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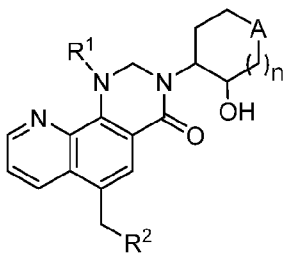
(54) Title: DIHYDROPYRIDO QUINAZOLINE M1 RECEPTOR POSITIVE ALLOSTERIC MODULATORS



(I)

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

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TITLE OF THE INVENTION

DIHYDROPYRIDO QUINAZOLINE M1 RECEPTOR POSITIVE ALLOSTERIC MODULATORS

FIELD OF THE INVENTION

The invention is directed to a class of substituted dihydropyrido quinazoline compounds, their salts, pharmaceutical compositions comprising them and their use in therapy of the human body. In particular, the invention is directed to a class of substituted dihydropyrido quinazoline 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

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 (Aβ). Aβ 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 Aβ in the brain.

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

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

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

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 αAPPs fragment, thereby preventing the formation of the Aβ peptide. Thus, M1 agonists may alter APP processing and enhance αAPPs secretion. *See* Fisher, *Jpn J Pharmacol*, 2000, 84:101-112.

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

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

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

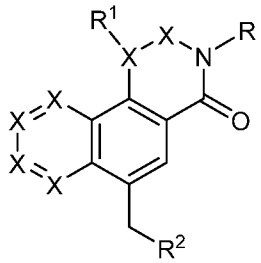
Disclosed herein are novel substituted dihydropyrido quinazoline compounds of generic formulas (I'), (I), (Ia), (Ib) and (Ic) described below, or pharmaceutically acceptable salts thereof, which is useful as M1 receptor positive allosteric modulators.

Also disclosed herein are methods of treating a patient (preferably a human) for diseases or disorders in which the M1 receptor is involved, such as Alzheimer's disease, cognitive impairment, schizophrenia, pain disorders and sleep disorders, by administering to the patient an effective amount of a compound of general formula (I'), (I), (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt thereof. Further disclosed herein are pharmaceutical

compositions which include an effective amount of a compound of formula (I'), (I), (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, and the use of the compounds and pharmaceutical compositions disclosed herein in the treatment of such diseases.

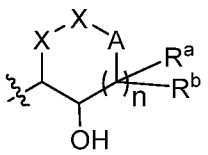
DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, disclosed herein is a compound of formula (I'):



(I'),

or a pharmaceutically acceptable salt thereof, wherein:

R is  ;

A is $-CH_2-$, $-O-$ or $-S-$ or $-N-R'$; R' is hydrogen or $-C_{1-6}$ alkyl;

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

each occurrence of X is independently selected from the group of $-CH_2-$, $-CH-$, -NH- and $-N-$;

R^1 is selected from the group consisting of

(1) hydrogen,

(2) halogen, and

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

R^2 is selected from the group consisting of

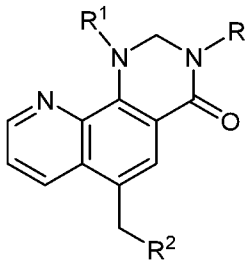
(1) a C_{5-10} heterocyclyl, and

(2) aryl;

wherein each of the C_{5-10} heterocycle of (1) and the aryl of (2) is optionally 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 optionally substituted with halogen or $-C_{1-6}$ alkyl; and

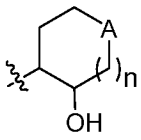
n is 0, 1 or 2.

In one embodiment, a compound disclosed herein is of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R is  ,

A is $-CH_2-$ or –O– or –S-;

R^1 is selected from the group consisting of

(1) hydrogen, and

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

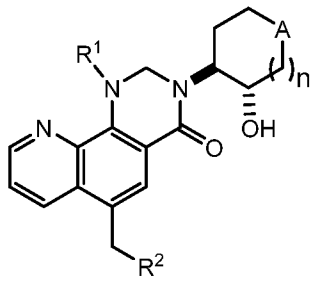
R2 is selected from the group consisting of

(1) a C_{5-10}heterocyclyl, said heterocyclyl is optionally 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 optionally substituted with $-C_{1-6}$ alkyl; and

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

n is 0, 1 or 2.

In one embodiment, a compound of formula (I) is of formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof, wherein each of A, R^1, R^2 and n is as defined above for formula (I).

In a particular embodiment of the compounds of formula (I'), (I) or (Ia):

R^1 is hydrogen or $-C_{1-6}$ alkyl, said alkyl is optionally substituted with 1 to 3 groups independently selected from oxo and –OH;

R^2 is aryl or C_{5-10}heteroaryl, each of said aryl and heteroaryl is optionally 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 optionally substituted with C_{1-4}alkyl; and

n is 1 or 2.

In one embodiment of any of the above embodiments, R^1 is hydrogen, methyl, ethyl, propyl, $-CH_2CH_2$-OH, $-C(O)CH_3$, or $-CH_2C(O)H$; R^2 is a phenyl or C_{5-6}heteroaryl, each of said phenyl and heteroaryl is optionally 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 optionally substituted with methyl or ethyl; and n is 1 or 2.

In one embodiment of any of the above embodiments, R^1 is methyl, ethyl, $-CH_2CH_2$-OH, $-C(O)CH_3$, or $-CH_2C(O)H$; and R^2 is a phenyl or pyridyl, each of said phenyl and pyridyl is optionally substituted with halogen, methyl, ethyl, –O-methyl, –O-ethyl, –S-methyl, or –S-ethyl, pyridyl optionally substituted with methyl or pyrazolyl optionally substituted with methyl.

In one embodiment of any of the above embodiments, A is $-CH_2-$; and n is 1 or 2.

In one embodiment of any of the above embodiments, A is –O–; and n is 1.

In one embodiment of any of the above embodiments, A is $-CH_2-$.

In one embodiment of any of the above embodiments, A is –O–.

In one embodiment of any of the above embodiments, R^1 is hydrogen.

In one embodiment of any of the above embodiments, R^1 is $-C_{1-4}$ alkyl, said alkyl is optionally substituted with 1 to 3 groups independently selected from oxo and –OH.

In one embodiment of any of the above embodiments, R^1 is methyl, ethyl, propyl, $-CH_2CH_2$-OH, $-C(O)CH_3$, or $-CH_2C(O)H$.

In one embodiment of any of the above embodiments, R^2 is phenyl, said phenyl is optionally substituted with a halogen. In one embodiment, the halogen is Cl or F.

In one embodiment of any of the above embodiments, R^2 is phenyl, said phenyl is optionally substituted with a methyl or ethyl.

In one embodiment of any of the above embodiments, R^2 is phenyl, said phenyl is optionally substituted with a pyridyl or pyrazolyl, said pyridyl or pyrazolyl is optionally substituted with $-C_{1-4}$ alkyl.

In one embodiment of any of the above embodiments, R^2 is pyridyl, said pyridyl is optionally substituted with a halogen, $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, or $-S-C_{1-4}$ alkyl.

In one embodiment of any of the above embodiments, R^2 is pyridyl, said pyridyl is optionally substituted with F, Cl, methyl, ethyl, propyl, –O-methyl, –O-ethyl, –O-propyl, –S-methyl, –S-ethyl or –S-propyl.

In one embodiment of any of the above embodiments, R^2 is pyridyl, said pyridyl is optionally substituted with another pyridyl or pyrazolyl, each of which is optionally substituted with a methyl, ethyl or propyl.

In one embodiment of any of the above embodiments, n is 0.

In one embodiment of any of the above embodiments, n is 1.

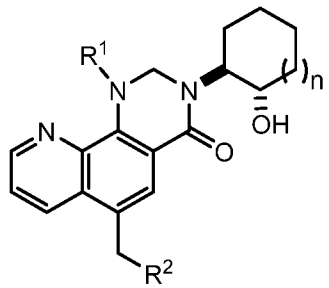
In one embodiment of any of the above embodiments, n is 2.

