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(71) Applicant: MERCK SHARP & DOHME CORP.

[US/US]; 126 East Lincoln Avenue, Rahway, New Jersey
07065-0907 (US).

(72) Inventors; and

(71) Applicants (for US only): KUDUK, Scott D. [US/US]; 219

Summerwind Lane, Harleysville, Pennsylvania 19438 (US).
BESHORE, Douglas C. [US/US]; 770 Sumneytown Pike,
West Point, Pennsylvania 19486 (US).

(74) Common Representative: MERCK SHARP & DOHME

CORP.; 126 East Lincoln Avenue, Rahway, New Jersey
07065-0907 (US).

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(54) Title: BENZOISOQUINOLINONE M1 RECEPTOR POSITIVE ALLOSTERIC MODULATORS

(57) Abstract: The present invention is directed to substituted benzoisoquinolinone compounds, their salts, pharmaceutical compositions comprising them and their use in therapy. In particular, the invention is directed substituted benzoisoquinolinone compounds which are muscarinic M1 receptor positive allosteric modulators. The present invention is also directed to uses of the compounds described herein in the potential treatment or prevention of neurological and psychiatric disorders and diseases in which M1 receptors are involved. The present invention is also directed to compositions comprising these compounds. The present invention is also directed to uses of these compositions in the potential prevention or treatment of such diseases in which M1 receptors are involved.



TITLE OF THE INVENTION

BENZOISOQUINOLINONE M1 RECEPTOR POSITIVE ALLOSTERIC MODULATORS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

10 Alzheimer's disease is a common neurodegenerative disease affecting the elderly, resulting in progressive memory impairment, loss of language and visuospatial skills, and 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 accumulation of $A\beta$ in the brain.

20 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, 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

25 cholinesterase inhibitors have provided some cognitive enhancement in Alzheimer's disease patients, the therapy has not been shown to change the underlying disease pathology.

30 A second potential pharmacotherapeutic target to counteract cholinergic hypofunction is 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.

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 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. 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, nausea and diarrhea.

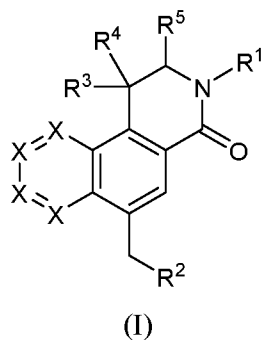
The muscarinic receptors are known to contain one or more allosteric sites, which may alter the affinity with which muscarinic ligands bind to the primary binding or orthosteric sites. Thus the compounds disclosed herein, which are muscarinic M1 receptor positive allosteric modulators, are believed to be potentially useful in the treatment of Alzheimer's disease and other diseases mediated by the muscarinic M1 receptor.

SUMMARY OF THE INVENTION

The present invention is directed to substituted benzoisoquinolinone compounds, their salts, pharmaceutical compositions comprising them and their use in therapy. In particular, the invention is directed substituted benzoisoquinolinone compounds which are muscarinic M1 receptor positive allosteric modulators. The present invention is also directed to uses of the compounds described herein in the potential treatment or prevention of neurological and psychiatric disorders and diseases in which M1 receptors are involved. The present invention is also directed to compositions comprising these compounds. The present invention is also directed to uses of these compositions in the potential prevention or treatment of such diseases in which M1 receptors are involved.

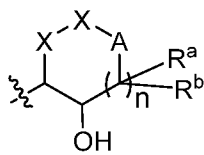
DETAILED DESCRIPTION OF THE INVENTION

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



5 or a pharmaceutically acceptable salt thereof, wherein:

R¹ is



wherein: A is -CH₂-, -O-, -S- or -N(R')-,

R' is hydrogen or -C₁₋₆ alkyl,

10 each of R^a and R^b is independently hydrogen or halogen, and

n is 0, 1 or 2;

each occurrence of X is independently selected from the group of -CH₂-, -CH=, -NH- and -N=, or one of the X may be absent;

15

R² is selected from the group consisting of:

(1) a C₅₋₁₀ heterocyclyl, and

(2) aryl;

wherein each of the C₅₋₁₀ heterocyclyl of (1) and the aryl of (2) is unsubstituted or

20 substituted with 1 to 3 groups independently selected from halogen, -C₁₋₆ alkyl, -O-C₁₋₆

alkyl, -S-C₁₋₆ alkyl, and C₅₋₁₀heteroaryl which is unsubstituted or substituted with

halogen or -C₁₋₆ alkyl; and

R³, R⁴ and R⁵ are independently selected from the group consisting of:

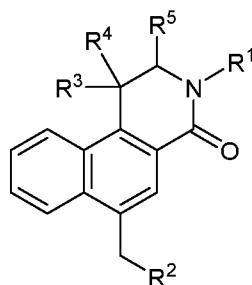
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(1) hydrogen,

(2) halogen, and

(3) $-C_{1-10}$ alkyl, said alkyl is unsubstituted or substituted with 1 to 3 groups independently selected from oxo and $-OH$.

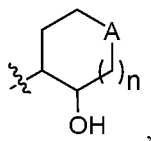
5 An embodiment of the present invention includes compounds of the formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, wherein:

10 R^1 is:



wherein A is $-CH_2-$ or $-O-$ or $-S-$, and

n is 0, 1 or 2;

15 R^2 is selected from the group consisting of:

(1) a C_{5-10} heterocyclyl, said heterocyclyl is unsubstituted or substituted with 1 to 3 groups independently selected from halogen, $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, and C_{5-10} heteroaryl unsubstituted or substituted with $-C_{1-6}$ alkyl; and

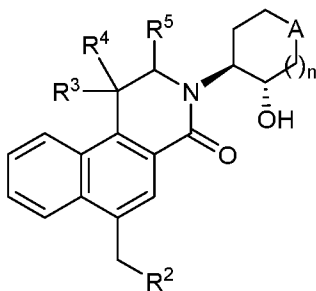
20 (2) aryl, said aryl is unsubstituted or substituted with 1 to 3 groups independently selected from halogen, $-C_{1-6}$ alkyl and C_{5-10} heteroaryl, said heteroaryl is unsubstituted or substituted with $-C_{1-6}$ alkyl;

R^3 , R^4 and R^5 are independently selected from the group consisting of:

(1) hydrogen, and

(2) $-C_{1-10}$ alkyl, said alkyl is unsubstituted or substituted with 1 to 3 groups independently selected from oxo and $-OH$.

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



(Ib)

or a pharmaceutically acceptable salt thereof, wherein each of A, R^2 , R^3 , R^4 , R^5 and n is as defined above for formula (I).

An embodiment of the present invention includes compounds of formula (I), (Ia)

or (Ib), wherein:

A is $-CH_2-$;

R^2 is aryl or C_{5-10} heteroaryl, each of said aryl and heteroaryl is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, methyl, ethyl, propyl, $-O$ -methyl, $-O$ -ethyl, $-O$ -propyl, $-S$ -methyl, $-S$ -ethyl, $-S$ -propyl, pyridyl and pyrazolyl; said pyridyl and pyrazolyl is unsubstituted or substituted with C_{1-4} alkyl; and

R^3 , R^4 and R^5 are independently hydrogen or $-C_{1-6}$ alkyl, said alkyl is unsubstituted or substituted with 1 to 3 groups independently selected from oxo and $-OH$; and
n is 1 or 2.

An embodiment of the present invention includes compounds wherein:

A is $-CH_2-$;

R^2 is a phenyl or C_{5-6} heteroaryl, each of said phenyl and heteroaryl is unsubstituted or substituted with halogen, methyl, ethyl, propyl, $-O$ -methyl, $-O$ -ethyl, $-O$ -propyl, $-S$ -methyl, $-S$ -ethyl, $-S$ -propyl, pyridyl or pyrazolyl; said pyridyl and pyrazolyl is unsubstituted or substituted with methyl or ethyl;

R^3 , R^4 and R^5 are independently hydrogen, methyl, ethyl, propyl, $-CH_2CH_2-OH$, $-C(O)CH_3$, or $-CH_2C(O)H$; and

n is 1 or 2.

An embodiment of the present invention includes compounds wherein;

A is $-\text{CH}_2-$;

R^2 is a phenyl or pyridyl, each of said phenyl and pyridyl is unsubstituted or substituted with halogen, methyl, ethyl, $-\text{O}$ -methyl, $-\text{O}$ -ethyl, $-\text{S}$ -methyl, or $-\text{S}$ -ethyl, pyridyl which is
5 unsubstituted or substituted with methyl, or pyrazolyl which is unsubstituted or substituted with methyl; and

R^3 , R^4 and R^5 are independently hydrogen, methyl, ethyl, $-\text{CH}_2\text{CH}_2-\text{OH}$, $-\text{C}(\text{O})\text{CH}_3$, or $-\text{CH}_2\text{C}(\text{O})\text{H}$.

10 An embodiment of the present invention includes compounds wherein A is $-\text{CH}_2-$, and n is 1 or 2.

An embodiment of the present invention includes compounds wherein A is $-\text{O}-$, and n is 1.

An embodiment of the present invention includes compounds wherein A is $-\text{CH}_2-$.

An embodiment of the present invention includes compounds wherein A is $-\text{O}-$.

15 An embodiment of the present invention includes compounds wherein R^2 is phenyl, said phenyl is unsubstituted or substituted with a halogen. In one embodiment, the halogen is Cl or F.

An embodiment of the present invention includes compounds wherein R^2 is phenyl, said phenyl is unsubstituted or substituted with a methyl or ethyl.

20 An embodiment of the present invention includes compounds wherein R^2 is phenyl, said phenyl is unsubstituted or substituted with a pyridyl or pyrazolyl, said pyridyl or pyrazolyl is unsubstituted or substituted with $-\text{C}_{1-4}$ alkyl.

An embodiment of the present invention includes compounds wherein R^2 is pyridyl, said pyridyl is unsubstituted or substituted with a halogen, $-\text{C}_{1-4}$ alkyl, $-\text{O}-\text{C}_{1-4}$ alkyl, or $-\text{S}-\text{C}_{1-4}$ alkyl.

25 In one embodiment of any of the above embodiments, R^2 is pyridyl, said pyridyl is unsubstituted or substituted with F, Cl, methyl, ethyl, propyl, $-\text{O}$ -methyl, $-\text{O}$ -ethyl, $-\text{O}$ -propyl, $-\text{S}$ -methyl, $-\text{S}$ -ethyl or $-\text{S}$ -propyl.

An embodiment of the present invention includes compounds wherein R^2 is pyridyl, said pyridyl is unsubstituted or substituted with halo, another pyridyl or pyrazolyl, each of which is unsubstituted or substituted with a methyl, ethyl or propyl.

30 An embodiment of the present invention includes compounds wherein R^3 , R^4 and R^5 are independently hydrogen or $-\text{C}_{1-6}$ alkyl. An embodiment of the present invention includes compounds wherein R^3 , R^4 and R^5 are independently hydrogen or methyl. An embodiment of

the present invention includes compounds wherein R³ is hydrogen, R⁴ is hydrogen and R⁵ is methyl. An embodiment of the present invention includes compounds wherein R³ is methyl, R⁴ is hydrogen and R⁵ is hydrogen. An embodiment of the present invention includes compounds wherein R³ is methyl, R⁴ is methyl and R⁵ is hydrogen.

5 An embodiment of the present invention includes compounds wherein n is 0.

An embodiment of the present invention includes compounds wherein n is 1.

An embodiment of the present invention includes compounds wherein n is 2.

An embodiment of the present invention includes compounds wherein n is 1 and A is – CH₂–.

10 An embodiment of the present invention includes compounds wherein n is 1 and A is – O–.

An embodiment of the present invention includes compounds wherein n is 2 and A is – CH₂–.

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

In an embodiment, the present invention is directed to a compound which is selected from the group consisting of:

6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2,3-

20 dihydrobenzo[f]isoquinolin-4(1H)-one;

6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycycloheptyl)-2,3-

dihydrobenzo[f]isoquinolin-4(1H)-one;

6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-

dihydrobenzo[f]isoquinolin-4(1H)-one;

25 6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one;

3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;

3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methylpyridin-3-yl)methyl)-2,3-

30 dihydrobenzo[f]isoquinolin-4(1H)-one;

3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one

- 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one;
- 5 3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(methylthio)pyridin-3-yl)methyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one;
- 3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one;
- trans-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1,1-dimethyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 10 3-(2-hydroxycyclohexyl)-1,1-dimethyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- trans-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one ;
- 15 3-(2-hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 20 6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycycloheptyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one
- 6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 25 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 30 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one

6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1,1-dimethyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
3-(2-hydroxycyclohexyl)-1,1-dimethyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
5 6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one; and
3-(2-hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
10 or a pharmaceutically acceptable salt thereof.

Also disclosed herein are methods of treating a patient (such 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 formula (I), or a pharmaceutically acceptable salt thereof.

Also disclosed herein is the use of a compound of formula (I), 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 compound of formula (I), or a pharmaceutically acceptable salt thereof.

Also disclosed herein are medicaments or pharmaceutical compositions for the treatment of diseases or disorders in a patient (such as 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 formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Also disclosed herein is 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 formula (I), or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.

