculated (M+H)⁺ C₂₅H₂₇ClN₃O₂ [calc'd 436.2, obs. 436.4].

20

EXAMPLE 7

3-(2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinolin-4(1*H*)-one





Scheme 7

Step 1: Preparation of 5-(((4-bromonaphthalen-1-yl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione

- 5 A stirred mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (1.43 g, 9.91 mmol) and trimethyl orthoformate (4.48 ml, 40.5 mmol) was refluxed for 30 minutes. 4-bromonaphthalen-1-amine (2.00 g, 9.01 mmol) was added portionwise to the mixture at the same temperature and the

solution was stirred for 40 minutes. The mixture was cooled to room temperature and the resulting precipitate was filtered, washed with n-hexane, and dried in vacuo to provide the titled compound: mass ion [ES⁺] of 376.0 for [M + H]⁺.

5 **Step 2: Preparation of 6-bromobenzo[*h*]quinolin-4(1*H*)-one**

Diphenyl ether (30 mL) was heated to 250°C and stirred vigorously under nitrogen. 5-(((4-bromonaphthalen-1-yl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (3.00 g, 7.97 mmol) was added portionwise to the mixture was stirred for 30 minutes. The mixture was cooled to 70°C and diluted with n-hexane (20 mL). The precipitate was filtered, washed with n-
10 hexane, and dried in vacuo to provide the titled compound: mass ion of [ES⁺] 274.2 for [M]⁺.

Step 3: Preparation of *tert*-butyl 6-bromo-4-oxobenzo[*h*]quinoline-1(4*H*)-carboxylate

To a stirred solution of 6-bromobenzo[*h*]quinolin-4(1*H*)-one (2.00 g, 7.30 mmol) in dichloromethane (30 mL) was added DMAP (0.891 g, 7.30 mmol) at room temperature. The
15 mixture was stirred for 5 minutes and was then treated with di-*tert*-butyl dicarboate (3.39 mL, 14.6 mmol). The mixture was stirred at room temperature for 16 hours, concentrated in vacuo, and the residue was purified by silica gel column chromatography (0–5% ethyl acetate in petroleum ether) to provide the titled compound: mass ion of [ES⁺] 276.4 for [M - Boc]⁺.

20 **Step 4: Preparation of *tert*-butyl 6-((6-chloropyridin-3-yl)methyl)-4-oxobenzo[*h*]quinoline-1(4*H*)-carboxylate**

To a solution of the *tert*-butyl 6-bromo-4-oxobenzo[*h*]quinoline-1(4*H*)-carboxylate (1.00 g, 2.67 mmol) in THF (5 mL) at 0°C was added (2-chloro-5-pyridyl)methylzinc chloride solution (13.4 mL, 6.68 mmol, 0.5 M in THF), followed by bis(tri-*tert*-butylphosphine)palladium(0) (0.068 g,
25 0.134 mmol). The mixture was warmed to room temperature and stirred 2 hours. The mixture was cooled to 0°C, treated with water (10 mL), and then diluted with dichloromethane and water. A tan solid precipitated, which was filtered through a bed of celite. The filtrate was extracted with dichloromethane and the combined organic extracts were dried with sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column
30 chromatography (10–70% ethyl acetate in petroleum ether) to provide the titled compound: mass ion of [ES⁺] 421.2 (⁸¹Br) for [M + H]⁺.

Step 5: Preparation of 6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinolin-4(1*H*)-one

To a stirred solution of *tert*-butyl 6-((6-chloropyridin-3-yl)methyl)-4-oxobenzo[*h*]quinoline-1(4*H*)-carboxylate (0.700 g, 1.66 mmol) in DMF (5 mL) under nitrogen were added Tetramethyltin (2.97 g, 16.6 mmol) and Bis(triphenylphosphine)palladium(II) dichloride (0.058 g, 0.083 mmol) at room temperature. The resultant solution was heated to 100°C for 4 hours, cooled to room temperature, diluted with cold water and extracted with ethyl acetate. The combined organic extracts were washed with cold water, dried with sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (20-50% ethyl acetate in petroleum ether) to provide the titled compound: mass ion of [ES⁺] 301.4 for [M + H]⁺.

Step 6: Preparation of 3-iodo-6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinolin-4(1*H*)-one

To a stirred solution of 6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinolin-4(1*H*)-one (250 mg, 0.832 mmol) in DMF (5 mL) at room temperature, *N*-iodosuccinimide (225 mg, 0.999 mmol) was added portionwise. The mixture was stirred for 3 hours at ambient temperature and then concentrated in vacuo. The residue was boiled in water (25 mL), the precipitate was filtered off and then washed with water, which was dried in vacuo provide the titled compound: mass ion of [ES⁺] 427.2 for [M + H]⁺.

Step 7: Preparation of *tert*-butyl 3-iodo-6-((6-methylpyridin-3-yl)methyl)-4-

oxobenzo[*h*]quinoline-1(4*H*)-carboxylate

To a stirred solution of 3-iodo-6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinolin-4(1*H*)-one (100 mg, 0.235 mmol) in dichloromethane (5 mL) at room temperature was added triethylamine (0.163 mL, 1.173 mmol) and DMAP (5.7 mg, 0.047 mmol). The mixture was stirred for 5 minutes and then treated with di-*tert*-butyl dicarbonate (0.163 mL, 0.704 mmol). The mixture was further stirred for 4 hours at ambient temperature and then concentrated in vacuo. The residue was purified by silica gel column chromatography (0-50% ethyl acetate in petroleum ether) to provide the titled compound: mass ion of [ES⁺] 527.0 for [M + H]⁺.