In one embodiment of any of the above embodiments, n is 1 and A is $-CH_2-$.

In one embodiment of any of the above embodiments, n is 1 and A is –O–.

In one embodiment of any of the above embodiments, n is 2 and A is $-CH_2-$.

In one embodiment, a compound of formula (I) is of formula (Ib):



(Ib),

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of

(1) hydrogen, and

(2) $-C_{1-4}$ alkyl, said alkyl is optionally substituted with oxo or –OH;

R2 is selected from the group consisting of

(1) a C_{5-10} heteroaryl, said heteroaryl is optionally substituted with halogen, $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, $-S-C_{1-4}$ alkyl, pyridyl or pyrazolyl, each of said pyridyl and pyrazolyl is optionally substituted with halogen or $-C_{1-4}$ alkyl; and

(2) phenyl, said phenyl is optionally substituted with halogen, $-C_{1-4}$ alkyl, pyridyl or pyrazolyl, each of said pyridyl and pyrazolyl is optionally substituted with halogen or $-C_{1-4}$ alkyl; and

n is 1 or 2.

In a particular embodiment of the compounds of formula (Ib), R^1 is hygrogen, or -C_{1-4} alkyl, said alkyl is optionally substituted with an oxo or –OH.

In a particular embodiment of the compounds of formula (Ib), R^1 is methyl, ethyl, -CH_2CH_2-OH, -C(O)CH_3, or -CH_2C(O)H.

In a particular embodiment of the compounds of formula (Ib), R^2 is phenyl, said phenyl is optionally substituted with a halogen. In one embodiment, the halogen is F or Cl.

In a particular embodiment of the compounds of formula (Ib), R^2 is phenyl, said phenyl is optionally substituted with a pyridyl or pyrazolyl, said pyridyl or pyrazolyl is optionally substituted with a methyl, ethyl or propyl.

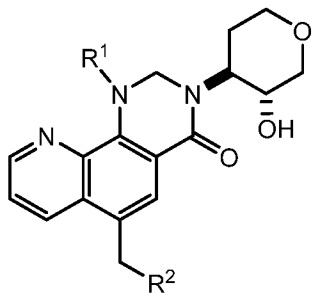
In a particular embodiment of the compounds of formula (Ib), R^2 is pyridyl or pyrazolyl, said pyridyl or pyrazolyl is optionally substituted with another pyridyl or pyrazolyl, each of which is optionally substituted with a methyl, ethyl or propyl.

In a particular embodiment of the compounds of formula (Ib), n is 1.

In a particular embodiment of the compounds of formula (Ib), n is 2.

In one embodiment of a compound of formula (Ib), R1 is hygrogen, methyl, ethyl, -CH_2CH_2-OH, -C(O)CH_3, or -CH_2C(O)H; R^2 is phenyl or pyridyl; each of said phenyl and pyridyl is optionally substituted with halogen, methyl, ethyl, -O-methyl, -O-ethyl, -S-methyl, -S-ethyl, pyridyl optionally substituted with methyl, or pyrazolyl optionally substituted with methyl; and n is 1 or 2.

In one embodiment, a compound of formula (I) is of formula (Ic):



(Ic),

or pharmaceutically acceptable salt thereof, wherein

R^1 is –C_{1-4} alkyl, said alkyl is optionally substituted with oxo or –OH; and

R^2 is a C_{5-10} heteroaryl, said heteroaryl is optionally substituted with halogen, –C_{1-4} alkyl, –O-C_{1-4} alkyl, –S-C_{1-4} alkyl, pyridyl or pyrazolyl, each of said pyridyl and pyrazolyl is optionally substituted with -C_{1-4} alkyl.

In a particular embodiment of the compounds of formula (Ic), R^1 is methyl, ethyl, or propyl.

In a particular embodiment of the compounds of formula (Ic), R^2 is pyridyl or pyrazolyl, said pyridyl or pyrazolyl is optionally substituted with F, Cl, methyl, ethyl, propyl, –O-methyl, –O-ethyl, –O-propyl, –S-methyl, –S-ethyl or –S-propyl.

In a particular embodiment of the compounds of formula (Ic), R^2 is pyridyl or pyrazolyl, said pyridyl or pyrazolyl is optionally substituted with another pyridyl or pyrazolyl, each of which is optionally substituted with a methyl, ethyl or propyl.

In a particular embodiment of the compounds of formula (Ic), R^1 is hygrogen, methyl or ethyl; and R^2 is pyridyl; said pyridyl is optionally substituted with halogen, methyl, ethyl, -O-methyl, -O-ethyl, -S-methyl, -S-ethyl, pyridyl optionally substituted with methyl, or pyrazolyl optionally substituted with methyl.

In one embodiment, a compound of formula (I) is selected from the group consisting of:
6-((6-Chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
6-((6-Chloropyridin-3-yl)methyl)-3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
6-((6-Chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycycloheptyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycycloheptyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,

3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((5'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido [3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-1-methyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
1-ethyl-3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-(2-hydroxyethyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
1-Acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
1-Acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
1-Acetyl-6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one,
1-Acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
1-acetyl-6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[h]quinazolin-4(1H)-one,

3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((5'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((6'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
1-ethyl-3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-(2-hydroxyethyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,

3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
1-acetyl-3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[h]quinazolin-4(1H)-one, and
1-acetyl-3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[h]quinazolin-4(1H)-one;
or a pharmaceutically acceptable salt thereof.

Also disclosed herein are methods of treating a patient (preferably a human) for diseases or disorders in which the M1 receptor is involved, such as Alzheimer's Disease, cognitive impairment, schizophrenia, pain disorders and sleep disorders, by administering to the patient a therapeutically effective amount of a compound of formula (I), (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt thereof.

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

Also disclosed herein are medicaments or pharmaceutical compositions for the treatment of diseases or disorders in a patient (preferably a human) in which the M1 receptor is involved, such as Alzheimer's Disease, cognitive impairment, schizophrenia, pain disorders, and sleep

disorders, which comprise a compound of formula (I), (Ia), (Ib) or (Ic), 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), (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.

When any variable (e.g. aryl, heterocycle, R^1, R^2 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 "C_{1-6}" 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, napthyl, tetrahydronapthyl, 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, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 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-flurophenyl, 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-cyclopentyloctyl. Included within this definition are methylenes (-CH_2-) substituted with oxygen to form carbonyl (-CO-).

Unless otherwise stated, as employed herein, when a moiety (e.g., aryl, alkyl, heteroaryl, heterocyclic, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, specifically from one to three, more specifically one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (e.g., an annular -CH- substituted with oxo is -C(O)-), nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl,

alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

(a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino, and

(b) C_1-C_6 alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C_1-C_8 alkyl, SO_2CF_3, CF_3, SO_2Me, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, C_2-C_8 acyl, C_2-C_8 acylamino, C_1-C_8 alkylthio, arylalkylthio, arylthio, C_1-C_8alkylsulfinyl, arylalkylsulfnyl, arylsulfnyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C_0-C_6 N-alkylcarbamoyl, C_2-C_{15} *N,N* dialkylcarbamoyl, C_3-C_7 cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C_3-C_7 heterocycle, or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above.

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

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

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise. Thus, for example, reference to "a primer" includes two or more such primers, reference to "an amino acid" includes more than one such amino acid, and the like.

The compounds of the invention may have one or more asymmetric centers. Compounds with asymmetric centers give rise to enantiomers (optical isomers), diastereomers (configurational isomers) or both, and it is intended that all of the possible enantiomers and diastereomers in mixtures and as pure or partially purified compounds are included within the scope of this invention. The present invention is meant to encompass all such isomeric forms of the compounds of formula (I).

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

The independent syntheses of the enantiomerically or diastereomerically enriched compounds, or their chromatographic separations, may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline

intermediates that are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers or diastereomers are isolated. The separation can be carried out by methods well 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 using chiral stationary phases, which methods are well known in the art.