When any variable (e.g. aryl, heterocycle, R¹, R² 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 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.

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

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, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdiny, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl and triazolyl.

In certain embodiments, the heterocyclic group is a heteroaryl group. 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 heterocyclic ring system which contains 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 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, 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.

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-).

"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.

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 present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all

such isomeric forms of these compounds. Formula I shows the structure of the class of compounds without specific stereochemistry. At least some of the chemical names of compounds of the invention as set forth in this application may have been generated on an automated basis by use of commercially available chemical naming software programs, and have not been independently verified.

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

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

The compounds of the invention may be prepared according to the following reaction Schemes, 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 above 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.

The term “substantially pure” means that the isolated material is at least 90% pure, for example, 95% pure, and, for example, 99% pure as assayed by analytical techniques known in the art.

As used herein, the term "muscarinic M1 receptor" refers to one of the five subtypes
5 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
10 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
15 allosteric modulators of the muscarinic M1 receptor. For example, a modulator or 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
20 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
25 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
30 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. 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 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 formula (I) 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 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 other embodiments, the compounds of the invention are 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 present invention provides 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
5 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
10 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
15 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'
20 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
25 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., vulvodynia,
30 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
5 (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
10 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
15 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
20 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.

25 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
30 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-HT_{1a} 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,

5 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;

10 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

15 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

20 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,

25 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,

30 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, 5 tracetamide, 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 10 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 15 alentemol, 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, alentemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, naxagolide hydrochloride and pergolide mesylate.

In another embodiment, the subject compound may be employed in combination with a 20 compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a 25 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 subject compound may be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, 30 acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine,

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, amisuipride, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, 5 levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, 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, 10 diclofenac, duflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, 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 B1 receptor antagonists, such as SSR240612 and NVPSAA164; sodium channel blockers and 15 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 blockers, such as ziconotide and NMED160; GABA-A receptor IO modulators (e.g., a GABA- 20 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-B") inhibitors; 5HT receptor agonists or antagonists; mGlu5 antagonists, such as AZD9272; 25 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; lithium; valproate; gabapentin; pregabalin; rizatriptan; zolmitriptan; naratriptan and sumatriptan.

30 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-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, melatnergic agents, other orexin antagonists, orexin agonists, prokineticin agonists and antagonists, pyrazolopyrimidines, T-type calcium channel antagonists, triazolopyridines, and the like, such as: adinazolam, allobarbitol, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, armodafinil, APD-125, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capromorelin, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, conazepam, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, EMD-281014, eplivanserin, estazolam, eszopiclone, ethchlorynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, gaboxadol, glutethimide, halazepam, hydroxyzine, ibutamoren, imipramine, indiplon, lithium, lorazepam, lormetazepam, LY-156735, maprotiline, MDL-100907, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, 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 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, 5 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 10 carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound, which is a compound of formula (I) 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 15 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 20 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 25 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 30 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
5 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
10 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 may contain from about 0.1 mg to about 500 mg of the active ingredient and each cachet or capsule may contain 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
15 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
20 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
25 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, should be preserved
30 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.

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

10 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.

15 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.

20 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.

25 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 (i.e., reversing the pathology and/or symptomatology).

30 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

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
5 of unit dosage forms is not intended to be limiting in any way, but merely to represent typical 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
10 actual dosage form by the patient or person administering the drug to the patient. Such kits may 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
15 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 kg of animal body weight, for example, 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, for example, from about 0.1 mg to about 20 mg per kg of body weight. In the
20 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, such as once or twice per day.

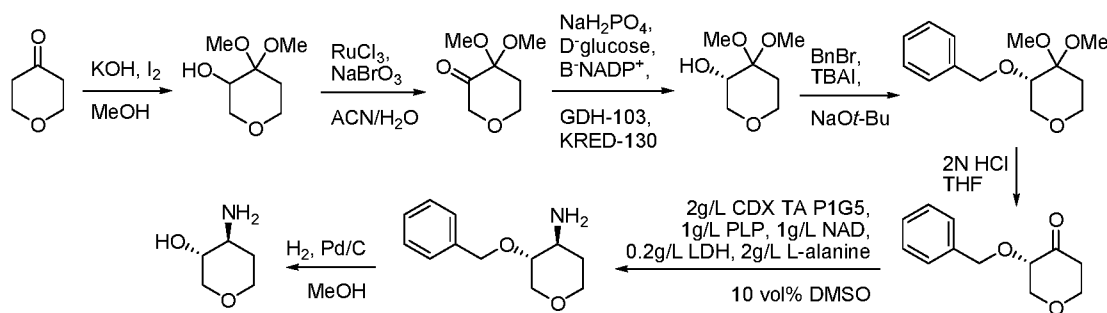
The amount of active ingredient that may be combined with the carrier materials to
25 produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from 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 contain between from about 0.005 mg to about 1000 mg of the active ingredient, typically 0.005,
30 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 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
 5 of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

EXPERIMENTALS

The following abbreviations may be used herein:

	Me:	methyl
10	Et:	ethyl
	<i>t</i> -Bu:	<i>tert</i> -butyl
	Ar:	aryl
	Ph:	phenyl
	Bn:	benzyl
15	DCE:	dichloroethylene
	HMDS:	hexamethyldisilazane
	DMF:	dimethylformamide
	DMFDMA:	<i>N,N</i> -dimethylformamide dimethylacetal
	THF:	tetrahydrofuran
20	BOP:	benzotriazolyloxytris (dimethylamino) phosphonium hexafluorophosphate
	Boc:	<i>tert</i> -butyloxycarbonyl
	TBS:	<i>tert</i> -butyldimethylsilyl
	TEA:	triethylamine
25	TPAP:	tetra- <i>n</i> -propyl ammonium perruthenate
	NMO:	<i>N</i> -methyl morpholine <i>N</i> -oxide
	ClZn:	Chlorozinc
	dppf:	diphenylphosphorousferrocenyl
	PMB:	<i>p</i> -methoxybenzyl
30	Ms:	mesyl
	Ac:	acetyl
	DMSO:	dimethylsulfoxide



A jacketed flask equipped with an overhead stirrer and a thermocouple was charged with 23.0 L of MeOH, and cooled to 5 °C. Potassium hydroxide (1.574 kg, 28.05 mol) was added to the flask, and the resulting solution was aged until homogeneous and re-cooled to 5 °C.

- 5 Tetrahydro-4H-pyran-4-one (1.00 kg, 10.0 mol) was then added at a steady rate over 20 min, and the resulting solution was aged for 20-30 min. A solution of iodine (2.778 kg, 10.95 mol) in 18.5 L of MeOH was then added via mechanical pump at a steady rate over 90-100 minutes. After an additional 30 min, the solution was warmed to rt and toluene (42.0 L) was added. The resulting slurry was concentrated *in vacuo* to a volume of ~8.4 L. Additional toluene (8.4 L) was added
- 10 and the resulting solution was concentrated to a volume of 8.4 L 2x. The resulting slurry was then filtered, and the filter cake was rinsed 2x with toluene (4.0 L). The combined toluene streams were concentrated to ~6 L, and the product is extracted 2x with water (3.0 L) to provide 4,4-dimethoxytetrahydro-2H-pyran-3-ol.

- To a solution of the above compound (1.00 kg, 6.17 mol) in 5 L of water was added
- 15 acetic acid to pH 5.2-5.4. The mixture was diluted with acetonitrile (4.0 L) and ruthenium trichloride hydrate (6.4 g, 0.028 mol) was added and rinsed in with additional acetonitrile (1.0 L). The flask was placed in a rt water bath and a solution of sodium bromate (650 g, 4.31 mol) in water (1.95 L) was added slowly over ~30 min, keeping the temperature below 30 °C. After 2 h, potassium bicarbonate (430 g, 4.30 mol), sodium thiosulfate (1.07 kg, 4.31 mol), potassium
 - 20 chloride (500 g, 6.71 mol) and acetonitrile (5 L) were added sequentially. The layers were separated and the aqueous layer was extracted 3x with acetonitrile (10 L). The combined organic extracts were concentrated to ~4 L. Toluene (5 L) was then added and the mixture reconcentrated to 4 L 4x. The mixture was diluted with toluene (7 L) and filtered to remove solids. The filtercake was washed 3x with toluene (2 L) and the combined filtrate and washes
 - 25 were concentrated to a total volume of 3 L to provide an organic solution of 4,4-dimethoxydihydro-2H-pyran-3(4H)-one.

To a 3L 3-neck RB flask with overhead stirring, thermocouple and heating mantle was added sodium dihydrogenphosphate (96.0 g, 800 mmol) in 1.6 L of water. Sodium hydroxide (29 mL, 50 wt%) was added to pH 7.13, followed by hydrochloric acid (5 mL, 6 N) to pH 7.02. The above organic solution of 4,4-dimethoxydihydro-2H-pyran-3(4H)-one was extracted 3x with phosphate buffered water (0.55 L). To the combined aqueous extracts was added D-glucose (180 g, 100 mmol), and the solution was heated to 30 °C. When the solution exceeded 27 °C upon heating B-NADP⁺ (1.60 g, 499 mmol), GDH-103 (1.60 g, 499 mmol), and KRED-130 (1.60 g, 499 mmol) were added and the mixture was stirred for 17 h at 30 °C. Potassium chloride (200g, 2.68 mol) and acetonitrile (1.3 L) were added. After 30 min, the reaction mixture was transferred to 6 L sep funnel and additional MeCN (0.67 L) and toluene (0.87 L) were added. The aqueous layer was back extracted 1x with a mixture of acetonitrile (1.95L) and toluene (0.65 L), and 1x with acetonitrile (1.5 L). The combined organic extracts were concentrated *in vacuo* to provide (3S)-4,4-dimethoxytetrahydro-2H-pyran-3-ol.

To a 2L RB flask with overhead stirring, thermocouple, heating mantle and N₂ inlet was added a solution of the above compound (72.0 g, 0.444 mol) in 750 mL of THF. After 15 h, sodium *tert*-butoxide (48.3 g, 492 mmol) was added in one portion, and the mixture was heated to 35 °C for 1 h, and aged at 22 °C for 1hr. Tetrabutylammonium iodide (8.19 g, 22.2 mmol) and benzyl bromide (56.5 ml, 466 mmol) were added, and the mixture was heated to 50°C for 2 h. The solution was cooled to 25 °C, and water (750 mL) and MtBE (2.25 L) were added. The organic layer was separated from the aqueous and concentrated in vacuo. The resultant brown oil was purified via silica gel chromatography, eluting with 0-15% ethyl acetate in hexanes to provide (3S)-3-(benzyloxy)-4,4-dimethoxytetrahydro-2H-pyran.

To a solution of the above compound (61.1 g, 225 mmol) in 300 mL of THF was added 2 N HCl (300 mL, 0.600 mol). After 1.5 h, saturated aqueous potassium carbonate (60 mL) was added via addition funnel to pH 7.4. The aqueous layer was extracted 3x with MtBE (300 mL) and the combined organic extracts were concentrated in vacuo to provide crude (3S)-3-(benzyloxy)-tetrahydro-4H-pyran-4-one.

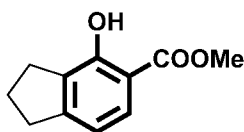
To a solution of L-Alanine (200 g, 2.24 mol), sodium formate (76.0 g, 1.12 mmol), and sodium phosphate dibasic (28.7 g, 202 mmol) in 2.25 L of water adjusted to pH 7.5 was added NAD (2.2 g, 3.21 mmol), pyridoxal-5-phosphate (2.2 g, 8.90 mmol), LDH (0.45 g, 0.22 mol), FDH (4.5 g, 0.20 mol), and TA PIG5 (4.5 g, 0.22 mol). After all the components were completely dissolved, (3S)-3-(benzyloxy)tetrahydro-4H-pyran-4-one (45 g, 0.22 mol) was added

and the pH was adjusted to pH 7.25 with 6 *N* HCl and aged at 30 °C. After 15 h, potassium carbonate (700 g, 5.06 mol) was added slowly, followed by ethyl acetate (2.2 L). The mixture was filtered through a bed of Solka Floc and the cake was washed with ethyl acetate (250 mL). The combined filtrates were separated and the aqueous layer was extracted a second time with ethyl acetate (2 L). The combined organic extracts were concentrated *in vacuo* to provide crude (3*R*, 4*S*)-3-(benzyloxy)tetrahydro-2*H*-pyran-4-amine.