Step 8: Preparation of *tert*-butyl 6-((6-methylpyridin-3-yl)methyl)-4-oxo-3-(2-

oxocyclohexyl)benzo[*h*]quinoline-1(4*H*)-carboxylate:

Cesium carbonate (0.371 g, 1.14 mmol) was added to a flask charged with tris(dibenzylideneacetone)dipalladium(0) (0.070 g, 0.076 mmol) and tri-*tert*-butylphosphine (0.038 g, 0.190 mmol) under nitrogen in anhydrous toluene (10 mL). To the suspension was

added *tert*-butyl 3-iodo-6-((6-methylpyridin-3-yl)methyl)-4-oxobenzo[*h*]quinoline-1(4*H*)-carboxylate (0.200 g, 0.380 mmol) and cyclohexanone (0.112 g, 1.14 mmol) under nitrogen. The mixture was heated to 80°C for 16 hours, cooled to room temperature, and diluted with ethylacetate. The mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25–100% ethyl acetate in petroleum ether) to provide the titled compound: mass ion of [ES⁺] 497.6 for [M + H]⁺.

Step 9: Preparation of 6-((6-methylpyridin-3-yl)methyl)-3-(2-oxocyclohexyl)benzo[*h*]quinolin-4(1*H*)-one:

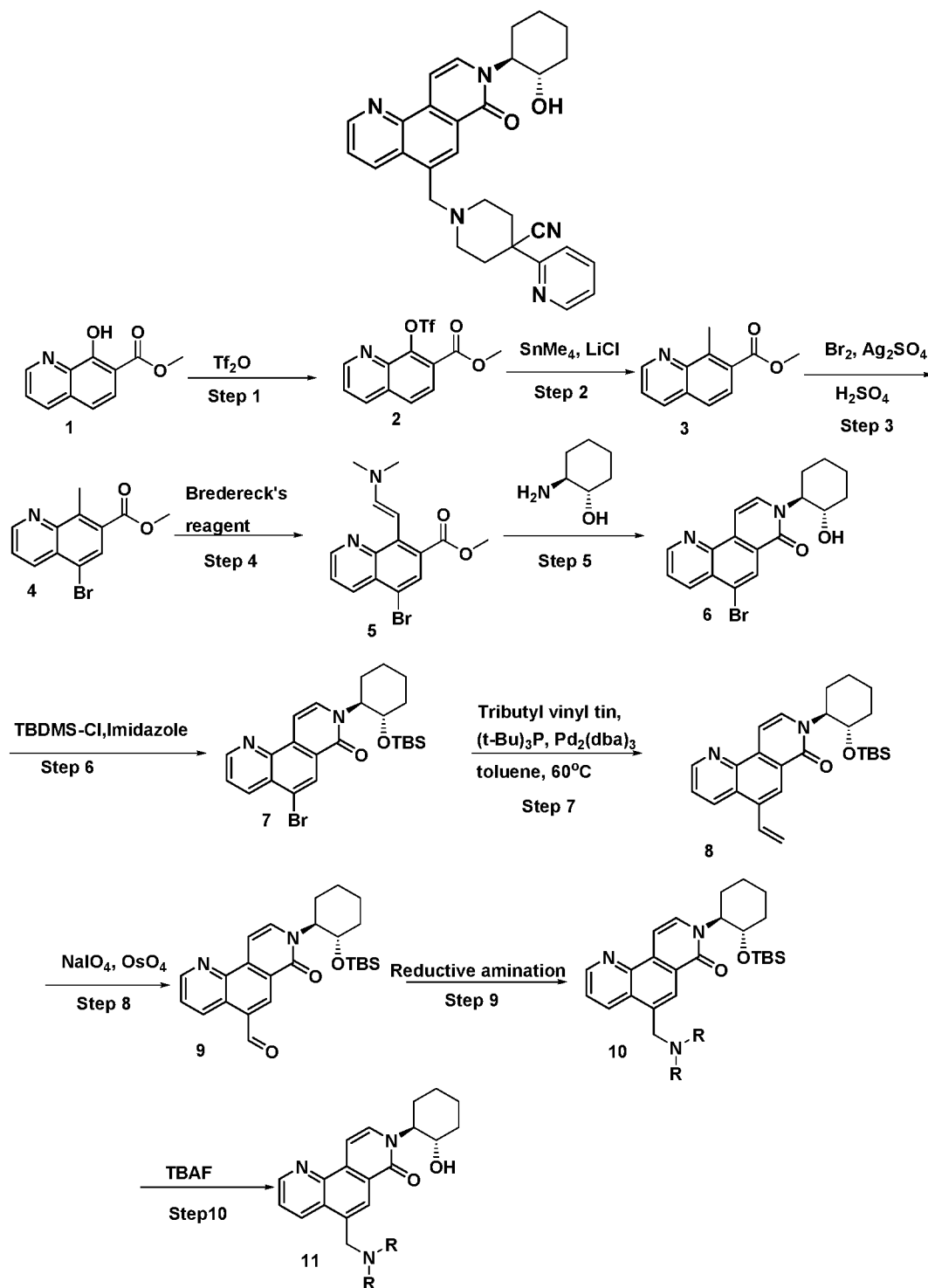
To a stirred solution of *tert*-butyl 6-((6-methylpyridin-3-yl)methyl)-4-oxo-3-(2-oxocyclohexyl)benzo[*h*]quinoline-1(4*H*)-carboxylate (0.080 g, 0.16 mmol) in MeOH (5 mL) at 0°C under nitrogen was added hydrochloric acid in dioxane (5.00 ml, 20.0 mmol). The mixture was warmed to room temperature and stirred for 2 hours, after which the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (0-15% methanol in dichloromethane) to provide the titled compound: mass ion of [ES⁺] 397.2 for [M + H]⁺.