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

In the compounds of generic Formula (I), (Ia), (Ib) or (Ic), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

The compounds of the invention may be prepared according to the 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, and preferably 95% pure, and even more preferably 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 of the muscarinic acetylcholine receptor, which is from the superfamily of G-protein coupled receptors. The family of muscarinic receptors is described, for example, in *Pharmacol Ther*, 1993, 58:319-379; *Eur J Pharmacol*, 1996, 295:93-102, and *Mol Pharmacol*, 2002, 61:1297-1302. The muscarinic receptors are known to contain one or more allosteric sites, which may alter the affinity with which muscarinic ligands bind to the primary binding or orthosteric sites. *See, e.g.,* S. Lazareno et al, *Mol Pharmacol*, 2002, 62:6, 1491-1505.

As used herein, the terms "positive allosteric modulator" and "allosteric potentiator" are used interchangeably, and refer to a ligand which interacts with an allosteric site of a receptor to activate the primary binding site. The compounds of the invention are positive allosteric modulators of the muscarinic M1 receptor. For example, a modulator or 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 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 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 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 preferred 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, ketanine and other dissociative anaesthetics, amphetamine and other psychostimulants and cocaine) psychosispsychotic 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, amnestic 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 these systems evolve with medical and scientific progress. Thus the term "schizophrenia or psychosis" is intended to include like disorders that are described in other diagnostic sources.

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

which is associated with respiratory disturbances during sleep; and conditions which result from a diminished quality of sleep.

Pain disorders for which the compounds of the invention may be useful include neuropathic pain (such as postherpetic neuralgia, nerve injury, the "dynias", e.g., vulvodynia, 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, dysmennorhea, as well as pain associated with angina, and inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno- synovitis and gout), headache, migraine and cluster headache, headache, primary hyperalgesia, secondary hyperalgesia, primary allodynia, secondary allodynia, or other pain caused by central sensitization.

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

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

Examples of combinations of the compounds of the present invention include combinations with anti-Alzheimer's Disease agents, for example beta-secretase inhibitors; alpha

7 nicotinic agonists, such as ABT089, SSR180711 and MEM63908; ADAM 10 ligands or activators; gamma-secretase inhibitors, such as LY450139 and TAK 070; gamma secretase modulators; tau phosphorylation inhibitors; glycine transport inhibitors; LXR β agonists; ApoE4 conformational modulators; NR2B antagonists; androgen receptor modulators; blockers of Aβ oligomer formation; 5-HT4 agonists, such as PRX-03140; 5-HT6 antagonists, such as GSK 742467, SGS-518, FK-962, SL-65.0155, SRA-333 and xaliproden; 5-HT1a antagonists, such as lecozotan; p25/CDK5 inhibitors; NK1/NK3 receptor antagonists; COX-2 inhibitors; HMG-CoA reductase inhibitors; NSAIDs including ibuprofen; vitamin E; anti-amyloid antibodies (including anti-amyloid humanized monoclonal antibodies), such as bapineuzumab, ACC001, CAD106, AZD3102, H12A11V1; anti-inflammatory compounds such as (R)-flurbiprofen, nitroflurbiprofen, ND-1251, VP-025, HT-0712 and EHT-202; PPAR gamma agonists, such as pioglitazone and rosiglitazone; CB-1 receptor antagonists or CB-1 receptor inverse agonists, such as AVE1625; antibiotics such as doxycycline and rifampin; N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine, neramexane and EVT101; cholinesterase inhibitors such as galantamine, rivastigmine, donepezil, tacrine, phenserine, ladostigil and ABT-089; growth hormone secretagogues such as ibutamoren, ibutamoren mesylate, and capromorelin; histamine H_3 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; GSK3β inhibitors, including AZD1080, SAR502250 and CEP16805; neuronal nicotinic agonists; selective M1 agonists; HDAC inhibitors; and microtubule affinity regulating kinase (MARK) ligands; or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the compounds of the present invention.

Examples of combinations of the compounds include combinations with agents for the treatment of schizophrenia, for example in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbital, alonimid, aiprazolam, amisulpride, amitriptyline, amobarbital, amoxapine, aripiprazole, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, clomipramine, clonazepam, cloperidone, clorazepate, chlordiazepoxide, clorethate, chlorpromazine, clozapine, cyprazepam, desipramine, dexclamol,

diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flupentixol, fluphenazine, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, haloperidol, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, olanzapine, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, quetiapine, reclazepam, risperidone, roletamide, secobarbital, sertraline, suproelone, temazepam, thioridazine, thiothixene, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, ziprasidone, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

In another embodiment, the subject compound may be employed in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as 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 compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone. 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, 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, alentemol, aripiprazole, amisuipride, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide, pramipexole, quetiapine, risperidone, sulpiride, tetrabenazine, frihexyphenidyl, thioridazine, thiothixene, trifluoperazine or ziprasidone.

Examples of combinations of the compounds include combinations with agents for the treatment of pain, for example non-steroidal anti-inflammatory agents, such as aspirin, diclofenac, duflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, oxaprozin, piroxicam, sulindac and tolmetin; COX-2 inhibitors, such as celecoxib, rofecoxib, valdecoxib, 406381 and 644784; CB-2 agonists, such as 842166 and SAB378; VR-1 antagonists, such as AMG517, 705498, 782443, PAC20030, V114380 and A425619; bradykinin B l receptor antagonists, such as SSR240612 and NVPSAA164; sodium channel blockers and antagonists, such as VX409 and SPI860; nitric oxide synthase (NOS) inhibitors (including iNOS and nNOS inhibitors), such as SD6010 and 274150; glycine site antagonists, including lacosamide; neuronal nicotinic agonists, such as ABT 894; NMDA antagonists, such as AZD4282; potassium channel openers; AMPA/kainate receptor antagonists; calcium channel blockers, such as ziconotide and NMED160; GABA-A receptor IO modulators (e.g., a GABA-A receptor agonist); matrix metalloprotease (MMP) inhibitors; thrombolytic agents; opioid analgesics such as codeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene; neutrophil inhibitory factor (NIF); pramipexole, ropinirole; anticholinergics; amantadine; monoamine oxidase Bl5 ("MAO-B") inhibitors; 5HT receptor agonists or antagonists; mGlu5 antagonists, such as AZD9272; alpha agonists, such as AGNXX/YY; neuronal nicotinic agonists, such as ABT894; NMDA receptor agonists or antagonists, such as AZD4282; NKI 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.

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, melatonergic agents, other orexin antagonists, orexin agonists, prokineticin agonists and antagonists, pyrazolopyrimidines, T-type calcium channel antagonists, triazolopyridines, and the like, such as: adinazolam, allobarbital, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, armodafinil, APD-125, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capromorelin, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, conazepam, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, EMD-281014, eplivanserin, estazolam, eszopiclone, ethchlorynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, gaboxadol, glutethimide, halazepam, hydroxyzine, ibutamoren, imipramine, indiplon, lithium, lorazepam, lormetazepam, LY-156735, maprotiline, MDL-100907, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, methyprylon, midaflur, midazolam, modafinil, nefazodone, NGD-2-73, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, ramelteon, reclazepam, roletamide, secobarbital, sertraline, suproclone, TAK-375, temazepam, thioridazine, tiagabine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zopiclone, zolpidem, and salts thereof, and combinations thereof, and the like, or the compound of the present invention may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

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

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

In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound, 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 acceptable carrier.

The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium

carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

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

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

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

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

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like.

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

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

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

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

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

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).