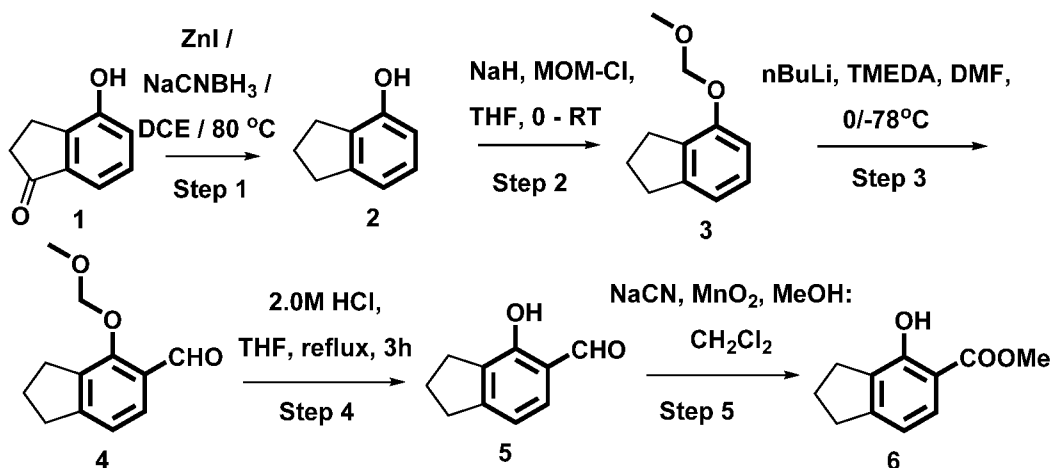
To a solution of the above compound (38.8 g, 0.187 mol) in 730 mL of methanol was added concentrated hydrochloric acid (23.3 mL). The solution was subjected to hydrogenation at 40 psi H₂, 25 °C over 10% Pd/C (5.8 g). After 15 h, the mixture was filtered through solka floc and the filtercake was washed 5x with methanol (100 mL). The combined filtrate and washes were concentrated *in vacuo* to provide (3*R*, 4*S*)-4-aminotetrahydro-2*H*-pyran-3-ol that gave proton NMR spectra consistent with theory.

The title compound was prepared employing the procedures described for the construction of 2-[(1*S*, 2*S*)-2-hydroxycyclohexyl]-5-(4-methoxybenzyl)-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one in Example 1, substituting (2-chloro-5-pyridyl)methylzinc chloride for 4-methoxybenzylzinc chloride and substituting (3*R*, 4*S*)-4-aminotetrahydro-2*H*-pyran-3-ol for (1*S*, 2*S*)-2-aminocyclohexanol. The resultant yellow solid gave a proton NMR spectra consistent with theory and a mass ion (ES⁺) of 409.1 for [M+H]⁺: ¹H NMR (400 MHz, d₆-DMSO) δ 8.43 (s, 1H), 8.22–8.19 (m, 1H), 8.10–8.08 (m, 1H), 7.71–7.62 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.13 (d, *J* = 5.6 Hz, 1H), 4.93–4.82 (m, 2H), 4.57 (s, 2H), 4.13–4.03 (m, 1H), 3.95–3.87 (m, 2H), 3.85–3.77 (m, 1H), 3.46–3.39 (m, 1H), 3.15–3.10 (m, 1H), 1.97–1.87 (m, 1H), 1.75–1.72 (m, 1H) ppm.

INTERMEDIATE 2



Methyl 4-hydroxy-2,3-dihydro-1*H*-indene-5-carboxylate



Step 1: Preparation of 2,3-dihydro-1H-inden-4-ol

To a stirred solution of 4-hydroxy-2,3-dihydro-1H-inden-1-one (17.5 g, 118 mmol) and zinc(II) iodide (113 g, 354 mmol) in 1,2-dichloroethene (400 mL) at 0 °C was added sodium cyanoborohydride (22.2 g, 354 mmol). The mixture was refluxed for 2 hours, cooled to room temperature, and treated with water. The mixture was extracted with dichloromethane and the combined organic layers were washed with water, brine and then dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (8 % ethyl acetate in petroleum ether) to provide the title compound that gave a mass ion [ES⁺] of 135.0 for [M + H]⁺.

Step 2: Preparation of 4-(methoxymethoxy)-2,3-dihydro-1H-indene

To a stirred solution of 2,3-dihydro-1H-inden-4-ol (7.3 g, 54 mmol) in THF (100 mL) under nitrogen was added sodium hydride (6.5 g, 0.16 mol) at 0 °C. The mixture was stirred at room temperature for 1 hour, cooled to 0 °C and treated with chloromethyl methylether (6.2 mL, 82 mmol). The mixture was then stirred at room temperature for 1 hour, diluted with cold water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 – 50 % ethyl acetate in petroleum ether) to provide the title compound that gave a NMR consistent with theory. ¹H NMR (400MHz, CDCl₃): δ. 7.13 – 7.08 (m, 1H), 6.93 – 6.86 (m, 2H), 5.20 (s, 2H), 3.41 (s, 3H), 2.96 – 2.88 (m, 4H), 2.13 – 2.03 (m, 2H) ppm.

Step 3: Preparation of 4-(methoxymethoxy)-2,3-dihydro-1H-indene-5-carbaldehyde

To a solution of 4-(methoxymethoxy)-2,3-dihydro-1*H*-indene (5.00 g, 28.1 mmol), under nitrogen, in anhydrous diethyl ether (50 mL) was added TMEDA (8.47 mL, 56.1 mmol). The mixture was cooled to -20 °C and was treated with *n*-butyl lithium (22.4 mL, 2.5 M in hexane, 56.1 mmol). The resultant solution was stirred for 30 minutes, cooled to -78 °C, and then treated with *N,N*-dimethylformamide (4.34 mL, 56.1 mmol). The mixture was slowly warmed to -40 °C over 1 hour and then treated with aqueous saturated ammonium chloride. The mixture was extracted with ethyl acetate and the combined organic extracts were washed with water and brine, dried with sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 – 1 % ethyl acetate in petroleum ether) to provide the title compound that gave a mass ion consistent with theory [ES⁺] of 207.4 for [M + H]⁺.

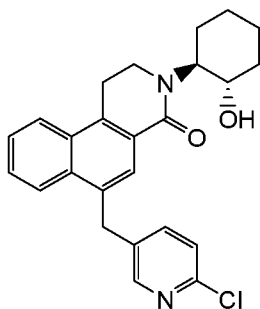
Step 4: Preparation of 4-hydroxy-2,3-dihydro-1*H*-indene-5-carbaldehyde

To a stirred solution of 4-(methoxymethoxy)-2,3-dihydro-1*H*-indene-5-carbaldehyde (4.00 g, 19.4 mmol) in THF (100 mL) at room temperature was added aqueous HCl (1.5 M, 50 mL, 75 mmol). The mixture was heated at 65 °C for 4 hours, cooled to room temperature, diluted with water and then extracted with ethyl acetate. The combined organic extracts were washed with aqueous saturated sodium bicarbonate, water and brine. The mixture was dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 – 10 % ethyl acetate in petroleum ether) to provide the title compound that gave a NMR spectra consistent with theory.

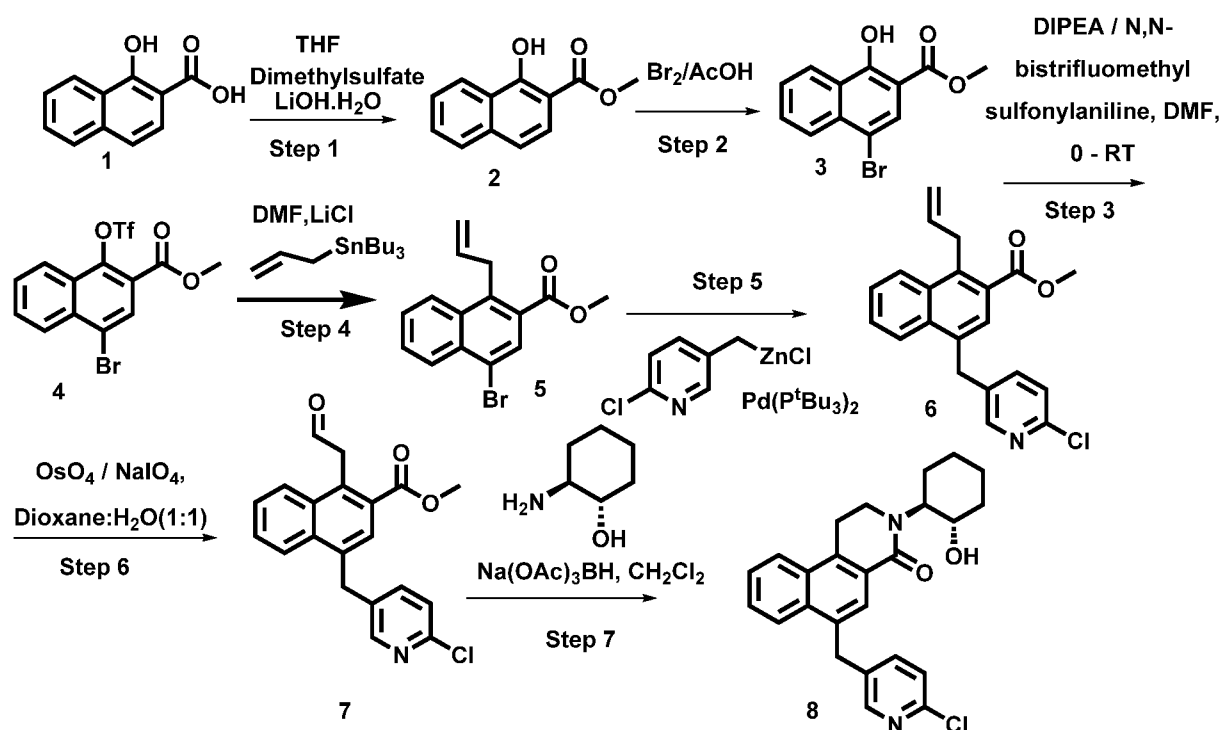
Step 5: Preparation of methyl 4-hydroxy-2,3-dihydro-1*H*-indene-5-carboxylate

To a stirred solution of 4-hydroxy-2,3-dihydro-1*H*-indene-5-carbaldehyde (2.5 g, 15 mmol) in a mixture of MeOH (120 mL) and dichloromethane (20 mL) at 0 °C was added sodium cyanide (0.75 g, 15 mmol). The mixture was stirred at room temperature for 1 hour, cooled to 0 °C and then treated with manganese dioxide (1.3 g, 15 mmol). The mixture was warmed to room temperature and stirred for an additional 16 hours. The mixture was cooled to 0 °C and treated with saturated sodium hydrogen sulfite solution. After stirring for 1 hour at ambient temperature, the mixture was diluted with water and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to provide the title compound gave a NMR spectra consistent with theory.

EXAMPLE 1



6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one



5

Step 1: Preparation of methyl 1-hydroxy-2-naphthoate, Compound 2:

To a solution of 1-hydroxy-2-naphthoic acid (15 g, 80 mmol) in THF (80 mL) at room temperature was added LiOH (3.3 g, 80 mmol). The mixture was stirred for 30 minutes and was treated with dimethyl sulfate (15 mL, 159 mmol). The mixture was refluxed for 3 hours, cooled to room temperature, and the volatiles removed under reduced pressure. Aqueous saturated NaHCO₃ (100 mL) was added and the mixture was extracted with diethyl ether (3 x 300 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated under

reduced pressure to afford the title compound, which gave a proton NMR spectra consistent with theory.

Step 2: Preparation of methyl 4-bromo-1-hydroxy-2-naphthoate, Compound 3:

To a solution of methyl 1-hydroxy-2-naphthoate (10 g, 49 mmol) in acetic acid (100 mL),
5 under nitrogen, was added bromine (3.1 mL, 59 mmol) at room temperature. The mixture was stirred for 30 minutes and then poured into water, which was extracted with diethyl ether (3 x 300 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated under reduced pressure to afford the title compound which gave a proton NMR spectra consistent with theory and a mass ion [ES⁺] of 281.0 for [M - H].

10 Step 3: Preparation of methyl 4-bromo-1-(((trifluoromethyl) sulfonyl) oxy)-2-naphthoate, Compound 4:

To a solution of methyl 4-bromo-1-hydroxy-2-naphthoate (6.00 g, 21.3 mmol) in DMF (40 mL) at room temperature was added DIPEA (3.73 mL, 21.34 mmol) followed by *N,N*-bis (trifluoromethyl sulfonyl) aniline (7.63 g, 21.3 mmol). The mixture was stirred at room
15 temperature for 1 hour and then the volatiles were removed under reduced pressure. The residue obtained was treated with ice-cold water (50 mL) and extracted with ethyl acetate. The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0–2% ethyl acetate in petroleum ether) to provide the title compound, which
20 gave a proton NMR spectra consistent with theory.

Step 4: Preparation of methyl 1-allyl-4-bromo-2-naphthoate, Compound 5:

To a solution of methyl 4-bromo-1-(((trifluoromethyl) sulfonyl) oxy)-2-naphthoate (4.60 g, 11.1 mmol) in DMF (40 mL) at room temperature was added lithium chloride (2.36 g, 55.7 mmol), tetrakis(triphenylphosphine)palladium(0) [0.64 g, 0.56 mmol] and allyltributylstannane
25 (3.80 mL, 12.2 mmol). The mixture was heated to 110 °C for 1 hour, cooled to ambient temperature, diluted with cold water and extracted with ethyl acetate. The combined organic extracts were washed with water, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0–5% ethyl acetate in petroleum ether) to afford the title compound, which gave a proton NMR spectra
30 consistent with theory and a mass ion [ES⁺] (⁸¹Br) of 307.0 for [M + H]⁺.