Step 10: Preparation of 3-(2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinolin-4(1*H*)-one:

To a stirred solution of 6-((6-methylpyridin-3-yl)methyl)-3-(2-oxocyclohexyl)benzo[*h*]quinolin-4(1*H*)-one (60 mg, 0.15 mmol) in methanol (5 mL) at 0°C under nitrogen was added sodium borohydride (5.7 mg, 0.15 mmol). The mixture was warmed to room temperature and stirred for 2 hours. The mixture was then cooled to 0°C, treated with cold water and then volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography (0-15% methanol in dichloromethane). Further purification by preparative reverse phase HPLC (90:10 to 0:100; water containing 0.1% formic acid : acetonitrile containing 0.1% formic acid) provided the titled compound. ¹H NMR (400MHz, DMSO-*d*₆): δ. 12.01 (br s, 1H), 8.73–8.71 (m, 1H), 8.42–8.39 (m, 1H), 8.16–8.13 (m, 1H), 7.97 (s, 1H), 7.79–7.70 (m, 3H), 7.45 (dd, *J* = 2.2, 7.9 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 4.40 (s, 2H), 3.80–3.70 (m, 1H), 2.75–2.65 (m, 1H), 2.41 (s, 3H), 2.09–1.98 (m, 1H), 1.82–1.61 (m, 3H), 1.55–1.25 (m, 4H) ppm. LRMS calculated (M+H)⁺ C₂₆H₂₇N₂O₂ [calc'd 399.2, obs. 399.4].

EXAMPLE 8

1-(((8-(((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)-4-(pyridin-2-yl)piperidine-4-carbonitrile



Scheme 10

Step-1: Preparation of 8-(((trifluoromethyl) sulfonyl)oxy)quinoline-7-carboxylate

To a stirred solution of methyl 8-hydroxyquinoline-7-carboxylate (10.0 g, 49.2 mmol) in pyridine (60 mL) cooled to 0°C was added trifluoromethanesulfonic anhydride (41.7 g, 148 mmol). The mixture was warmed to room temperature and stirred for 1 hour at room temperature. The mixture diluted with ice-cold water (125 mL). After stirring for 30 minutes, a solid was collected via filtration, washed with water, and dried in vacuo to provide the titled compound: mass ion (ES+) of 336.2 [M+H].

Step-2: Preparation of methyl 8-methylquinoline-7-carboxylate

To a stirred solution of methyl 8-(((trifluoromethyl)sulfonyl)oxy)quinoline-7-carboxylate (12.0 g, 35.8 mmol) in DMF (120 mL) was added lithium chloride (7.59 g, 179 mmol), tetramethylstannane (14.1 g, 79.0 mmol) followed by bis(triphenylphosphine)palladium (II) chloride (1.25 g, 1.79 mmol) at room temperature. The mixture was then heated at 110 °C for 3 hours, cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium bicarbonate, water and brine. The organic extract was dried with Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (8-10% ethyl acetate in petroleum ether) to provide the titled compound: mass ion (ES+) of 202.2 [M+H].

Step-3: Preparation of 5-bromo-8-methylquinoline-7-carboxylate

To a solution of methyl 8-methylquinoline-7-carboxylate (5.00 g, 24.8 mmol) and silver (I) sulfate (3.87 g, 12.4 mmol) in sulfuric Acid (10 mL) was added bromine (2.55 mL, 49.7 mmol). After stirring for 15 hours, the mixture was poured into 500 mL of ice water and neutralized with 5.0 N aqueous sodium hydroxide to pH>9. After 5 minutes, a light brown solid was collected via filtration, which was washed with water and then dried in vacuo. The residue was purified by silica gel column chromatography (2-5 % ethyl acetate in petroleum ether) to provide the titled compound: mass ion (ES+) of 280.0 [M+H].

Step-4: Preparation of (E)-methyl 5-bromo-8-(2-(dimethylamino)vinyl)quinoline-7-carboxylate

A solution of methyl 5-bromo-8-methylquinoline-7-carboxylate (4.00 g, 14.2 mmol) and 1-*tert*-butoxy-N,N,N',N'-tetramethylmethanediamine (19.91 g, 114 mmol) in DMF (20 mL) was irradiated in microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and concentrated in vacuo to provide the titled compound.

Step-5: Preparation of 5-bromo-8-((1*S*,2*S*)-2-hydroxycyclohexyl)-1,8-phenanthroline-7(8*H*)-one

(*E*)-Methyl 5-bromo-8-(2-(dimethylamino)vinyl)quinoline-7-carboxylate (4.00 g, 11.9 mmol) and (1*S*,2*S*)-2-aminocyclohexanol (2.75 g, 23.8 mmol) were combined in DMF (40 mL) and heated at 110°C for 16 hours. The mixture was cooled to room temperature and then concentrated in vacuo. The residue was purified by silica gel column chromatography (45-50% ethyl acetate in petroleum ether) to provide the titled compound: mass ion (ES⁺) of 372.8 [M+H].