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 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 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 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, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. The total daily dosage is from about 1.0 mg to about 2000 mg, preferably from about 0.1 mg to about 20 mg per kg of body weight. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 mg to about 1,400 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

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

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that

compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

EXPERIMENTAL

The following abbreviations are used throughout the text:

Me:	methyl
Et:	ethyl
t-Bu:	*tert*-butyl
Ar:	aryl
Ph:	phenyl
Bn:	benzyl
DCE:	dichloroethylene
HMDS:	hexamethyldisilazane
DMF:	dimethylformamide
DMFDMA:	*N,N*-dimethylformamide dimethylacetal
THF:	tetrahydrofuran
BOP:	benzotriazolyloxytris (dimethylamino) phosphonium hexafluorophosphate
Boc:	*tert*-butyloxycarbonyl
TBS:	*tert*-butyldimethylsilyl
TEA:	triethylamine
TPAP:	tetra-*n*-propyl ammonium perruthenate
NMO:	*N*-methyl morpholine *N*-oxide
ClZn:	Chlorozinc
dppf:	diphenylphosphorousferrocenyl
PMB:	*p*-methoxybenzyl
Ms:	mesyl
Ac:	acetyl
DMSO:	dimethylsulfoxide
DCM:	dichloromethane
m-CPBA:	meta-chloroperoxybenzoic acid
DMEM:	Dulbecco's Modified Eagle Medium (High Glucose)
FBS:	fetal bovine serum

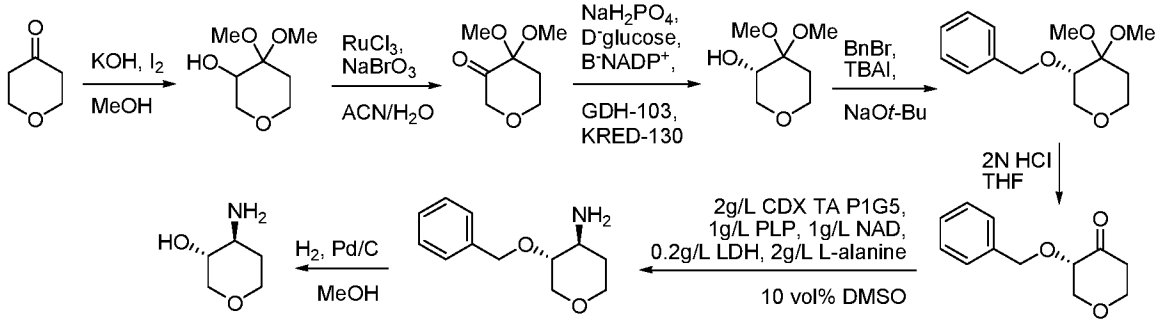
rt:	room temperature
aq:	aqueous
HPLC:	high performance liquid chromatography
MS:	mass spectrometry
CDX TA P1G5	**
GDH-103	**
KRED-130	**

**Codex Transaminase panel enzyme P1G5 (commercially available from Codex (Redwood City, California,USA) panel products.

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

Scheme 1

Preparation of (3*R*,4*S*)-4-aminotetrahydro-2*H*-pyran-3-ol:



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 recooled to 5°C. 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 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-dimethyoxytetrahydro-*2H*-pyran-3-ol.

To a solution of the above compound (1.00 kg, 6.17 mol) in 5 L of water was added 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 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 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) 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 N_2 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 heatedto 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-(benzylyoxy)-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 P1G5 (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 (*3R*, *4S*)-3-(benzyloxy)tetrahydro-*2H*-pyran-4-amine.

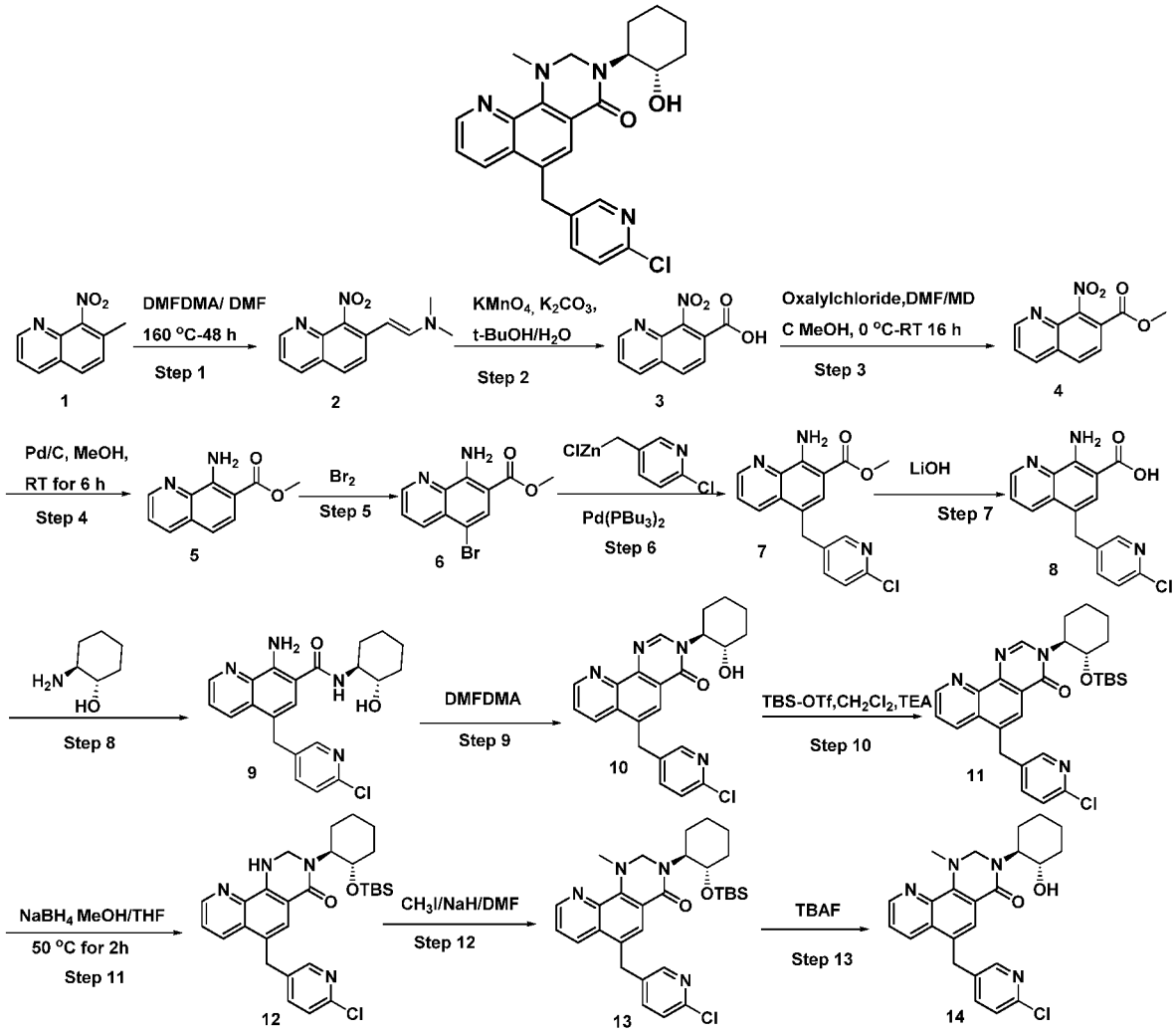
To a solution of the above compound (38.8 g, 0.187 mol) in 730 mL of methanol was added concentrated hydrochloric acid (23.3 mL). The solution was subjected to hydrogenation at 40 psi H_2, 25°C over 10% Pd/C (5.8 g). After 15 h, the mixture was filtered through solka floc and the filtercake was washed 5x with methanol (100 mL). The combined filtrate and washes were concentrated *in vacuo* to provide (*3R*, *4S*)-4-aminotetrahydro-*2H*-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-[(*1S*, *2S*)-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 (*3R*, *4S*)-4-aminotetrahydro-*2H*-pyran-3-ol for (*1S*, *2S*)-2-aminocyclohexanol. The resultant yellow solid gave a proton NMR spectra consistent with theory and a mass ion (ES+) of 409.1 for $[M+H]^+$: ^{1}H NMR (400 MHz, d_6-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.