Step 5: Preparation of methyl 1-allyl-4-((6-chloropyridin-3-yl)methyl)-2-naphthoate, Compound 6:

To a solution of methyl 1-allyl-4-bromo-2-naphthoate (2.4 g, 7.9 mmol) in THF (5 mL) at 0 °C was added a solution of (2-chloro-5-pyridyl) methylzinc chloride (0.5 M in THF, 39.3 mL, 19.7 mmol) followed by bis(tri-*tert*-butylphosphine)palladium(0) [0.12 g, 0.24 mmol]. The mixture was warmed to room temperature and stirred for 2 hours. The mixture was cooled to 0 °C, treated with water (10 mL), and then further diluted with dichloromethane and water, after which a solid was filtered off through a pad of celite. The filtrate was extracted with dichloromethane (2 x 200 mL) and the combined organic extracts were dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 – 20 % ethyl acetate in petroleum ether) to provide the title compound. ¹H NMR (400MHz, DMSO-*d*₆): δ. 8.41 (d, *J* = 2.0 Hz, 1H), 8.30 – 8.27 (m, 1H), 8.13 – 8.10 (m, 1H), 7.73 (s, 1H), 7.66 – 7.60 (m, 3H), 7.4 (d, *J* = 8.0 Hz, 1H), 6.07 – 5.97 (m, 1H), 5.02 – 4.99 (m, 2H), 4.49 (s, 2H), 4.12 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H) ppm; observed LRMS *m/z*: 352.2 (M+H)⁺.

Step 6: Preparation of methyl 4-((6-chloropyridin-3-yl)methyl)-1-(2-oxoethyl)-2-naphthoate, Compound 7:

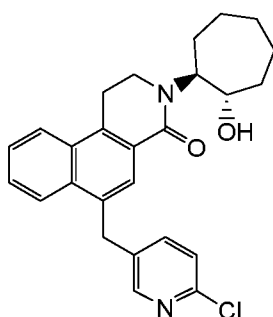
To a solution of methyl 1-allyl-4-((6-chloropyridin-3-yl)methyl)-2-naphthoate (200 mg, 0.568 mmol) in an 8 mL 1:1 mixture of dioxane and water at room temperature was added sodium periodate (365 mg, 1.70 mmol) followed by osmium tetroxide (0.14 mL, 0.011 mmol). The mixture was stirred for 16 hours at ambient temperature, cooled to 0 °C and then treated with ice water (10 mL). The mixture was extracted with ethyl acetate (2 x 70 mL) and the combined organic extracts were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 – 20 % ethyl acetate in petroleum ether) to provide the title compound, which gave a mass ion [ES⁺] of 354.4 for [M + H]⁺.

Step 7: Preparation of 6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[*f*]isoquinolin-4(1*H*)-one, Compound 8:

To a solution of methyl 4-((6-chloropyridin-3-yl)methyl)-1-(2-oxoethyl)-2-naphthoate (70 mg, 0.12 mmol) in dichloromethane (5 mL) under nitrogen at 0 °C was added (1*S*,2*S*)-2-aminocyclohexanol (34 mg, 0.30 mmol). The mixture was warmed to room temperature and stirred for 4 hours. Sodium triacetoxyborohydride (84 mg, 0.40 mmol) was then added to the mixture and the mixture was stirred for an additional 16 hours. The mixture was treated with ice water (10 mL) and extracted with dichloromethane (2 x 70 mL). The combined organic extracts

were washed with water (20 mL), brine (20 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20–60 % ethyl acetate in petroleum ether) to provide the title compound. ¹H NMR (400MHz, DMSO-d₆): δ. 8.40 (bs, 1H), 8.23 – 8.20 (m, 1H), 8.14 – 8.11 (m, 1H), 7.88 (s, 1H), 7.66 – 7.59 (m, 3H), 7.40 (d, *J* = 8.2 Hz, 1H), 4.67 – 4.65 (m, 1H), 4.51 (s, 2H), 4.27 (s, 1H), 3.62 – 3.58 (m, 3H), 3.47 – 3.38 (m, 1H), 3.29 – 3.23 (m, 1H), 1.99 – 1.95 (m, 1H), 1.68 – 1.54 (m, 4H), 1.28 – 1.16 (m, 3H) ppm; LRMS *m/z*: 421.4 (M+H)⁺.

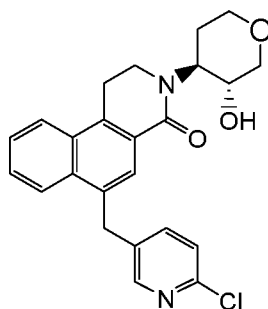
EXAMPLE 2



10 6-(((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycycloheptyl)-2,3-dihydrobenzo[flisoquinolin-4(1H)-one

To a solution of methyl 4-(((6-chloropyridin-3-yl)methyl)-1-(2-oxoethyl)-2-naphthoate (Example 1, Compound 7, 100 mg, 0.283 mmol) in dichloromethane (5 mL) under nitrogen at 0°C was added (1S,2S)-2-aminocycloheptanol (54.8 mg, 0.424 mmol). The mixture was warmed to room temperature and stirred for 4 hours. Sodium triacetoxyborohydride (300 mg, 1.41 mmol) was added and the mixture was stirred for an additional 16 hours at ambient temperature. The mixture was treated with ice water (10 mL) and extracted with dichloromethane (2 x 80 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20–60 % ethyl acetate in petroleum ether) to provide the title compound. ¹H NMR (400MHz, DMSO-d₆): δ. 8.40 (d, *J* = 2.0 Hz, 1H), 8.22 – 8.18 (m, 1H), 8.15 – 8.11 (m, 1H), 7.87 (m, 1H), 7.66 – 7.59 (m, 3H), 7.42 – 7.38 (m, 1H), 4.57 (d, *J* = 5.2 Hz, 1H), 4.50 (s, 2H), 4.35 – 4.32 (m, 1H), 3.80 – 3.74 (m, 1H), 3.64 – 3.57 (m, 2H), 3.50 – 3.49 (m, 1H), 3.33 – 3.30 (m, 1H), 1.85 – 1.74 (m, 3H), 1.63 – 1.57 (m, 4H), 1.52 – 1.47 (m, 3H) ppm. LRMS C₂₆H₂₈ClN₂O₂: calc'd 435.9, obs 435.4 (M+H)⁺.

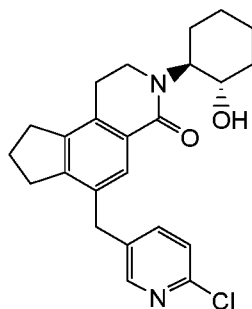
EXAMPLE 3



6-((6-chloropyridin-3-yl)methyl)-3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-2,3-dihydrobenzo[*f*]isoquinolin-4(1*H*)-one

5 To a solution of methyl 4-((6-chloropyridin-3-yl)methyl)-1-(2-oxoethyl)-2-naphthoate (Example 1, Compound 7, 100 mg, 0.283 mmol) in dichloroethane (10 mL) under nitrogen at room temperature was added (3*R*,4*S*)-4-aminotetrahydro-2*H*-pyran-3-ol (Intermediate 1, 49.7 mg, 0.424 mmol) and acetic acid (0.016 mL, 0.283 mmol). The mixture was stirred for 5 minutes and then treated with MP-CNBH₃ Resin (200 mg, 3.18 mmol). The mixture was irradiated in a
10 microwave reactor to 110 °C for 30 minutes. The mixture was cooled to room temperature, and the resin filtered off through Celite. The filtrate was then concentrated and the crude thus obtained was purified by column chromatography on silica using 50 – 100 % gradient elution of ethylacetate in petroleum ether to afford the title compound. ¹H NMR (400MHz, DMSO-*d*₆): δ. 8.40 (d, *J* = 2.4 Hz, 1H), 8.23 – 8.20 (m, 1H), 8.15 – 8.12 (m, 1H), 7.90 (s, 1H), 7.66 – 7.63 (m, 2H), 7.62 – 7.59 (m, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 5.05 (d, *J* = 5.5 Hz, 1H), 4.57 – 4.43 (m, 3H),
15 3.92 – 3.86 (m, 2H), 3.75 – 3.62 (m, 3H), 3.48 – 3.44 (m, 2H), 3.38 – 3.31 (m, 1H), 3.10 – 3.05 (m, 1H), 1.91 – 1.81 (m, 1H), 1.64 – 1.61 (m, 1H) ppm. LRMS C₂₄H₂₄ClN₂O₃: calc'd 423.9, obs 423.2 (M+H)⁺.

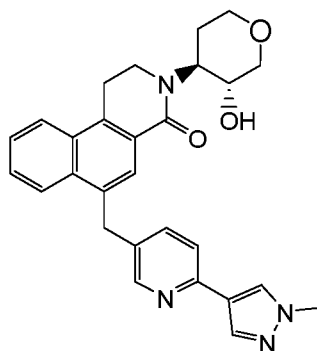
EXAMPLE 4



6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one

Utilizing the procedures described in Example 1, substituting Intermediate 2 for methyl 4-bromo-1-hydroxy-2-naphthoate, the title compound was obtained: ^1H NMR (400MHz, DMSO- d_6): δ . 8.29 – 8.28 (m, 1H), 7.61 – 7.58 (m, 1H), 7.50 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.57 (br s, 1H), 4.25 – 4.15 (m, 1H), 3.97 (s, 2H), 3.55 – 3.45 (m, 1H), 3.41 – 3.40 (m, 2H), 2.86 – 2.79 (m, 5H), 2.74 – 2.67 (m, 1H), 2.07 – 2.00 (m, 2H), 1.98 – 1.91 (m, 1H), 1.70 – 1.60 (m, 2H), 1.54 – 1.46 (m, 2H), 1.30 – 1.20 (m, 3H) ppm. LRMS $\text{C}_{24}\text{H}_{28}\text{ClN}_2\text{O}_2$: calc'd 411.2, obs 411.2 (M+H) $^+$.

EXAMPLE 5

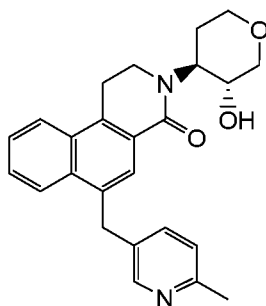


3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one

To a stirred solution of 6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one (Example 3, 50 mg, 0.12 mmol) in 4:1 mixture of 1,4-dioxane (4 mL) and water (1 mL) under an atmosphere of nitrogen were added sodium carbonate (37 mg, 0.35 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (74 mg, 0.35 mmol) at room temperature. The mixture was sparged under nitrogen for 10 minutes, tetrakis(triphenylphosphine)-palladium(0) (27 mg,

0.024 mmol) was added and again the mixture was sparged under nitrogen for 5 minutes. The mixture was heated to 90 °C for 16 hours, cooled to ambient temperature, and diluted with water (10 mL). The mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were washed with brine (10 mL), dried with sodium sulfate, filtered and concentrated in vacuo. The residue was purified by preparative reverse phase HPLC (90:10 to 0:100; water containing 0.1% formic acid : acetonitrile containing 0.1% formic acid) to provide the title compound. ¹H NMR (400MHz, DMSO-d₆): δ. 8.47 (s, 1H), 8.23 – 8.17 (m, 2H), 7.91 (s, 2H), 7.66 – 7.63 (m, 2H), 7.51 (s, 2H), 5.09 – 5.03 (m, 1H), 4.50 – 4.43 (m, 3H), 3.99 – 3.86 (m, 5 H), 3.71 – 3.68 (m, 2H), 3.65 – 3.63 (m, 2H), 3.46 – 3.38 (m, 2H), 3.09 – 3.04 (m, 1 H), 1.88 – 1.84 (m, 1H), 1.65 – 1.62 (m, 1H) ppm. LRMS C₂₈H₂₉N₄O₃: calc'd 469.2, obs 469.4 (M+H)⁺.

EXAMPLE 6



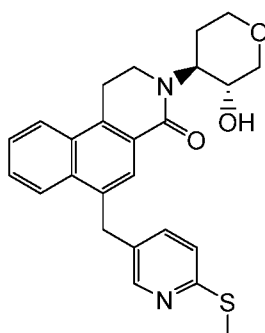
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one

To a stirred solution of 6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one (Example 1, 100 mg, 0.236 mmol) in DMF (5 mL) under an atmosphere of nitrogen were added tetramethyltin (423 mg, 2.36 mmol) and bis(triphenylphosphine)palladium(II) dichloride (33.2 mg, 0.047 mmol) at room temperature. The resultant solution was heated to 100 °C for 4 hours. The mixture was cooled to 0 °C, diluted with cold water (20 mL), extracted with ethyl acetate (2 x 70 mL). The combined organic extracts were washed with cold water (20 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 - 100 % ethyl acetate in petroleum ether) and then 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 provide the title compound. ¹H NMR (400MHz,

DMSO- d_6): δ . 8.40 – 8.39 (m, 1H), 8.21 – 8.18 (m, 1H), 8.14 – 8.08 (m, 1H), 7.86 (s, 1H), 7.64 – 7.60 (m, 2H), 7.43 – 7.40 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 5.04 (bs, 1H), 4.49 – 4.43 (m, 3H), 3.90 – 3.85 (m, 2H), 3.73 – 3.58 (m, 3H), 3.49 – 3.45 (m, 3H), 3.08 – 3.03 (m, 1H), 2.37 (s, 3H), 1.89 – 1.81 (m, 1H), 1.64 – 1.60 (m, 1H) ppm. LRMS $C_{25}H_{27}N_2O_3$: calc'd 403.2, obs 403.4

5 (M+H)⁺.