Step-6: Preparation of 5-bromo-8-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1,8-phenanthroline-7(8*H*)-one

To a stirred solution of 5-bromo-8-((1*S*,2*S*)-2-hydroxycyclohexyl)-1,8-phenanthroline-7(8*H*)-one (100 mg, 0.268 mmol) in dichloromethane (5 mL), was added triethylamine (0.112 mL, 0.804 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulphonate (106 mg, 0.402 mmol) at 0°C. The mixture was warmed to ambient temperature and stirred for 1 hour. The mixture was cooled to 0°C, diluted with ice-cold water (20 mL) and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (2-5% ethyl acetate in petroleum ether) to provide the titled compound: mass ion (ES⁺) of 489.0 [M+H].

Step-7: Preparation of 8-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-5-vinyl-1,8-phenanthroline-7(8*H*)-one

To a stirred solution of 5-bromo-8-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1,8-phenanthroline-7(8*H*)-one (90 mg, 0.18 mmol) in toluene (2 mL), tris(dibenzylideneacetone)dipalladium(0) (0.84 mg, 0.92 μmol), tri-*tert*-butylphosphine (0.10 mL, 0.020 mmol) and tributyl(vinyl)tin (61 mg, 0.19 mmol). The vessel was sealed and the mixture was heated to 60°C for 3 hours. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (2-5 % ethyl acetate in hexane) to provide the titled compound: mass ion (ES⁺) of 435.4 [M+H].

Step-8: Praration of 8-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthroline-5-carbaldehyde

To a solution of 8-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-5-vinyl-1,8-phenanthrolin-7(8*H*)-one (50 mg, 0.11 mmol) in dichloromethane (1 mL), methanol (0.5 mL), and water (0.2 mL) was added osmium tetroxide (0.035 mL, 3.4 μ mol, 2.5% in tertiary butanol) and sodium periodate (74 mg, 0.34 mmol). The mixture was stirred for 3 hours at room temperature, diluted with water, and extracted with dichloromethane. The combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2-5 % ethyl acetate in hexanes) to provide the titled compound: mass ion (ES⁺) of 438.0 [M+H].

Step-9: Preparation of 1-((8-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)-4-(pyridin-2-yl)piperidine-4-carbonitrile

8-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthroline-5-carbaldehyde (70 mg, 0.16 mmol) was dissolved in 1,2-dichloroethane (4 mL) under a nitrogen atmosphere, cooled to 0°C and treated with 4-(pyridin-2-yl)piperidine-4-carbonitrile (33 mg, 0.17 mmol). After stirring for 4 hours, sodium triacetoxymethylborohydride (68 mg, 0.32 mmol) was added and the mixture was stirred for another 16 hours at room temperature. The mixture was poured into water and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (40-45% ethyl acetate in hexanes) to provide the titled compound: mass ion (ES⁺) of 608.4 [M+H].

Step-10: Preparation of 1-((8-((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)-4-(pyridin-2-yl)piperidine-4-carbonitrile:

To a stirred solution of 1-((8-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)-4-(pyridin-2-yl)piperidine-4-carbonitrile (35 mg, 0.058 mmol) in tetrahydrofuran (5 mL) at 0°C was added tetrabutylammonium fluoride (0.14 mL, 0.14 mmol, 1M in THF). The mixture was stirred at room temperature for 5 hours and then poured into water and extracted with ethyl acetate. The combined organic extracts were dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified via preparative reverse phase HPLC (90:10 to 0:100; water containing 0.1% formic acid : acetonitrile containing

0.1% formic acid) to provide the titled compound. ^1H NMR (400MHz, CD_3OD): δ . 9.15 (s, 1H), 8.87 (d, $J = 8.8$ Hz, 1H), 8.69 (s, 1H), 8.61 (s, 1H), 8.05 (d, $J = 7.6$ Hz, 1H), 7.94–7.89 (m, 3H), 7.73 (d, $J = 7.6$ Hz, 1H), 5.10 (s, 2H), 4.03 (s, 1H), 3.84–3.81 (m, 1H), 3.68–3.62 (m, 2H), 2.63–2.48 (m, 3H), 2.20 (s, 1H), 1.96–1.83 (m, 3H), 1.55–1.51 (m, 3H), 1.30–1.26 (m, 2H) ppm.

5 LRMS calculated $(\text{M}+\text{H})^+$ $\text{C}_{30}\text{H}_{32}\text{N}_5\text{O}_2$ [calc'd 494.2, obs. 494.4].

The compounds in **Table 1** were prepared utilizing the procedures described in Example 8, substituting the appropriate amine for 4-(pyridin-2-yl)piperidine-4-carbonitrile (Step 9). Any additional reagents used in the syntheses are either commercially available or may be made from commercially available reagents using conventional reactions well known in the art.