EXAMPLES

Example 1: 6-((6-Chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one



Step 1: Preparation of (*E*)-*N*,*N*-dimethyl-2-(8-nitroquinolin-7-yl)ethen-1-amine: A solution of 7-methyl-8-nitroquinoline (25.0 g, 133 mmol) and *N*,*N*-dimethyl formamide dimethyl acetal (35.6 mL, 266 mmol) in anhydrous DMF (10 mL) was refluxed at 160°C for 48 hours. The mixture was cooled to room temperature and hexane (50 mL) was added. After vigorously stirring for 30 minutes, a brick red solid was collected, washed with additional hexane, and dried to provide the titled compound that gave proton NMR spectra consistent with theory.

Step 2: Preparation of 8-nitroquinoline-7-carboxylic acid**:** To a solution of (*E*)-*N*,*N*-dimethyl-2-(8-nitroquinolin-7-yl)ethen-1-amine (25.0 g, 103 mmol) and potassium carbonate (34.1 g, 247 mmol) in 300 mL of 1:1 *t*-BuOH:H_2O at 0°C was added potassium permanganate (39.0 g, 247 mmol) over 20 minutes. The mixture was stirred at room temperature for 4 hours, afterwhich a black precipitate was filtered and washed twice with 100 mL water. The filtrate was concentrated to 40 mL in volume, and acidified with 6 N HCl to pH ~2. The solid obtained, which was filtered washed with 100 mL of water, and dried in vacuo provided the titled compound that gave proton NMR spectra consistent with theory.

Step 3: Preparation of methyl 8-nitroquinoline-7-carboxylate: To a solution of 8-nitroquinoline-7-carboxylic acid (16.0 g, 73.3 mmol) in dichloromethane (150 mL) at 0°C was added DMF (0.284 mL, 3.67 mmol) followed by oxalylchloride (6.42 mL, 73.3 mmol) dropwise. After stirring for 1 hour, the mixture was concentrated *in vacuo* and, under nitrogen atmosphere, was dissolved in methanol (200 mL). After 15 hours, the mixture was concentrated *in vacuo,* diluted with 10% aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was washed with hexanes, filtered, and dried to provide the titled compound that gave proton NMR spectra consistent with theory.

Step 4: Preparation ofmethyl 8-aminoquinoline-7-carboxylate: To a solution of methyl 8-nitroquinoline-7-carboxylate (15.0 g, 64.6 mmol) in methanol (300 mL) and tetrahydrofuran (10 mL) was added palladium on carbon (1.50 g, 14.10 mmol). The mixture was sparged under an atmosphere of hydrogen for 6 hours. The mixture was sparged under nitrogen, filtered, and the solids were washed with additional methanol. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (5-10% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory.

Step 5: Preparation of methyl 8-amino-5-bromoquinoline-7-carboxylate: To a stirred solution of methyl 8-aminoquinoline-7-carboxylate (10.0 g, 49.5 mmol) in mixture of 1:1 Dioxane : CCl_4 (100 mL) at 0°C was added a solution of bromine (2.55 mL, 49.5 mmol) in mixture of 1:1 dioxane: CCl_4 (30 mL) dropwise. The mixture was stirred at 0°C for 2 hours. The mixture was filtered and the resulting solid was washed with hexane and dried to provide the titled compound that gave proton NMR spectra consistent with theory.

Step 6: Preparation of methyl 8-amino-5-((6-chloropyridin-3-yl)methyl)quinoline-7-carboxylate: To a solution of methyl 8-amino-5-bromoquinoline-7-carboxylate (3.50 g, 12.4 mmol) in tetrahydrofuran (30 mL) at 0°C was added a solution of (2-chloro-5-pyridyl)methylzinc chloride

(74.7 mL, 37.4 mmol), followed by bis(tri-*tert*-butylphosphino)palladium(0) (0.318 g, 0.623 mmol). The mixture was stirred at ambient temperature for 4 hours, was cooled to 0°C and then treated with with water (20 mL). The mixture was diluted with dichloromethane /water and the resulting solid was filtered off through a pad of celite. The filtrate was extracted with dichloromethane (2x 50 mL) and the combined organic extracts were dried with Na_2SO_4, filtered, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (20 - 30% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 328.4 $[M+H]^+$ [Calc'd for $C_{17}H_{15}ClN_3O_2$ $[M+H]^+$= 328.1].

Step 7: Preparation of 8-amino-5-((6-chloropyridin-3-yl)methyl)quinoline-7-carboxylic acid: To a stirred solution of methyl 8-amino-5-((6-chloropyridin-3-yl)methyl)quinoline-7-carboxylate (2.40 g, 7.32 mmol) in methanol (10 mL), tetrahydrofuran (10 mL) and water (5 mL) at 0°C, was added lithium hydroxide (0.877 g, 36.6 mmol). After stirring at 0°C for 5 minutes, the mixture was warmed to room temperature and stirred for an additional 24 hours. The mixture was concentrated in vacuo, and the residue was acidified with hydrochloric acid to pH ~3. The solid was collected via filtration, washed twice with water and dried to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 314.2 $[M+H]^+$ [Calc'd for $C_{16}H_{13}ClN_3O_2$ $[M+H]^+$= 314.1.

Step 8: Preparation of 8-amino-5-((6-chloropyridin-3-yl)methyl)-*N*-((1*S*,2*S*)-2-hydroxycyclohexyl)quinoline-7-carboxamide: To a stirred solution of 8-amino-5-((6-chloropyridin-3-yl)methyl)quinoline-7-carboxylic acid (1.80 g, 5.74 mmol) in DMF (10 mL) at room temperature was added BOP (3.81 g, 8.61 mmol), (1*S*,2*S*)-2-aminocyclohexanol (0.661 g, 5.74 mmol), and triethylamine (2.4 mL, 17.21 mmol). The mixture was stirred for 3 hours at room temperature, treated with cold water, and then extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (40 - 50% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 411.4 $[M+H]^+$ [Calc'd for $C_{22}H_{24}ClN_4O_2$ $[M+H]^+$= 411.1.

Step 9: Preparation of 6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one: To a solution of 8-amino-5-((6-chloropyridin-3-yl)methyl)-*N*-((1*S*,2*S*)-2-hydroxycyclohexyl) quinoline-7-carboxamide (1.00 g, 2.43 mmol) in DMF (10 mL), was added *N*,*N*-dimethyl formamide dimethyl acetal (1.28 mL,

12.17 mmol). The mixture was heated at 140°C for 16 hours, cooled to room temperature, and then concentrated under reduced pressure. The solid obtained was filtered, washed with 10 mL of water, and dried in vacuo to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 421.2 $[M+H]^+$ [Calc'd for $C_{23}H_{22}ClN_4O_2$ $[M+H]^+$= 421.1]

Step 10: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one: To a solution of 6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one (800 mg, 1.90 mmol) in dichloromethane (10 mL) was added triethylamine (577 mg, 5.70 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (754 mg, 2.85 mmol) at 0°C. The mixture was warmed to room temperature and stirred for an additional 1 hour. Cold water was added and the mixture was extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography with (0 - 5% methanol in dichloromethane) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 535.2 $[M+H]^+$ [Calc'd for $C_{29}H_{36}ClN_4O_2Si$ $[M+H]^+$= 535.2].

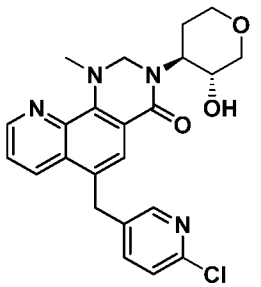
Step 11: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one (600 mg, 1.12 mmol) in a mixture of 10 mL of methanol and 10 mL of tetrahydrofuran was cooled to 0°C and added sodium borohydride (424 mg, 11.21 mmol). The mixture was heated at 50°C for 2 hours, cooled to room temperature, and treated with water. The mixture was extracted with dichloromethane and the combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 537.4 $[M+H]^+$ [Calc'd for $C_{29}H_{38}ClN_4O_2Si$ $[M+H]^+$= 537.2]

Step 12: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (300 mg, 0.558 mmol) in 4 mL of DMF at 0°C was added sodium hydride (26.8 mg, 0.670 mmol). After 10 minutes, iodomethane (0.070 mL, 1.117 mmol) was added. After 18 hours, the mixture was treated with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine,

dried with Na_2SO_4, filtered, and concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 551.4 $[M+H]^+$ [Calc'd for $C_{30}H_{40}ClN_4O_2Si$ $[M+H]^+$= 550.25].