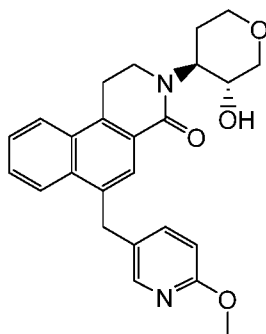
EXAMPLE 7



3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one

10 To a stirred solution of 6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one (Example 1, 100 mg, 0.236 mmol) in *N*-methylpyrrolidinone (2 mL) was added sodium thiomethoxide (49.7 mg, 0.709 mmol). The vessel was sealed and then heated at 95 °C for 3 hours. The mixture was cooled to room temperature and the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (0 - 10% methanol in dichloromethane) and then 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 provide the title compound. ¹H NMR (400MHz, DMSO- d_6): δ . 8.41 (d, J = 1.9 Hz, 1H), 8.22 – 8.20 (m, 1H), 8.17 – 8.14 (m, 1H), 7.87 (s, 1H), 7.65 – 7.63 (m, 2H), 7.43 – 7.40 (m, 1H), 7.19 (d, J = 8.3 Hz, 1H), 5.03 (d, J = 5.6 Hz, 1H), 4.49 – 4.43 (m, 3H), 3.91 – 3.85 (m, 2H), 3.74 – 3.61 (m, 3H), 3.47 – 3.35 (m, 2H), 3.28 – 3.24 (m, 1H), 3.09 – 3.04 (m, 1H), 2.46 (s, 3H), 1.91 – 1.80 (m, 1H), 1.65 – 1.58 (m, 1H) ppm. LRMS $C_{25}H_{27}N_2O_3S$: calc'd 435.2, obs 435.4 (M+H)⁺.

EXAMPLE 8



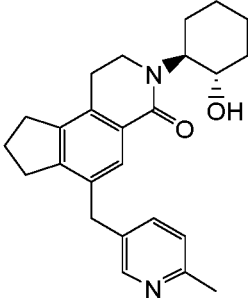
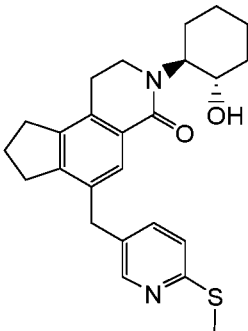
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one

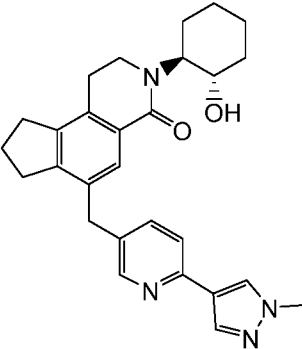
To a stirred solution of 6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one (Example 1, 100 mg, 0.236 mmol) in *N*-methylpyrrolidinone (2 mL) was added sodium methoxide (63.9 mg, 1.18 mmol). The vessel was sealed and then heated at 140 °C for 3 hours. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 – 10 % methanol in dichloromethane) to provide the title compound. ¹H NMR (400MHz, DMSO-d₆): δ. 8.21 – 8.19 (m, 2H), 8.18 – 8.13 (m, 1H), 7.86 – 7.85 (m, 1H), 7.66 – 7.63 (m, 2H), 7.49 – 7.45 (m, 1H), 6.73 – 6.70 (m, 1H), 5.03 – 5.01 (m, 1H), 4.46 – 4.40 (m, 3H), 3.90 – 3.87 (m, 2H), 3.81 – 3.79 (m, 3H), 3.70 – 3.60 (m, 3H), 3.45 – 3.36 (m, 3H), 3.09 – 3.04 (m, 1H), 1.88 – 1.81 (m, 1H), 1.65 – 1.61 (m, 1H) ppm. LRMS C₂₅H₂₇N₂O₄: calc'd 419.2, obs 419.4 (M+H)⁺.

TABLE 1

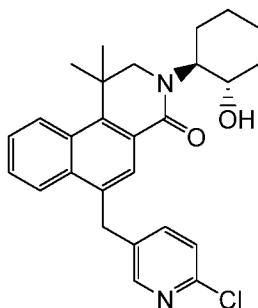
Utilizing the procedures described in Examples 5-8, substituting Example 4 [6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one] for Example 1 [6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one], the following compounds were prepared.

Ex.	Structure	Name	¹ H-NMR (400MHz, DMSO-d ₆)	MS (ES+), [M+H] ⁺

9		3-((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-1,2,3,7,8,9-hexahydro-4 <i>H</i> -cyclopenta[<i>f</i>]isoquinolin-4-one	8.29 (s, 1H), 7.47 (s, 1H), 7.39 (dd, <i>J</i> = 7.8, 2.0 Hz, 1H), 7.14 (d, <i>J</i> = 7.6 Hz, 1H), 4.55 (d, <i>J</i> = 5.6 Hz, 1H), 4.25 – 4.15 (m, 1H), 3.90 (s, 2H), 3.45 – 3.39 (m, 3H), 2.84 – 2.72 (m, 5H), 2.66 – 2.55 (m, 1H), 2.40 (s, 3H), 2.05 – 1.90 (m, 4H), 1.63 – 1.52 (m, 5H) ppm	C ₂₅ H ₃₁ N ₂ O ₂ [M+H] calc'd 391.2 obs. 391.2
10		3-((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclohexyl)-6-((6-(methylthio)pyridin-3-yl)methyl)-1,2,3,7,8,9-hexahydro-4 <i>H</i> -cyclopenta[<i>f</i>]isoquinolin-4-one	8.30 (s, 1H), 7.47 (s, 1H), 7.39 (dd, <i>J</i> = 8.0, 2.0 Hz, 1H), 7.20 (d, <i>J</i> = 8.0 Hz, 1H), 4.55 (d, <i>J</i> = 5.2 Hz, 1H), 4.25 – 4.15 (m, 1H), 3.89 (s, 2H), 3.49 – 3.39 (m, 3H), 2.83 – 2.82 (m, 5H), 2.73 – 2.66 (m, 1H), 2.47 (s, 3H), 2.01 – 1.99 (m, 2H), 1.95 – 1.90 (m, 1H), 1.65 – 1.60 (m, 2H), 1.56 – 1.45 (m, 2H), 1.23 – 1.21 (m, 3H) ppm	C ₂₅ H ₃₁ N ₂ O ₂ S [M+H] calc'd 423.2 obs. 423.2

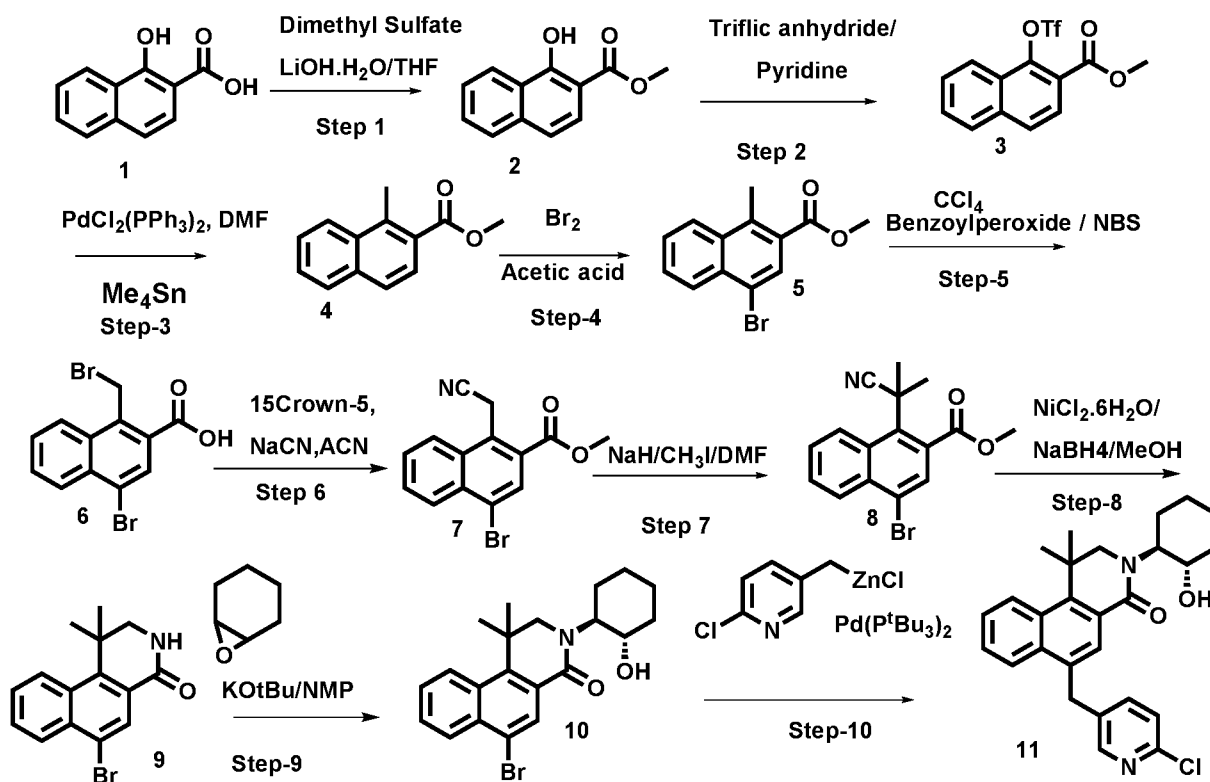
11		3-((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)methyl)-1,2,3,7,8,9-hexahydro-4 <i>H</i> -cyclopenta[<i>f</i>]isoquinolin-4-one	8.36 (d, <i>J</i> = 1.6 Hz, 1H), 8.20 (s, 1H), 7.92 (s, 1H), 7.54 – 7.47 (m, 3H), 4.55 (d, <i>J</i> = 5.2 Hz, 1H), 4.25 – 4.15 (m, 1H), 3.93 (s, 2H), 3.86 (s, 3H), 3.53 – 3.43 (m, 1H), 3.40 – 3.30 (m, 2H), 2.85 – 2.80 (m, 5H), 2.74 – 2.67 (m, 1H), 2.07 – 2.00 (m, 2H), 1.95 – 1.89 (m, 1H), 2.67 – 2.61 (m, 2H), 1.56 – 1.45 (m, 2H), 1.25 – 1.21 (m, 3H) ppm	C ₂₈ H ₃₃ N ₄ O ₂ [M+H] calc'd 457.3 obs. 457.2
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EXAMPLE 12



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

5



Step 1: Preparation of methyl 1-hydroxy-2-naphthoate

To a stirred solution of 1-hydroxy-2-naphthoic acid (5.0 g, 26 mmol) in THF (25 mL) at room temperature was added lithium hydroxide monohydrate (1.1 g, 26 mmol). The mixture was stirred for 30 minutes followed by the addition of dimethyl sulfate (2.5 mL, 26 mmol). The mixture was then refluxed for 3 hours, cooled to room temperature, and concentrated in vacuo. The residue was diluted with saturated aqueous NaHCO_3 and extracted with diethyl ether. The combined organic extracts were washed with water, dried with sodium sulfate, filtered, and concentrated under reduced pressure to provide the title compound, which gave a proton NMR spectra consistent with theory.

Step 2: Preparation of methyl 1-(((trifluoromethyl)sulfonyl)oxy)-2-naphthoate

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 trifluoromethanesulfonic anhydride (1.25 mL, 7.42 mmol). The mixture was warmed to room temperature and stirred for 1 hour. The mixture was cooled to 0°C , diluted with ice-cold water (25 mL) and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried with sodium sulfate, filtered, and concentrated

under reduced pressure. The residue was purified by silica gel column chromatography (10 – 20 % ethyl acetate in petroleum ether) to provide the title compound which gave a proton NMR spectra consistent with theory.

Step 3: Preparation of methyl 1-methyl-2-naphthoate

5 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, 1.31 mmol). The resultant solution was heated at 110 °C for 3 hours, cooled to room temperature, diluted with cold water, and extracted with ethyl acetate. The
10 combined organic extracts were washed with cold water, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 3 % ethyl acetate in petroleum ether) to provide the title compound which gave a proton NMR spectra consistent with theory.