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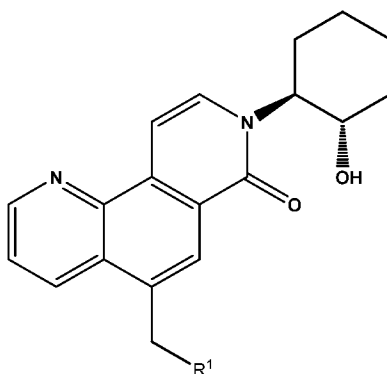


TABLE 1

Chemical Name	Ex.#	R^1	^1H -NMR (400MHz, CD_3OD)	MS (ES+), $[\text{M}+\text{H}]^+$
6-(4-((8-((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthroline-5-yl)methyl)piperazin-1-yl)nicotinonitrile	9		9.15 (s, 1H), 8.84 (d, $J = 8.80$ Hz, 1H), 8.66 (s, 1H), 8.05 (d, $J = 7.60$ Hz, 1H), 7.93 (d, $J = 7.20$ Hz, 1H), 7.90-7.86 (m, 1H), 7.61 (d, $J = 8.80$ Hz, 2H), 7.10 (d, $J = 9.20$ Hz, 2H), 4.96 (s, 2H), 4.04 (s, 1H), 3.55 (s, 4H), 3.32-3.26 (m, 2H), 2.29-2.20 (m, 1H), 2.20-1.99 (m, 1H), 1.89 (s, 2H), 1.69-1.63 (m, 2H), 1.60-1.55 (m, 3H), 1.47-1.42 (m, 2H) ppm	$\text{C}_{30}\text{H}_{32}\text{N}_5\text{O}_2$ [M+H] calc 494.2 obs. 494.4
1-((8-((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthroline-5-yl)methyl)-4-	10		9.13 (s, 1H), 8.88 (d, $J = 8.32$ Hz, 1H), 8.66 (s, 1H), 8.04 (d, $J = 7.56$ Hz, 1H), 7.94-7.87 (m, 2H), 7.55 (d, $J = 7.64$ Hz, 2H), 7.49-7.46 (m, 2H), 7.42 (d, $J = 7.16$	$\text{C}_{31}\text{H}_{32}\text{N}_4\text{O}_2$ [M+H] calc 493.2 obs. 493.2

phenylpiperidine-4-carbonitrile			Hz, 1H), 5.00 (s, 2H), 4.06 (s, 1H), 3.75 (s, 2H), 3.56-3.53 (m, 2H), 2.50-2.46 (m, 2H), 2.46-2.37 (m, 2H), 2.22 (d, J = 8.04 Hz, 1H), 1.97-1.90 (m, 3H), 1.75-1.68 (m, 2H), 1.55-1.48 (m, 3H) ppm	
5-((4-fluoropiperidin-1-yl)methyl)-8-((1S,2S)-2-hydroxycyclohexyl)-1,8-phenanthroline-7(8H)-one	11		9.04 (s, 1H), 8.90 (dd, J = 8.40, 1.60 Hz, 1H), 8.33 (s, 1H), 7.99 (d, J = 7.60 Hz, 1H), 7.81 (d, J = 7.60 Hz, 1H), 7.76-7.73 (m, 1H), 4.73 (t, J = 7.20 Hz, 1H), 4.62 (s, 2H), 4.02 (s, 3H), 2.80-2.72 (m, 2H), 2.52-2.49 (m, 2H), 2.23-2.20 (m, 1H), 2.00-1.90 (m, 2H), 1.87-1.81 (m, 4H), 1.80-1.77 (m, 2H), 1.57-1.53 (m, 3H) ppm	$C_{24}H_{39}FN_3O_2$ [M+H] calc 410.2 obs. 410.4
4-fluoro-1-((8-((1S,2S)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthroline-5-yl)methyl)piperidine-4-carbonitrile	12		9.04-9.02 (m, 1H), 8.88 (d, J = 8.40 Hz, 1H), 8.34 (s, 1H), 7.99 (d, J = 7.60 Hz, 1H), 7.82 (d, J = 7.20 Hz, 1H), 7.75 (dd, J = 8.40, 4.20 Hz, 1H), 4.08 (s, 3H), 2.86-2.76 (m, 4H), 2.71-2.66 (m, 2H), 2.22-2.18 (m, 3H), 2.17-2.14 (m, 3H), 2.03-1.97 (m, 1H), 1.97-1.89 (m, 2H), 1.59-1.51 (m, 2H) ppm	$C_{25}H_{28}FN_4O_2$ [M+H] calc 435.2 obs. 435.2
5-((4,4-difluoropiperidin-1-yl)methyl)-8-((1S,2S)-2-hydroxycyclohexyl)-1,8-phenanthroline-7(8H)-one	13		9.04-9.03 (m, 1H), 8.90 (dd, J = 8.40, 1.80 Hz, 1H), 8.33 (s, 1H), 7.99 (d, J = 7.60 Hz, 1H), 7.81 (d, J = 7.60 Hz, 1H), 7.82-7.73 (m, 1H), 4.14 (s, 3H), 2.68 (s, 4H), 2.26-2.20 (m, 1H), 2.02-1.97 (m, 4H), 1.96-1.88 (m, 3H), 1.54-1.47 (m, 4H), 1.33-1.31 (m, 1H) ppm	$C_{24}H_{28}F_2N_3O$ 2 [M+H] calc 428.2 obs. 428.2

EXAMPLE 14

M1 Receptor Positive Allosteric Modulator Activity

The utility of the compounds as M1 receptor positive allosteric modulators may be demonstrated by methodology known in the art, including by the assay described below. The assay is designed to select compounds that possess modulator activity at the acetylcholine muscarinic M1 receptor or other muscarinic receptors expressed in CHOnfat cells by measuring the intracellular calcium with a FLIPR³⁸⁴ Fluorometric Imaging Plate Reader System. The assay studies the effect of one or several concentrations of test compounds on basal or acetylcholine-stimulated Ca^{2+} levels using FLIPR.