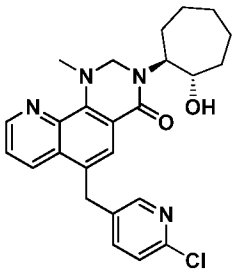
Step 13: Preparation of 6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one**:** To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (50 mg, 0.091 mmol) in 4 mL of tetrahydrofuran was cooled to 0°C and treated with tetra-n-butyl ammonium fluoride (1.0 M in tetrahydrofuran, 0.227 mL, 0.227 mmol). The mixture was warmed to room temperature, and after 5 hours, was concentrated *in vacuo.* The residue was extracted with ethyl acetate and the combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 - 5% methanol in dichloromethane) to provide thte titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 437.4 $[M+H]^+$ [Calc'd for $C_{24}H_{26}ClN_4O_2$ $[M+H]^+$= 437.2. ^1H NMR (400MHz, CD_3OD): δ. 8.95-8.94 (m, 1H), 8.49 (dd, *J* = 8.8, 1.4 Hz, 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.66-7.60 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 4.79 (s, 2H), 4.50 (s, 2H), 4.26-4.22 (m, 1H), 3.78-3.75 (m, 1H), 3.28 (s, 3H), 2.19-2.12 (m, 1H), 1.85-1.73 (m, 4H), 1.46-1.41 (m, 3H), 0.93-0.87 (m, 1H) ppm.

Example 2: 6-((6-Chloropyridin-3-yl)methyl)-3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one



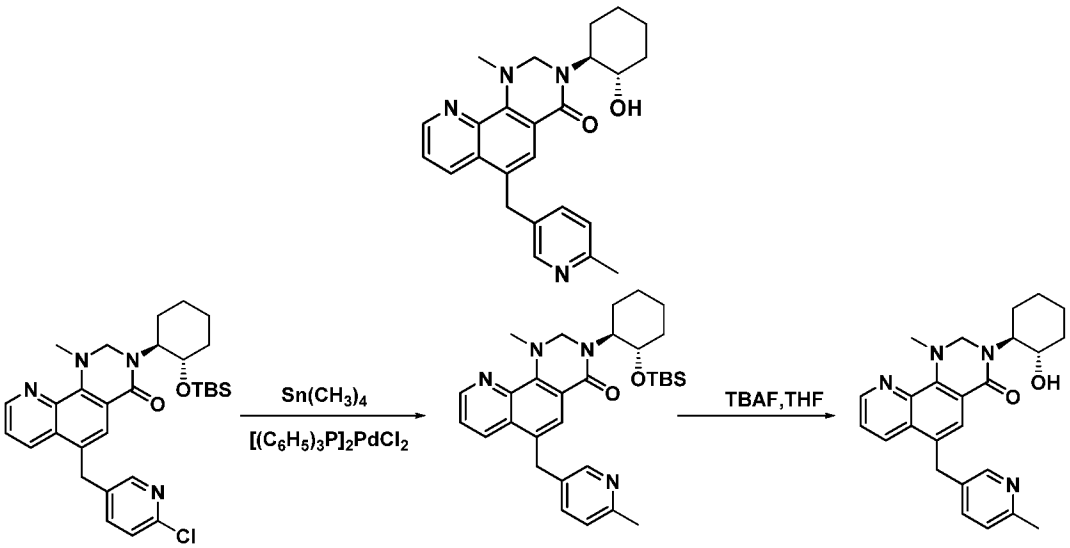
Utiling the procedures described in Example 1, substituting (3*R*,4*S*)-4-aminotetrahydro-2*H*-pyran-3-ol for (1*S*,2*S*)-2-aminocyclohexanol (Step 8), the titled compound was obtained. ^1H NMR (400MHz, CD_3OD): δ. 8.97-8.96 (m, 1H), 8.51 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.33 (s, 1H), 7.95 (s, 1H), 7.67-7.62 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 4.85 (s, 2H), 4.62 (s, 1H), 4.52 (s, 2H), 4.48-4.42 (m, 1H), 4.08-4.01 (m, 2H), 3.94-3.89 (m, 1H), 3.52-3.49 (m, 1H), 3.34-3.31 (m, 3H), 2.10-2.03 (m, 1H), 1.89-1.86 (m, 1H). LRMS $C_{23}H_{24}ClN_4O_3$: calc'd 439.2, obs 439.2 $(M+H)^+$.

Example 3: 6-((6-Chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycycloheptyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one



Utiling the procedures described in Example 1, substituting (1*S*,2*S*)-2-aminocycloheptanol for (1*S*,2*S*)-2-aminocyclohexanol (Step 8), the titled compound was obtained. ^{1}H NMR (400MHz, CD_3OD): δ 8.95 – 8.94 (m, 1H), 8.50 (d, *J* = 8.6 Hz, 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.62 – 7.61 (m, 2H), 7.37 (d, *J* = 8.3 Hz, 1H), 4.79 (s, 2H), 4.51 (s, 2H), 4.29 – 4.25 (m, 1H), 3.93 – 3.92 (m, 1H), 3.23 (s, 3H), 1.96 – 1.93 (m, 3H), 1.78 – 1.76 (m, 4H), 1.65 – 1.62 (m, 3H) ppm. LRMS $C_{25}H_{28}ClN_4O_2$: calc'd 451.2, obs 451.4 $(M+H)^+$.

Example 4: 3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido [3,2-*h*]quinazolin-4(1*H*)-one

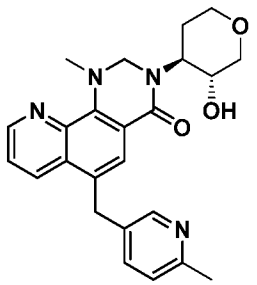


Step 1: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one**:** To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (75 mg, 0.14 mmol) in DMF (2 mL) under an atmosphere of nitrogen was added bis(triphenylphosphine) palladium(II)dichloride (2.9 mg, 4.1 μmol) and tetramethyltin (36 mg, 0.20 mmol) at room temperature. The reaction was heated at 110°C for 24 hours, cooled to room temperature and treated with water (2 mL). The mixture was

was extracted twice with ethyl acetate and the combined organic extracts were dried with sodium sulfate, filtered, concentrated *in vacuo*. The residue was purified via silica gel chromatography (30 – 35% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 531.4 $[M+H]^+$ [Calc'd for $C_{31}H_{43}N_4O_2Si$ $[M+H]^+$= 531.8].

Step 2: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (50 mg, 0.094 mmol) in tetrahydrofuran (2 mL) cooled to 0°C was added tetra-n-butyl ammonium fluoride (0.471 mL, 0.471 mmol). The mixture was warmed to room temperature, stirred for 5 hours, and then extracted with ethyl acetate. The organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 - 4 % methanol in dichloromethane) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 417.4 $[M+H]^+$ [Calc'd for $C_{25}H_{29}ClN_4O_2$ $[M+H]^+$= 417.5]. ^{1}H NMR (400MHz, CD_3OD): δ 8.95-8.94 (m, 1H), 8.51 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.36 (s, 1H), 7.95 (s, 1H), 7.63-7.56 (m, 2H), 7.23 (d, *J* = 8.1 Hz, 1H), 4.79 (s, 2H), 4.48 (s, 2H), 4.29-4.20 (m, 1H), 3.79-3.76 (m, 1H), 3.22 (s, 3H), 2.50 (s, 3H), 2.19-2.10 (m, 1H), 1.86-1.68 (m, 4H), 1.50-1.40 (m, 3H) ppm. LRMS $C_{25}H_{29}N_4O_2$: calc'd 417.2, obs 417.4 $(M+H)^+$.