Step 4: Preparation of methyl 4-bromo-1-methyl-2-naphthoate

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

Step 5: Preparation of 4-bromo-1-(bromomethyl)-2-naphthoic acid

 To a solution of methyl 4-bromo-1-methyl-2-naphthoate (450 mg, 1.61 mmol) in CCl₄ (8
25 mL) was added *N*-Bromosuccinimide (430 mg, 2.42 mmol) and benzoyl peroxide (46.9 mg, 0.193 mmol) under nitrogen at room temperature. The mixture was refluxed for 3 hours, cooled to room temperature and diluted with ethylacetate (10 mL). The organic extract was washed with water, aqueous saturated sodium bicarbonate, and brine. The extract was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel
30 column chromatography (0 - 3 % ethyl acetate in petroleum ether) to provide the title compound which gave a proton NMR spectra consistent with theory.

Step 6: Preparation of methyl 4-bromo-1-(cyanomethyl)-2-naphthoate

To a stirred solution of methyl 4-bromo-1-(bromomethyl)-2-naphthoate (5.00 g, 13.9 mmol) in acetonitrile (20 mL) was treated with NaCN (1.36 g, 27.9 mmol) and then 15-Crown-5 (1.53 g, 6.98 mmol). The mixture was stirred for 2 hours at room temperature, treated with water (50 mL) and then extracted with ethylacetate (2 x 300 mL). The combined organic extracts were washed with water (50 mL), dried sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20 % ethyl acetate in petroleum ether) to provide the title compound that gave a mass ion [ES⁺] of 302.2 for [M - H]⁻

Step 7: Preparation of methyl 4-bromo-1-(2-cyanopropan-2-yl)-2-naphthoate

To a stirred solution of methyl 4-bromo-1-(cyanomethyl)-2-naphthoate (1.50 g, 4.93 mmol) in DMF (20 mL) at 0 °C, was added NaH (0.592 g, 14.8 mmol). After stirring at 0 °C for 10 minutes, methyl iodide (0.925 mL, 14.80 mmol) slowly added and the mixture was stirred at 0 °C for an additional 1 hour. The mixture was treated with ice-cold water and then extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried with sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (0 – 10 % ethyl acetate in petroleum ether) to provide the title compound.

Step 8: Preparation of 6-bromo-1,1-dimethyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one

To a stirred solution of methyl 4-bromo-1-(2-cyanopropan-2-yl)-2-naphthoate (1.50 g, 4.52 mmol) in MeOH (20 mL) at 0 °C, was added nickel(II) chloride hexahydrate (0.537 g, 2.26 mmol). After stirring at 0 °C for 10 minutes, sodium borohydride (0.854 g, 22.58 mmol) was added portion wise. The mixture was stirred at room temperature for 4 hours, treated with ice-cold water (50 mL), and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with brine, dried with sodium sulfate, filtered, and concentrated under pressure. The residue was purified by silica gel column chromatography (0 – 30 % ethyl acetate in petroleum ether) to provide the title compound that gave a mass ion [ES⁺] of (⁸¹Br)306.2 for [M + H]⁺

Step 9: Preparation of (±)-*trans*-6-bromo-3-(2-hydroxycyclohexyl)-1,1-dimethyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one

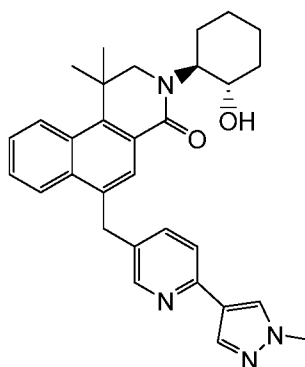
To a stirred solution of 6-bromo-1,1-dimethyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one (0.200 g, 0.658 mmol) in NMP (10 mL) was added KO^tBu (0.369 g, 3.29 mmol). After stirring at room temperature for 10 minutes, 7-oxabicyclo[4.1.0]heptane (0.323 g, 3.29 mmol) was added slowly. The mixture was heated at 100 °C for 2 hours, cooled to room temperature, treated with

ice-cold water, and then extracted with ethyl acetate (2 x 80 mL). The combined organic extracts were washed with brine (10 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 - 30% ethyl acetate in petroleum ether) to provide the title compound that gave a mass ion [ES⁺] of (⁸¹Br) 402.2 for [M + H]⁺

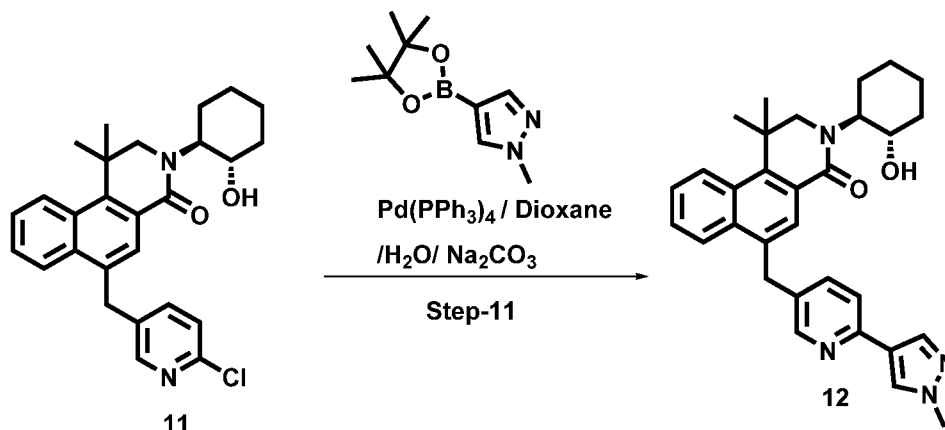
Step 10: Preparation of (±)-*trans*-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1,1-dimethyl-2,3-dihydrobenzo[*f*]isoquinolin-4(1*H*)-one

To a solution of the (±)-*trans*-6-bromo-3-(2-hydroxycyclohexyl)-1,1-dimethyl-2,3-dihydrobenzo[*f*]isoquinolin-4(1*H*)-one (150 mg, 0.373 mmol) in THF (2 mL) at 0 °C was added (2-chloro-5-pyridyl)methylzinc chloride (0.5 M in THF, 1.86 mL, 0.932 mmol), followed by bis(tri-*tert*-butylphosphine)palladium(0) (5.72 mg, 0.011 mmol). The mixture was warmed to room temperature and stirred for 4 hours. The mixture was cooled to 0 °C, treated with water (10 mL), and then diluted with dichloromethane and water. The resultant precipitate was collected via filtration using Celite. The filtrate was extracted with dichloromethane (2x 100 mL) and the combined organic layer was washed with brine (50 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 – 60 % ethyl acetate in petroleum ether) to provide the title compound. ¹H NMR (400MHz, DMSO-*d*₆) δ 8.49 – 8.46 (m, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 8.15 – 8.12 (m, 1H), 7.82 (s, 1H), 7.64 – 7.56 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 1H), 4.62 (d, *J* = 5.6 Hz, 1H), 4.48 (d, *J* = 2.8 Hz, 2H), 4.30 – 4.20 (m, 1H), 3.55 – 3.54 (m, 1H), 3.38 – 3.36 (m, 1H), 3.30 – 3.27 (m, 1H), 1.99 – 1.91 (m, 1H), 1.68 – 1.63 (m, 6 H), 1.55 (s, 3H), 1.30 – 1.15 (m, 4H) ppm. LRMS C₂₇H₃₀ClN₂O₂: calc'd 449.2, obs 449.4 (M+H)⁺.

EXAMPLE 13

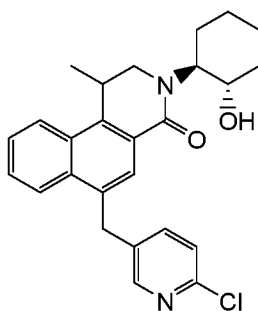


(±)-3-(2-hydroxycyclohexyl)-1,1-dimethyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[*f*]isoquinolin-4(1*H*)-one



Following the procedures described in Example 5, substituting (±)-trans-6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1,1-dimethyl-2,3-dihydrobenzo[*f*]-isoquinolin-4(1*H*)-one (Example 12) for 6-((6-chloropyridin-3-yl)methyl)-3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-2,3-dihydrobenzo[*f*]isoquinolin-4(1*H*)-one (Example 3, the title compound was prepared. ¹H NMR (400MHz, DMSO-*d*₆): δ. 8.48 – 8.46 (m, 2H), 8.20 – 8.17 (m, 2H), 7.92 (s, 1H), 7.84 (s, 1H), 7.62 – 7.55 (m, 2H), 7.53 (s, 2H), 4.61 (d, *J* = 5.6 Hz, 1H), 4.44 (d, *J* = 2.4 Hz, 2H), 4.30 – 4.20 (m, 1H), 3.86 (s, 3H), 3.55 – 3.53 (m, 1H), 3.44 – 3.40 (m, 1H), 3.33 – 3.30 (m, 1H), 1.99 – 1.91 (m, 1H), 1.70 – 1.63 (m, 7H), 1.54 (s, 3H), 1.33 – 1.24 (m, 3H) ppm. LRMS C₃₁H₃₅N₄O₂: calc'd 495.3, obs 495.4 (M+H)⁺.

EXAMPLE 14



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

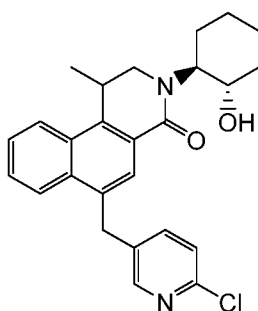
Step 1: Preparation of (±)-methyl 4-bromo-1-(1-cyanoethyl)-2-naphthoate

To a stirred solution of methyl 4-bromo-1-(cyanomethyl)-2-naphthoate (Example 12, 5 Step 7, 2 g, 6.58 mmol) in THF (20 mL) at 0 °C, was added LiHMDS (9.86 mL, 1M THF, 9.86 mmol). After stirring at -78 °C for 10 minutes, methyl iodide (2.05 ml, 32.9 mmol) was added slowly. The mixture was stirred at -78 °C for an additional 2 hours and then treated with aqueous saturated NH₄Cl (20 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated under vacuum. The 10 residue was purified by column chromatography on silica using 0 – 10 % gradient elution of ethylacetate in petroleum ether to yield the title compound that gave a mass ion [ES⁺] of (⁸¹Br) 316.2 for [M - H]⁻

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

Utilizing the procedures described in Example 12, substituting (±)-methyl 4-bromo-1-(1- 15 cyanoethyl)-2-naphthoate for methyl 4-bromo-1-(2-cyanopropan-2-yl)-2-naphthoate, the title compound was obtained. ¹H NMR (400MHz, DMSO-d₆): δ.8.42 – 8.41 (m, 1H), 8.25 – 8.22(m, 1H), 8.15 – 8.04 (m, 1H), 7.84 (s, 1H), 7.66 – 7.60 (m, 3H), 7.42 – 7.39 (m, 1H), 4.65 (d, J = 5.2 Hz, 1H), 4.50 (d, J = 8.7 Hz, 2H), 4.37 – 4.34 (m, 1H), 3.85 – 3.78 (m, 1H), 3.71 – 3.67 (m, 1H), 20 3.54 – 3.48 (m, 2H), 1.99 – 1.91 (m, 1H), 1.73 – 1.68 (m, 2H), 1.60 – 1.54 (m, 2H), 1.30 – 1.28 (m, 2H), 1.26 – 1.24 (m, 4H) ppm. LRMS C₂₆H₂₈ClN₂O₂: calc'd 435.2, obs 435.2 (M+H)⁺.

EXAMPLE 15

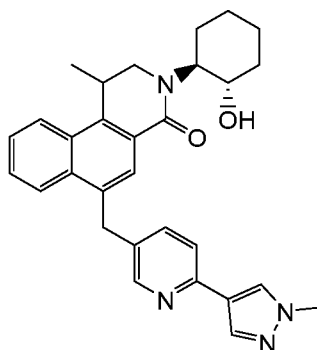


6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one; Peak 2

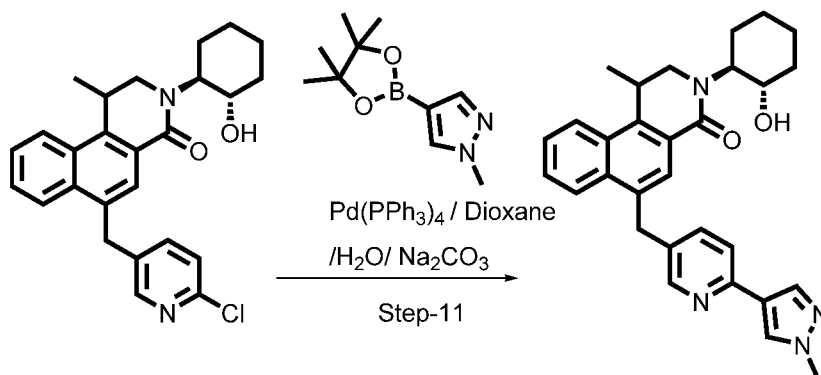
25

Utilizing the procedures described in Example 14, the title compound was obtained. ¹H NMR (400MHz, D₂O): δ.8.36 (s, 1H), 8.21 – 8.18 (m, 1H), 8.10 – 8.08 (m, 1H), 7.82 (s, 1H), 7.65 – 7.58 (m, 3H), 7.38 (d, *J* = 8.2 Hz, 1H), 4.45 (d, *J* = 5.9 Hz, 2H), 4.21 – 4.17 (m, 1H), 3.85 – 3.80 (m, 1H), 3.78 – 3.50 (m, 2H), 3.55 – 3.40 (m, 1H), 1.97 – 1.95 (m, 1H), 1.65 – 1.60 (m, 3H), 1.51 – 1.48 (m, 1H), 1.32 – 1.24 (m, 6H) ppm. LRMS C₂₆H₂₈ClN₂O₂: calc'd 435.2, obs 435.4 (M+H)⁺.