Compounds are prepared and subjected to a preincubation period of 4 min. Thereafter, a single EC_{20} concentration of acetylcholine is added to each well (3nM final). The intracellular Ca^{2+} level of each sample is measured and compared to an acetylcholine control to determine any modulatory activity.

Cells: CHOnfat/hM1, hM2, hM3 or hM4 cells are plated 24 hr before the assay at a density of 18,000 cells/well (100 μL) in a 384 well plate. CHOnfat/hM1 and CHOnfat/hM3 Growth Medium: 90% DMEM (Hi Glucose); 10% HI FBS; 2 mM L-glutamine; 0.1 mM NEAA; Pen-Strep; and 1mg/ml Geneticin, are added. For M2Gqi5CHOnfat and M4Gqi5CHOnfat cells, an additional 600 ug/ml hygromycin is added.

Equipment: 384 well plate, 120 μL addition plate; 96-well Whatman 2 ml Uniplate Incubator, 37°C, 5% CO_2 ; Skatron EMBLA-384 Plate Washer; Multimek Pipetting System; Genesis Freedom 200 System; Mosquito System; Temo Nanolitre Pipetting System; and FLIPR³⁸⁴ Fluorometric Imaging Plate Reader System are used.

Buffers. Assay Buffer: Hanks Balanced Salt Solution, with 20 mM Hepes, 2.5 mM Probenecid (Sigma P-8761) first dissolved in 1 N NaOH, 1% Bovine Serum Albumin (Sigma A-9647). Dye Loading Buffer: Assay Buffer plus 1% Fetal Bovine Serum and Fluo-4AM/Pluronic Acid Mixture. 2 mM Fluo-4AM ester stock in DMSO (Molecular Probes F-14202) Concentration of 2 μM in buffer for a final concentration of 1 μM in Assay. 20% Pluronic Acid Solution stock, with concentration of 0.04% in Buffer, 0.02% in Assay.

65 μL of 2 mM Fluo-4AM are mixed with 130 μL of 20% Pluronic Acid. The resulting solution and 650 μL FBS is added to the assay buffer for a total volume of 65 mL. Positive Controls: 4-Br-A23187: 10 mM in DMSO; final concentration 10 μM . Acetylcholine: 10 mM in water, working stock at both 20 μM and 30 μM in assay buffer, final concentration of 10 μM . This is used to check the maximum stimulation of the CHOK1/hM1 cells. 20 μM (2x) acetylcholine is added in the preincubation part of the assay, and the 30 μM (3x) stock is added in the second part. (EC_{20})Acetylcholine: 10 mM in water, working stock of 9 nM (3x), and final

concentration in assay is 3 nM. This is used after the preincubation with test compounds. Addition of the EC₂₀ Acetylcholine to each well with a test compound will ascertain any modulator activity. 24 wells contain 3nM Acetylcholine alone as a control.

Determining Activity of Putative Compounds:

- 5 Screening Plate: Compounds are titrated in 96-well plates (columns 2-11), 100% DMSO, started at a concentration of 15 mM (150x stock concentration), and 3-fold serial dilutions using Genesis Freedom200 System. Four 96-well plates are combined into a 384-well plate using Mosquito Nanolitre Pipetting System by transferring 1µl of serial diluted compounds to each well, and 1 mM acetylcholine (100x stock concentration) were added as a control. Using Temo,
10 49 µl assay buffer is added to each well of the 384-well plate right before assay.

In a 96-well Whatman 2ml Uniplate, 9 nM Acetylcholine (3x) is pipetted into wells corresponding to the screening compounds, and into control wells. The 30 µM acetylcholine control (3x) is added into control wells, and the 3x agonist plate is transferred into a 384 well plate.

- 15 Cells are washed three times with 100 µL of buffer, leaving 30µL of buffer in each well. Using Multimek, 30 µL of Dye Loading Buffer is added into each well and incubated at 37°C, 5% CO₂ for up to one hr.

- 20 After 60 min, the cells are washed three times with 100 µL of buffer, leaving 30 µL of buffer in each well. The cell plate, screening plate, and agonist addition plates are placed on the platform in the FLIPR and the door closed. A signal test to check background fluorescence and basal fluorescence signal is performed. Laser intensity is adjusted if necessary.

- 25 4 min of preincubation with the test compounds is provided to determine any agonist activity on the M1 receptor by comparison to the 1 mM acetylcholine control. After preincubation, the EC₂₀ value of acetylcholine (3 nM final) is added to determine any modulator activity.

A further description of the muscarinic FLIPR assay can be found in International patent application WO2004/073639.

- 30 In particular, the compounds of the following examples had activity in the aforementioned assay, generally with an IP (inflection point) of 10 µM (10,000 nM) or less. The inflection point is calculated from the FLIPR values, and is a measure of activity. Such a result is indicative of the intrinsic activity of the compounds in use as M1 allosteric modulators.

IP values from the aforementioned assay for representative exemplary compounds of the invention (as described herein) are provided below in Table 2 below.