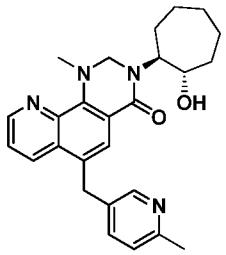
Example 5: 3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one



Utilizing the procedures described in Example 4, substituting 3-((1*S*,2*S*)-2-((tert-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one for 3-((1S,2S)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one the titled compound was prepared. ^{1}H NMR (400MHz, CD_3OD): δ. 8.96-8.94 (m, 1H), 8.52 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.35 (s, 1H), 7.95 (s,

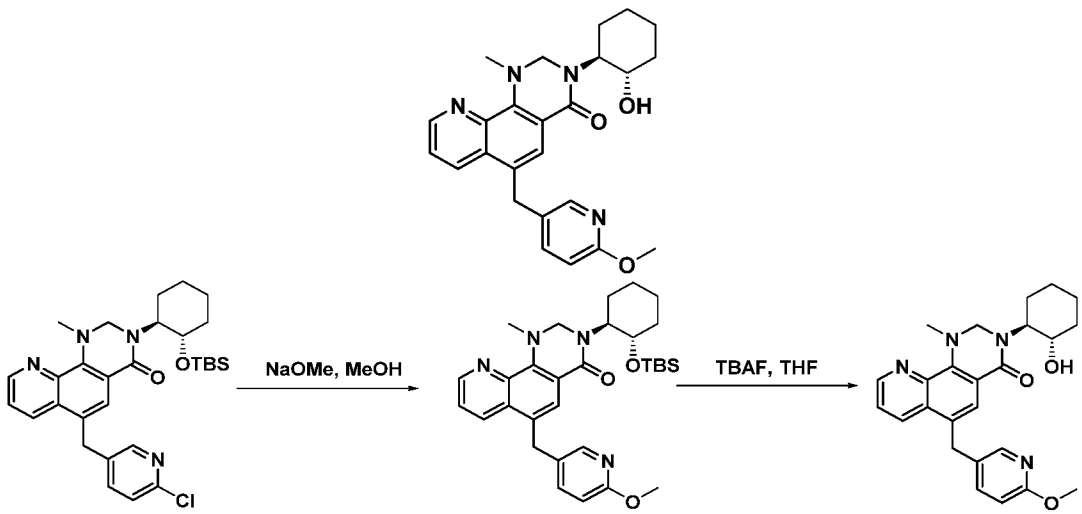
1H), 7.63-7.60 (m, 1H), 7.57 (dd, J = 8.0, 2.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 4.83 (s, 2H), 4.49 (s, 2H), 4.46-4.39 (m, 1H), 4.08-4.00 (m, 2H), 3.94-3.88 (m, 1H), 3.56-3.50 (m, 1H), 3.37-3.24 (m, 4H), 2.50 (s, 3H), 2.10-2.06 (m, 1H), 1.88-1.84 (m, 1H) ppm. LRMS $C_{24}H_{27}N_4O_3$: calc'd 419.2, obs 419.2 $(M+H)^+$.

Example 6: 3-((1*S*,2*S*)-2-Hydroxycycloheptyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one



Utilizing the procedures described in Example 4, substituting 3-((1S,2S)-2-((*tert*-butyldimethylsilyl)oxy)cycloheptyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one for 3-((1S,2S)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one the titled compound was prepared. ^{1}H NMR (400MHz, CD_3OD): δ. 8.95 – 8.94 (m, 1H), 8.51 (dd, J = 8.6, 1.6 Hz, 1H), 8.35 (s, 1H), 7.94 (s, 1H), 7.62 – 7.61 (m, 2H), 7.23 (d, J = 8.1 Hz, 1H), 4.79 (s, 2H), 4.48 (s, 2H), 4.30 – 4.27 (m, 1H), 3.97 – 3.96 (m, 1H), 3.25 (s, 3H), 2.50 (s, 3H), 1.97 – 1.94 (m, 2H), 1.82 – 1.80 (m, 8H) ppm. LRMS $C_{26}H_{31}N_4O_2$: calc'd 431.2, obs 431.4 $(M+H)^+$.

Example 7: 3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one

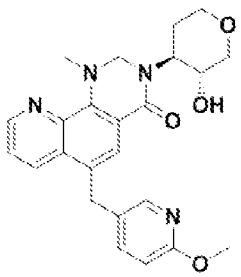
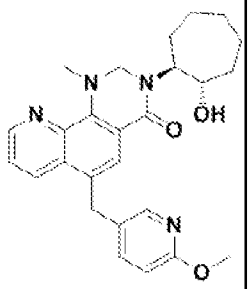


Step 1: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (75 mg, 0.14 mmol) in methanol (2 mL) was added sodium methoxide (0.056 mL, 0.204 mmol) at room temperature. The vessel was sealed and the mixture was heated in a sealed tube at 140°C in microwave for 60 minutes. The mixture was cooled to room temperature, diluted with ethyl acetate and waterm and the aqueous layer extracted thrice with ethyl acetate. The combined organic extracts were dried with Na_2SO_4, filtered, concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 547.2 $[M+H]^+$ [Calc'd for $C_{31}H_{43}N_4O_3Si$ $[M+H]^+$= 546.8].

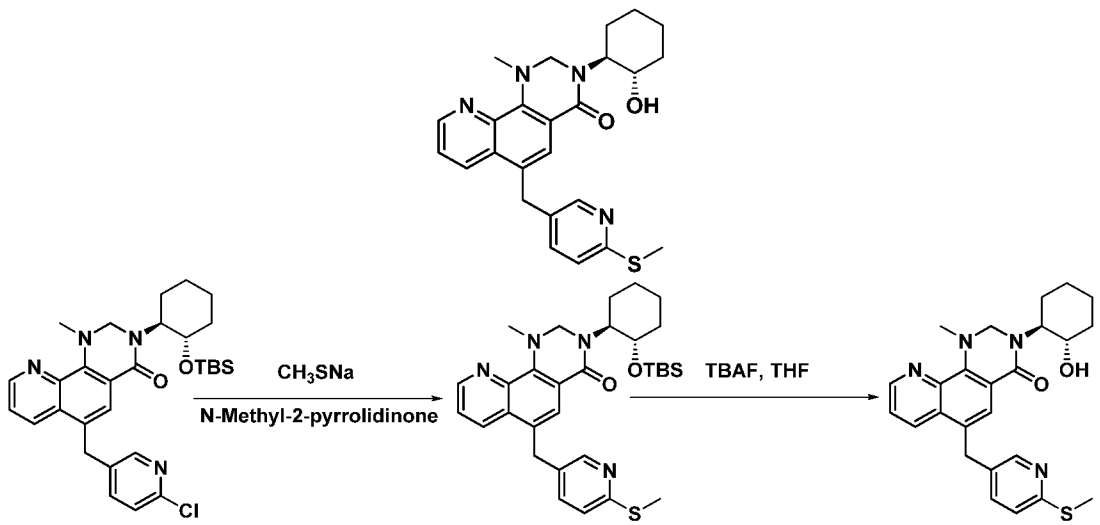
Step 2: Preparation of 3-((1S,2*S*)-2-hydroxycyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (50 mg, 0.091 mmol) in 2 mL of tetrahydrofuran cooled to 0°C was added tetra-n-butyl ammonium fluoride (1.0 M in tetrahydrofuran, 0.457 mL, 0.457 mmol). The mixture was warmed to room temperature and stirred for 5 hours, afterwhich the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 - 5% methanol in dichloromethane) to provide the titled compound. ^{1}H NMR (400MHz, CD_3OD): δ. 8.95-8.94 (m, 1H), 8.54 (dd, *J* = 8.6, 1.4 Hz, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.62 (dd, *J* = 12.8 Hz, 1H), 7.53 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 4.79 (s, 2H), 4.41 (s, 2H), 4.27-4.23 (m, 1H), 3.88 (s, 3H), 3.81-3.73 (m, 1H), 3.21 (s, 3H), 2.20-2.10 (m, 1H), 1.89-1.74 (m, 4H), 1.50-1.39 (m, 3H) ppm. LRMS $C_{25}H_{29}N_4O_3$: calc'd 433.2, obs 433.4 $(M+H)^+$.