EXAMPLE 16



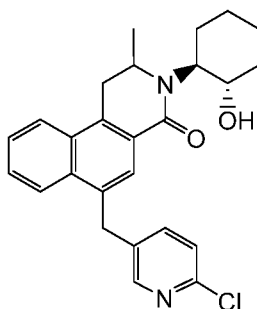
(±)-trans-3-(2-hydroxycyclohexyl)-1-methyl-6-(((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one



Following the procedures described in Example 5, substituting (±)-trans-6-(((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one (Example 14) for 6-(((6-chloropyridin-3-yl)methyl)-3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one (Example 3), the title compound was obtained. ¹H NMR (400MHz, D₂O): δ.8.54 (s, 1H), 8.35 (s, 1H), 8.23 – 8.15 (m, 2H), 8.06 (s, 1H), 7.92 – 7.90 (m, 1H), 7.84 (s, 2H), 7.65 – 7.63 (m, 2H), 4.53 (d, *J* = 7.0 Hz, 2H), 4.38 – 4.32

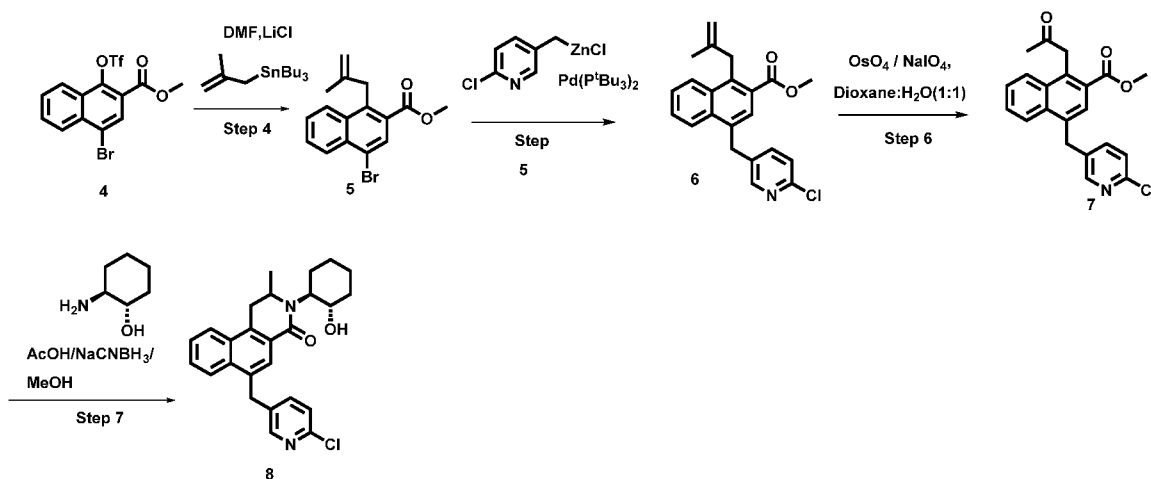
(m, 1H), 3.87 (s, 3H), 3.85 – 3.63 (m, 3H), 3.61 – 3.58 (m, 2H), 1.92 – 1.90 (m, 1H), 1.67 – 1.56 (m, 4H), 1.24 – 1.13 (m, 6H). LRMS $C_{30}H_{33}N_4O_2$: calc'd 481.3, obs 481.4 (M+H)⁺.

EXAMPLE 17



5

6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one



Step 4: Preparation of methyl 4-bromo-1-(2-methylallyl)-2-naphthoate

To a stirred solution of methyl 4-bromo-1-((trifluoromethyl)sulfonyl)oxy)-2-naphthoate (2.00 g, Example 1[Step 3, Compound 4], 4.84 mmol) in DMF (5 mL) was added lithium chloride (1.02 g, 24.2 mmol), tetrakis(triphenylphosphine)palladium(0) (0.280 g, 0.242 mmol) followed by methylallyltri-n-butyltin (2.00 g, 5.81 mmol) at room temperature. The resultant mixture was heated at 100 °C for 1 hour, cooled to room temperature, diluted with cold water (20 mL), and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with cold water, dried with sodium sulfate, filtered, and concentrated under vacuum.

The residue was purified by silica gel column chromatography (0 – 2 % ethyl acetate in petroleum ether) to provide the title compound that gave a mass ion [ES+] of (⁸¹Br) 321.2 for [M + H]⁺

Step 5: Preparation of methyl 4-((6-chloropyridin-3-yl)methyl)-1-(2-methylallyl)-2-naphthoate

5 To a solution of methyl 4-bromo-1-(2-methylallyl)-2-naphthoate (500 mg, 1.566 mmol) in THF (5 ml) at 0 °C was added (2-chloro-5-pyridyl)methylzinc chloride (7.83 ml, 3.92 mmol), followed by bis(tri-*tert*-butylphosphine)palladium(0) (24.0 mg, 0.047 mmol). The mixture was warmed to ambient temperature and stirred 2 hours. The mixture was cooled to 0 °C, treated with water (10 mL), and diluted with dichloromethane. A solid precipitated and the mixture was
10 filtered through a bed of celite. The filtrate was extracted with dichloromethane and the combined organic extracts were dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (10 - 20% ethyl acetate in petroleum ether) to provide the title compound

Step 6: Preparation of methyl 4-((6-chloropyridin-3-yl)methyl)-1-(2-oxopropyl)-2-naphthoate

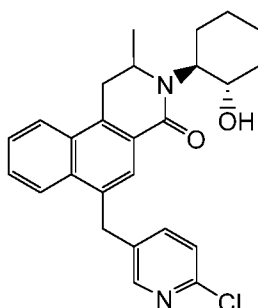
15 To a stirred solution of methyl 4-((6-chloropyridin-3-yl)methyl)-1-(2-methylallyl)-2-naphthoate (250 mg, 0.683 mmol) in 1:1 mixture of 1,4 -dioxane (5 mL) and water (5 mL) at room temperature was added sodium periodate (438 mg, 2.05 mmol) followed by osmium tetroxide (0.343 mL, 0.027 mmol). The mixture was stirred at ambient temperature for 16 hours, cooled to 0 °C, diluted with ice-cold water (5 mL) and extracted with ethyl acetate (2 x 80 mL).
20 The combined organic extracts were washed with brine (10 mL), dried with sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (10 – 20 % ethyl acetate in petroleum ether) to provide the title compound that gave a mass ion [ES+] of 368.4 for [M + H]⁺

Step 7: Preparation of 6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[*f*]isoquinolin-4(1*H*)-one:

25 To a solution of methyl 4-((6-chloropyridin-3-yl)methyl)-1-(2-oxopropyl)-2-naphthoate (50 mg, 0.136 mmol) in MeOH (5 mL) at room temperature was added (1*S*,2*S*)-2-aminocyclohexanol (31.3 mg, 0.272 mmol) and AcOH (0.016 mL, 0.272 mmol). The mixture was stirred for 5 minutes and then treated with sodium cyanoborohydride (42.7 mg, 0.680
30 mmol). The vessel was sealed and then heated in microwave reactor to 100 °C for 1 hour. The mixture was cooled to room temperature and concentrated in vacuo. To the residue was added ice water and the mixture was extracted with dichloromethane. The combined organic extracts

were washed with water (10 mL), dried with sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by preparative reverse phase HPLC (90:10 to 0:100; water containing 0.1% formic acid : acetonitrile containing 0.1% formic acid) to afford the title compound as a mixture of diastereomers. ¹H NMR (400MHz, DMSO-d₆): δ. 8.4 (d, *J* = 2.4 Hz, 1H), 8.22 – 8.19 (m, 1H), 8.14 – 8.11 (m, 1H), 7.83 (d, *J* = 14.8 Hz, 1H), 7.65 – 7.61 (m, 3H), 7.42 (d, *J* = 8.0 Hz, 1H), 4.63 – 4.59 (m, 1H), 4.51 (s, 2H), 4.14 – 4.02 (m, 2H), 3.72 – 3.56 (m, 1H), 3.40 – 2.39 (m, 2H), 2.05 – 1.95 (m, 1H), 1.78 – 1.62 (m, 3H), 1.28 – 1.25 (m, 4H), 1.14 – 1.08 (m, 3H) ppm. LRMS C₂₆H₂₈ClN₂O₂: calc'd 435.2, obs 435.4 (M+H)⁺.

EXAMPLES 18 AND 19



6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one (Diastereomers A and B)

The title compound of Example 17 was further purified by separation using a Kromasil C18 (250x19mm) 7 micron column [mobile phase of A: 0.1%TFA in water, B:

100%Acetonitrile; Gradient: 90:10 to 0:100 (A:B); Flow rate: 15mL/min] to provide Diastereomers A and B:

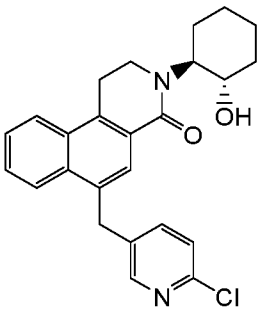
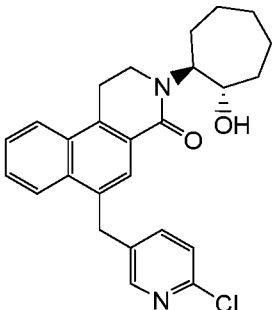
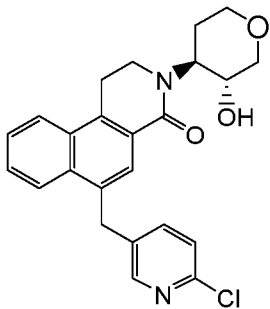
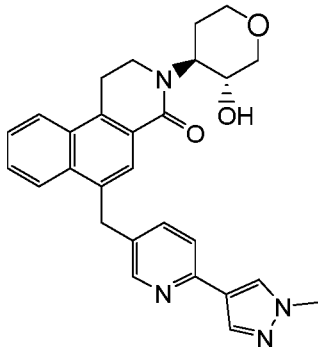
Example 18, Diastereomer A: ¹H NMR (400MHz, DMSO-d₆): δ. 8.41 (d, *J* = 2.0 Hz, 1H), 8.21 – 8.18 (m, 1H), 8.14 – 8.11 (m, 1H), 7.81 (s, 1H), 7.66 – 7.61 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 1H), 4.67 – 4.63 (m, 1H), 4.55 (s, 2H), 4.07 – 4.06 (m, 2H), 3.76 – 3.74 (m, 1H), 3.49 – 3.40 (m, 2H), 2.02 – 1.95 (m, 1H), 1.65 – 1.62 (m, 4H), 1.28 – 1.25 (m, 3H), 1.14 – 1.08 (m, 3H) ppm. LRMS C₂₆H₂₈ClN₂O₂: calc'd 435.2, obs 435.9 (M+H)⁺.

Example 19, Diastereomer B: ¹H NMR (400MHz, DMSO-d₆): δ. 8.41 (d, *J* = 2.4 Hz, 1H), 8.22 – 8.19 (m, 1H), 8.14 – 8.11 (m, 1H), 7.85 (s, 1H), 7.66 – 7.61 (m, 3H), 7.41 (d, *J* = 8.4 Hz, 1H), 4.65 – 4.62 (m, 1H), 4.51 (s, 2H), 4.20 – 4.10 (m, 2H), 3.80 – 3.68 (m, 1H), 3.49 – 3.36 (m, 2H),

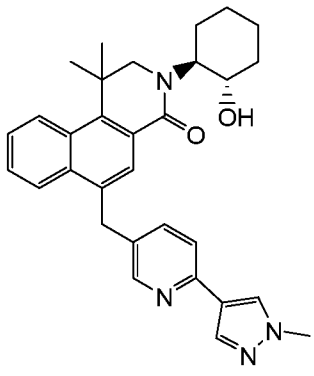
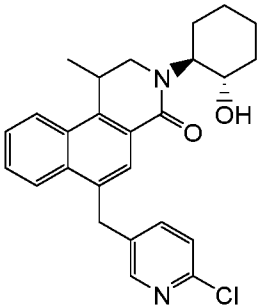
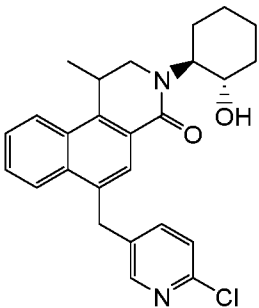
1.99 – 1.95 (m, 1H), 1.78 – 1.71 (m, 2H), 1.59 – 1.54 (m, 1H), 1.28 – 1.24 (m, 4H), 1.09 (d, J = 6.4 Hz, 3H) ppm. LRMS $C_{26}H_{28}ClN_2O_2$: calc'd 435.2, obs 435.4 (M+H)⁺.