Table 2: FLIPR Assay Data (different laboratory values are noted where present)

Example	IP (nM)	
	Lab 1	Lab 2
1	207	
2	71	342
3	396	923
4	287	
5	334	
6		202
7		741
8	132	1174
9	480	619
10	203	356
11	1332	
12	224	
13	218	

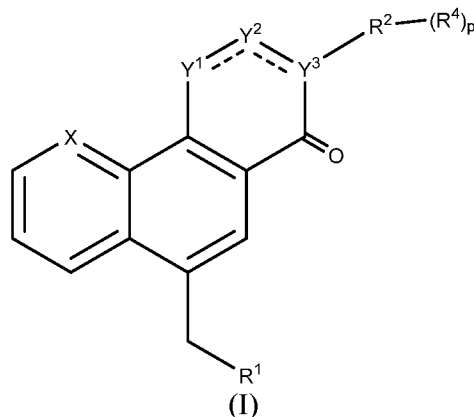
5

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

10

What is claimed is:

1. A compound of formula (I):



or pharmaceutically acceptable salts thereof, wherein

— represents an optional double bond, provided that there is only one double bond in the ring;

X is selected from the group consisting of CR^a and N;

Y¹ and Y² are independently selected from the group consisting of C(R^b)_n and N(R^b)_m;

Y³ is selected from the group consisting of C(R^a)_q and N;

Provided at least one of Y¹ and Y³ is a nitrogen substitution;

R, R^a and R^b are independently selected from the group consisting of H and C¹⁻⁶ alkyl;

R¹ is selected from the group consisting of aryl, heteroaryl and heterocyclyl, wherein the aryl, heteroaryl and heterocyclyl are optionally substituted with one to three substituents selected from R⁵;

R² is heterocyclyl or C₃₋₈ cycloalkyl;

R^4 is independently selected from the group consisting of OR, halo, C_{1-6} alkyl, heteroaryl and heterocyclyl, wherein the alkyl, heteroaryl and heterocyclyl group is optionally substituted with one to three substituents selected from OR, halo, C_{1-6} alkyl, heteroaryl or heterocyclyl;

- 5 R^5 is independently selected from the group consisting of CN, halo, C_{1-6} alkyl, OR, SR, NR^2 , aryl, heteroaryl, and heterocyclyl, wherein the alkyl, aryl, heteroaryl or heterocyclyl groups are optionally substituted with one to three substituents selected from R^6 ;

- R^6 is independently selected from the group consisting of C_{1-6} alkyl, OR, CN, halo, SR, NR^2 ,
10 heteroaryl and aryl;

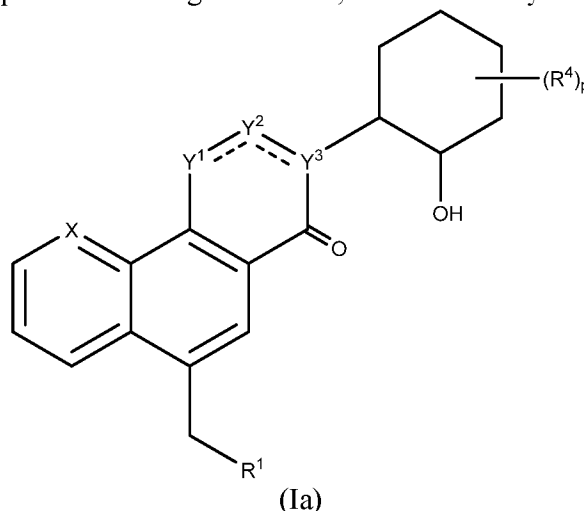
m is independently 0 or 1;

n is independently 1 or 2;

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

- 15 q is 0 or 1.

2. The compound according to Claim 1, as illustrated by formula (Ia)



- 20 or pharmaceutically acceptable salts thereof, wherein

----- represents an optional double bond, provided that there is only one double bond in the ring;

- 25 X is selected from the group consisting of CR^a and N;

Y^1 and Y^2 are independently selected from the group consisting of $C(R^b)_n$ and $N(R^b)^m$;

Y^3 is selected from the group consisting of $C(R^a)_q$ and N;

5 Provided at least one of Y^1 and Y^3 is a nitrogen substitution;

R , R^a and R^b are independently selected from the group consisting of H and C_{1-6} alkyl;

10 R^1 is selected from the group consisting of C_{6-10} aryl, 6-membered monocyclic heteroaryl, 9- to 10-membered fused bicyclic heteroaryl, 6-membered monocyclic heterocycl, and 8- to 11-bicyclic heterocycl, wherein each of the aryl, heteroaryl and heterocycl are optionally substituted with one to three substituents selected from R^5 ;

15 R^5 is independently selected from the group consisting of H, CN, halo, C_{1-6} alkyl, -OR, -SR, aryl and, heteroaryl, wherein the alkyl, aryl and heteroaryl groups are optionally substituted with one to three substituents selected from R^6 ;

20 R^6 is independently selected from the group consisting of C_{1-6} alkyl, OR, CN, SR, halo, heteroaryl, and aryl;

m is independently 0 or 1;

n is independently 1 or 2;

p is 0, 1 or 2; and

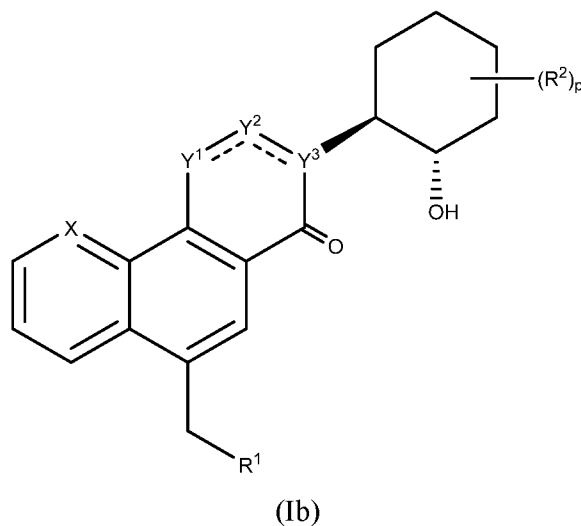
q is 0 or 1.