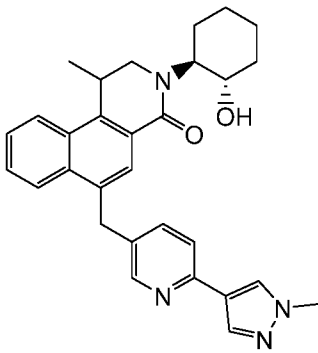
Utilizing the procedures described in the foregoing Examples, the following compounds
5 were prepared.

Ex.	Structure	Name	Molecular Weight
20		6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: $C_{26}H_{27}ClN_2O_2$ Molecular Weight: 434.96
21		6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: $C_{26}H_{27}ClN_2O_2$ Molecular Weight: 434.96
22		6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: $C_{26}H_{27}ClN_2O_2$ Molecular Weight: 434.96

23		6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxy-cyclohexyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: C ₂₅ H ₂₅ ClN ₂ O ₂ Molecular Weight: 420.94
24		6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxy-cycloheptyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: C ₂₆ H ₂₇ ClN ₂ O ₂ Molecular Weight: 434.96
25		6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: C ₂₄ H ₂₃ ClN ₂ O ₃ Molecular Weight: 422.91
26		3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: C ₂₈ H ₂₈ N ₄ O ₃ Molecular Weight: 468.56

27		3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-(((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: C ₂₅ H ₂₆ N ₂ O ₃ Molecular Weight: 402.49
28		3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-(((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: C ₂₅ H ₂₆ N ₂ O ₃ S Molecular Weight: 434.55
29		3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-(((6-methoxypyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one	Chemical Formula: C ₂₅ H ₂₆ N ₂ O ₄ Molecular Weight: 418.49
30		6-(((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1,1-dimethyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one [trans racemic]	Chemical Formula: C ₂₇ H ₂₉ ClN ₂ O ₂ Molecular Weight: 448.99

31		3-((2-hydroxycyclohexyl)-1,1-dimethyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one [trans racemic]	Chemical Formula: C ₃₁ H ₃₄ N ₄ O ₂ Molecular Weight: 494.64
32		6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one [Racemic Trans]	Chemical Formula: C ₂₆ H ₂₇ ClN ₂ O ₂ Molecular Weight: 434.96
33		6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one [trans racemic]	Chemical Formula: C ₂₆ H ₂₇ ClN ₂ O ₂ Molecular Weight: 434.96

34		3-(2-hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one [trans racemic]	Chemical Formula: C ₃₀ H ₃₂ N ₄ O ₂ Molecular Weight: 480.61
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ASSAY PROTOCOL

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 Ca²⁺ levels using FLIPR.

Compounds are prepared and subjected to a preincubation period of 4 min. Thereafter, a single EC₂₀ concentration of acetylcholine is added to each well (3 nM final). The intracellular Ca²⁺ 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 μ L) 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 1 mg/ml Geneticin, are added. For M2Gqi5CHOnfat and M4Gqi5CHOnfat cells, an additional 600 ug/ml hygromycin is added.

Equipment: 384 well plate, 120 μ L addition plate; 96-well Whatman 2 ml Uniplate Incubator, 37°C, 5% CO₂; 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: Flasks Balanced Salt Solution, with 20 mM Hepes, 2.5 mM Probenecid (Sigma P-8761) first dissolved in 1N 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)

- 5 Concentration of 2 μ M in buffer for a final concentration of 1 μ M in Assay. 20% Pluronic Acid Solution stock, with concentration of 0.04% in Buffer, 0.02% in Assay.

65 μ L of 2 mM Fluo-4AM are mixed with 130 μ L of 20% Pluronic Acid. The resulting solution and 650 μ L 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 μ M. Acetylcholine: 10 mM in
10 water, working stock at both 20 μ M and 30 μ M in assay buffer, final concentration of 10 μ M. This is used to check the maximum stimulation of the CHOK1/hM1 cells. 20 μ M (2 $\times$) acetylcholine is added in the preincubation part of the assay, and the 30 μ M (3 $\times$) stock is added in the second part. (EC20) Acetylcholine: 10 mM in water, working stock of 9 nM (3 $\times$), and final concentration in assay is 3 nM. This is used after the preincubation with test compounds.

- 15 Addition of the EC20 Acetylcholine to each well with a test compound will ascertain any modulator activity. 24 wells contain 3 nM Acetylcholine alone as a control.

Determining Activity of Compounds:

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

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

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

After 60 min, the cells are washed three times with 100 μ L of buffer, leaving 30 μ L 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.

Four minutes 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 publication WO2004/073639 (U.S. Patent Publication US2006/0233843).

In particular, the compounds of the following examples had activity in the aforementioned assay, generally with an IP (inflection point) of 10 μ M (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 as described herein are provided in the table below.

The following table shows representative data for the compounds of the Examples as positive allosteric modulators of the M1 receptor as determined by the assays described herein. Such results are indicative of the intrinsic activity of the compounds for use as positive allosteric modulators of the M1 receptor.

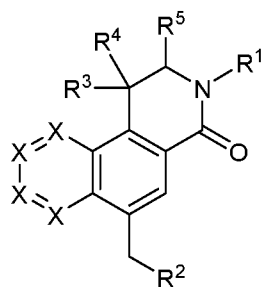
Ex. #	M1 Pot Nf Hu Ace V1 4p Ip Geo	M1 Pot Hf Hu Ace V3 4p Ip Geo
1	11	-
2	101	-
3	-	10
4	-	52
5	-	40
6	-	33
7	-	14
8	-	36
9	-	64
10	-	85

11	-	80
12	91	211
13	61	-
14	346	691
15	81	239
16	263	274
17	57	119
18	354	211
19	70	-
20	57	120
21	354	-
22	70	-
23	11	-
24	101	-
25	-	10
26	-	40
27	-	33
28	-	15
29	-	36
30	91	211
31	61	-
32	346	692
33	81	239
34	263	275

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

WHAT IS CLAIMED IS:

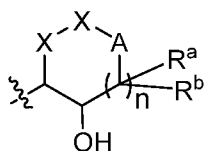
1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is



wherein: A is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$ or $-\text{N}(\text{R}')-$,

R' is hydrogen or $-\text{C}_{1-6}$ alkyl,

each of R^a and R^b is independently hydrogen or halogen, and

n is 0, 1 or 2;

each occurrence of X is independently selected from the group of $-\text{CH}_2-$, $-\text{CH}=-$, $-\text{NH}-$ and $-\text{N}=-$,

or one of the X may be absent;

R^2 is selected from the group consisting of:

(1) a C_{5-10} heterocyclyl, and

(2) aryl;

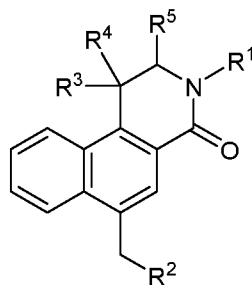
wherein each of the C_{5-10} heterocyclyl of (1) and the aryl of (2) is unsubstituted or substituted with 1 to 3 groups independently selected from halogen, $-\text{C}_{1-6}$ alkyl, $-\text{O}-\text{C}_{1-6}$ alkyl, $-\text{S}-\text{C}_{1-6}$ alkyl, and C_{5-10} heteroaryl which is unsubstituted or substituted with halogen or $-\text{C}_{1-6}$ alkyl; and

R^3 , R^4 and R^5 are independently selected from the group consisting of:

- (1) hydrogen,
 (2) halogen, and
 (3) $-C_{1-10}$ alkyl, said alkyl is unsubstituted or substituted with 1 to 3 groups independently selected from oxo and $-OH$.

5

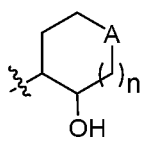
2. The compound of Claim 1 of the formula (Ia):



(Ia)

10 or a pharmaceutically acceptable salt thereof, wherein:

R^1 is:



wherein A is $-CH_2-$ or $-O-$ or $-S-$, and

n is 0, 1 or 2;

15

R^2 is selected from the group consisting of:

- (1) a C_{5-10} heterocyclyl, said heterocyclyl is unsubstituted or substituted with 1 to 3 groups independently selected from halogen, $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, and C_{5-10} heteroaryl unsubstituted or substituted with $-C_{1-6}$ alkyl; and
 (2) aryl, said aryl is unsubstituted or substituted with 1 to 3 groups independently selected from halogen, $-C_{1-6}$ alkyl and C_{5-10} heteroaryl, said heteroaryl is unsubstituted or substituted with $-C_{1-6}$ alkyl;

20

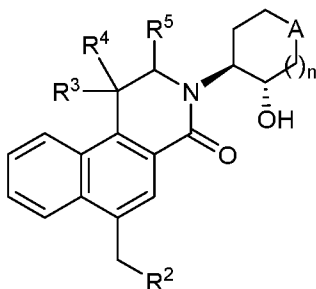
R^3 , R^4 and R^5 are independently selected from the group consisting of:

25

- (1) hydrogen, and

(2) $-C_{1-10}$ alkyl, said alkyl is unsubstituted or substituted with 1 to 3 groups independently selected from oxo and $-OH$.

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



(Ib)

or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 1 wherein:

A is $-\text{CH}_2-$;

R² is a phenyl or C₅₋₆heteroaryl, each of said phenyl and heteroaryl is unsubstituted or substituted with halogen, methyl, ethyl, propyl, -O-methyl, -O-ethyl, -O-propyl, -S-methyl, -S-ethyl, -S-propyl, pyridyl or pyrazolyl; said pyridyl and pyrazolyl is unsubstituted or substituted with methyl or ethyl;

R³, R⁴ and R⁵ are independently hydrogen, methyl, ethyl, propyl, -CH₂CH₂-OH, -C(O)CH₃, or -CH₂C(O)H; and
n is 1 or 2.

5. The compound of Claim 1 wherein R² is pyridyl, said pyridyl is unsubstituted or substituted with halo, another pyridyl or pyrazolyl, each of which is unsubstituted or substituted with a methyl, ethyl or propyl.

6. The compound of Claim 1 wherein R³, R⁴ and R⁵ are independently hydrogen or –C₁₋₆ alkyl.

7. The compound of Claim 1 wherein R³, R⁴ and R⁵ are independently hydrogen or methyl.

8. A compound which is selected from the group consisting of:

- 6-(((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 6-(((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycycloheptyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 5 6-(((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 6-(((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one;
- 10 3-(((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-(((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-(((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 15 3-(((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-(((1S,2S)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one;
- 20 3-(((1S,2S)-2-hydroxycyclohexyl)-6-((6-(methylthio)pyridin-3-yl)methyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one;
- 3-(((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-1,2,3,7,8,9-hexahydro-4H-cyclopenta[f]isoquinolin-4-one;
- trans-6-(((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1,1-dimethyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 25 3-(2-hydroxycyclohexyl)-1,1-dimethyl-6-(((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- trans-6-(((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one ;
- 30 3-(2-hydroxycyclohexyl)-1-methyl-6-(((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;

- 6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 5 6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycycloheptyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one
- 6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 10 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 15 3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one
- 6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1,1-dimethyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 3-(2-hydroxycyclohexyl)-1,1-dimethyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 20 6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- 6-((6-chloropyridin-3-yl)methyl)-3-(2-hydroxycyclohexyl)-1-methyl-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one; and
- 25 3-(2-hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[f]isoquinolin-4(1H)-one;
- or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1-8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition 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, comprising a therapeutically effective amount of a compound of any of claims 1-8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

11. Use of a pharmaceutical composition of any of Claims 9-10 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.

12. Use of a compound of any of Claims 1-8, 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.

13. 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 an effective amount of a compound of any of Claims 1-8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/38889

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 31/473; C07D 217/24 (2017.01)
 CPC - C07D217/24; C07D217/00; A61K31/473

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.
Y	WO 2012/003147 A1 (MERCK SHARP & DOHME CORP.) 05 January 2012 (05.01.2012) pg 1, ln 5 9; pg 10, ln 26 to pg 11, ln 10; pg 34, ln 20-25, Example 6; pg 76, ln 24-29; pg 77, Table 2	1-10, 12-13
Y	US 2013/0116272 A1 (KUDUK et al.) 09 May 2013 (09.05.2013) para [009], [0120], Example 1; para [0175], Table 1	1-10, 12-13
A	US 2015/0307451 A1 (TAKEDA PHARMACEUTICAL COMPANY LIMITED) 29 October 2015 (29.10.2015) Entire Document	1-10, 12-13
A	US 2015/0065498 A1 (KUDUK et al.) 05 March 2015 (05.03.2015) Entire Document	1-10, 12-13
A	US 2013/0090352 A1 (GILBERT et al.) 11 April 2013 (11.04.2013) Entire Document	1-10, 12-13
A	US 2011/0201607 A1 (KUDUK et al.) 18 August 2011 (18.08.2011) Entire Document	1-10, 12-13

☐ 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

30 August 2017 (30.08.2017)

Date of mailing of the international search report

26 SEP 2017

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
 P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/38889

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.: 11
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.