25

3. The compound according to any of Claims 1-2 or a pharmaceutically acceptable salt thereof, wherein X is N.

30 4. The compound according to any of Claims 1-2, or a pharmaceutically acceptable salt thereof, wherein X is CR^a .

5. The compound according to Claim 2, as illustrated by formula (Ib):



or pharmaceutically acceptable salts thereof, wherein

5 ----- represents an optional double bond, provided there is only one double bond in the ring;

X is CH or N;

Y^1 is $C(R^b)_n$;

10

Y^2 is $C(R^b)_n$ or $N(R^b)_m$;

Y^3 is N; and

15 p is 0 or 1.

6. The compound according to any of Claims 1-5, or a pharmaceutically acceptable salt thereof, wherein Y^1 is $C(R^b)_n$, Y^2 is $N(R^b)_m$, and Y^3 is N.

20 7. The compound according to any of Claims 1-5, or a pharmaceutically acceptable salt thereof, wherein Y^1 is $C(R^b)_n$, Y^2 is $C(R^b)_n$, and Y^3 is N.

8. The compound according to Claim 6 or 7, or a pharmaceutically acceptable salt thereof, wherein there is a double bond between Y^1 and Y^2 .

25

9. The compound according to any of Claims 1-2, or a pharmaceutically acceptable salt thereof, wherein Y^1 is $N(R^b)_m$, Y^2 is $C(R^b)_n$, and Y^3 is $C(R^a)_q$.

10. The compound according to any of Claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyridinyl, piperidinyl, isoquinoline, quinolone, and piperazinyl, wherein the pyridinyl, piperidinyl, isoquinoline, quinolone, and piperazinyl is optionally substituted with one to three substituents selected from R^5 .

11. The compound according to Claim 1 which is

(±)-*trans*-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)benzo[*f*]phthalazin-4(3*H*)-one;

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)benzo[*f*] phthalazin-4(3*H*)-one;

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)benzo[*f*]phthalazin-4(3*H*)-one;

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)benzo[*f*]phthalazin-4(3*H*)-one;

(±)-*trans*-3-(2-hydroxycyclohexyl)-6-((6-(methylthio)pyridin-3-yl)methyl)benzo[*f*]phthalazin-4(3*H*)-one;

(±)-*trans*-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[*f*]phthalazin-4(1*H*)-one;

3-(2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinolin-4(1*H*)-one;

1-((8-((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)-4-(pyridin-2-yl)piperidine-4-carbonitrile;

6-(4-((8-((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)piperazin-1-yl)nicotinonitrile;

1-((8-((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)-4-phenylpiperidine-4-carbonitrile;

5-((4-fluoropiperidin-1-yl)methyl)-8-((1*S*,2*S*)-2-hydroxycyclohexyl)-1,8-phenanthrolin-7(8*H*)-one;

4-fluoro-1-((8-((1*S*,2*S*)-2-hydroxycyclohexyl)-7-oxo-7,8-dihydro-1,8-phenanthrolin-5-yl)methyl)piperidine-4-carbonitrile;

5-((4,4-difluoropiperidin-1-yl)methyl)-8-((1*S*,2*S*)-2-hydroxycyclohexyl)-1,8-phenanthroline-7(8*H*)-one;
or pharmaceutically acceptable salts thereof.

5 12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10 13. Use of a compound of any of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for the manufacture of a medicament for the treatment of a disease or disorder mediated by the muscarinic M1 receptor, wherein said disease or disorder is selected from the group consisting of Alzheimer's disease, schizophrenia, pain or sleep disorders.

15 14. A method of treating a disease or disorder mediated by the muscarinic M1 receptor, wherein said disease or disorder is selected from the group consisting of Alzheimer's disease, schizophrenia, pain or sleep disorders in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/22000

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/4745; C07D 215/60, 471/04 (2017.01)

CPC - A61K 31/4745; C07D 215/60, 471/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2013/0116272 A1 (KUDUK, SD et al.) 09 May 2013; paragraph [0120]	1-2, 3/1-2, 5 ----- 4/2, 9/1-2, 11
X -- Y	US 2014/0364395 A1 (MERCK SHARP & DOHME CORP.) 11 December 2014; paragraph [0609], table 1	1, 4/1 ----- 4/2
Y	US 2009/0042928 A1 (GROOTENHUIS, PDJ et al.) 12 February 2009; paragraphs [0011], [0013], [0018], [0035]	9/1-2, 11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

28 April 2017 (28.04.2017)

Date of mailing of the international search report

25 MAY 2017

Name and mailing address of the ISA/

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P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/22000

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 6-8, 10, 12-14
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.