Utilizing the procedures described in Example 7, the following compounds were prepared substituting the appropriate reagents for 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one:

Ex #	Structure	1H-NMR (400MHz,CD3OD)	Chemical Name	MS (ES+), [M+H]+

8		8.96-8.94 (m, 1H), 8.55 (dd, *J* = 8.40, 1.60 Hz, 1H), 8.06 (s, 1H), 7.94 (s, 1H), 7.64-7.61 (m, 1H), 7.53 (dd, *J* = 8.40, 2.60 Hz, 1H), 6.74 (d, *J* = 8.40 Hz, 1H), 4.82 (s, 2H), 4.42 (s, 3H), 4.08-4.01 (m, 3H), 3.91-3.88 (m, 3H), 3.53-3.50 (m, 1H), 3.33-3.32 (m, 1H), 3.23 (s, 3H), 2.10-2.06 (m, 1H), 1.88-1.83 (m, 1H) ppm	3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one	$C_{24}H_{27}N_4O_4$ [M+H] calc'd 435.2 obs. 435.2
9		8.95 – 8.94 (m, 1H), 8.54 (dd, *J* = 8.62, 1.60, Hz, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.63 – 7.62 (m, 1H), 7.54 -7.53 (m, 1H), 6.73 (d, *J* = 8.56 Hz, 1H), 4.79 (s, 2H), 4.41 (s, 2H), 4.32 - 4.29 (m, 1H), 3.98 - 3.97 (m, 1H), 3.88 (s, 3H), 3.21 (s, 3H), 2.00 -1.99 (m, 3H), 1.82 – 1.80 (m, 4H), 1.69 -1.66 (m, 3H) ppm	3-((1S,2S)-2-hydroxycycloheptyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one	$C_{26}H_{31}N_4O_3$ [M+H] calc'd 447.2 obs. 447.4

Example 10: 3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one

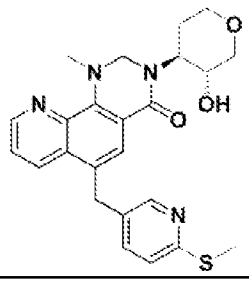
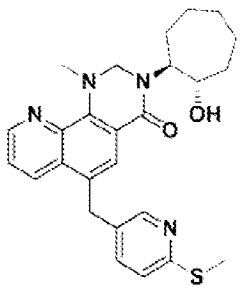


Step 1: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (75 mg, 0.14 mmol) in *N*-methyl-2-

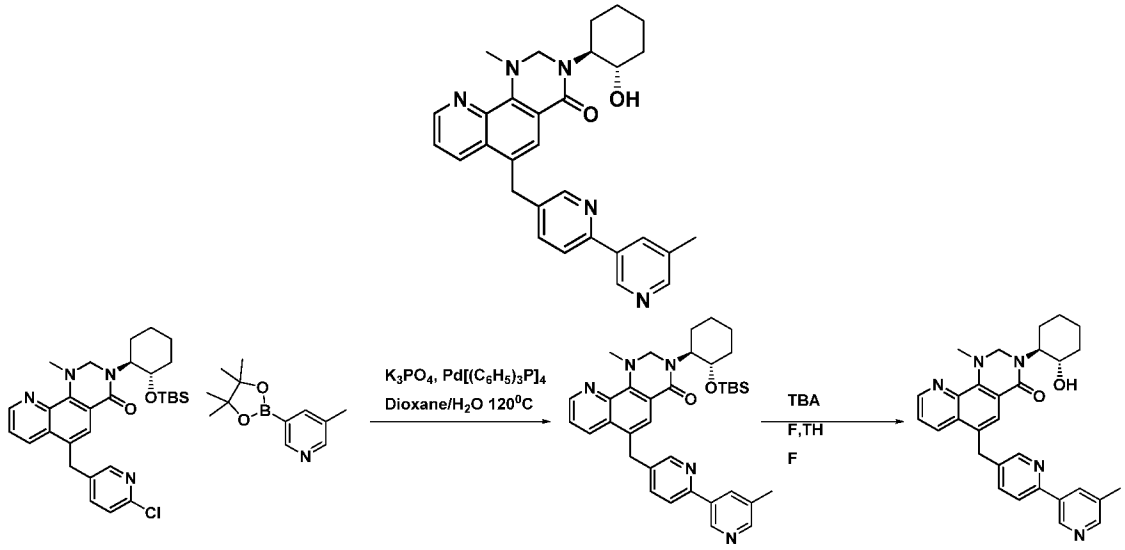
pyrrolidinone (2 mL) was added sodium thiomethoxide (48 mg, 0.68 mmol) at room temperature. temperature. The vessel was sealed and the mixture was heated in a sealed tube at 90°C in microwave reactor for 15 minutes. The mixture was cooled to room temperature, treated with water (2 mL) and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (30 – 35% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 562.8 $[M+H]^+$ [Calc'd for $C_{31}H_{43}N_4O_2Si$ $[M+H]^+$= 563.4].

Step 2: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (30 mg, 0.053 mmol) in 2 mL of tetrahydrofuran at 0°C and added tetra-n-butyl ammonium fluoride (1.0 M in THF, 0.267 mL, 0.267 mmol). The mixture was stirred at room temperature for 5 hours and then concentrated *in vacuo*. The residue was extracted with ethyl acetate and the combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 - 4 % methanol in dichloromethane) to provide the titled compound. ^{1}H NMR (400MHz, CD_3OD): δ 8.94 (s, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.63-7.60 (m, 1H), 7.46 (dd, J = 8.4, 2.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 4.78 (s, 2H), 4.44 (s, 2H), 4.27-4.21 (m, 1H), 3.78-3.73 (m, 1H), 3.21 (s, 3H), 2.51(s,3H), 2.17-2.12 (m, 1H), 1.88-1.73 (m, 4H), 1.49-1.41 (m 3H), 0.93- 0.88 (m, 1H) ppm. LRMS $C_{25}H_{29}N_4O_2S$: calc'd 449.2, obs 449.2 $(M+H)^+$.

Utilizing the procedures described in Example 10, the following compounds were prepared substituting the appropriate reagents for 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one:

Ex #	Structure	1H-NMR (400MHz,CD3OD)	Chemical Name	MS (ES+), [M+H]+
11		8.96-8.95 (m, 1H), 8.53 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.33 (s, 1H), 7.95 (s, 1H), 7.64-7.61 (m, 1H), 7.48 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.20 (d, *J* = 8.80 Hz, 1H), 4.87 (s, 2H), 4.45 (s, 3H), 4.43-4.39 (m, 2H), 3.95-3.88 (m, 1H), 3.51-3.49 (m, 1H), 3.33-3.24 (m, 4H), 2.52 (s, 3H), 2.10-2.04 (m, 1H), 1.88-1.84 (m, 1H) ppm	3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one	$C_{24}H_{27}N_4O_3S$ [M+H] calc'd 451.2 obs. 451.2
12		8.95 – 8.94 (m, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 8.14 (s, 1H), 7.63 - 7.62 (m, 1H), 7.49 - 7.48 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 4.75 (s, 3H), 4.45 (s, 2H), 4.29 - 4.27 (m, 1H), 3.97 - 3.94 (m, 1H), 3.22 (s, 4H), 1.97 - 1.82 (m, 3H), 1.80 - 1.72 (m, 5H), 1.65 - 1.57 (m, 3H) ppm	3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one	$C_{26}H_{31}N_4O_2S$ [M+H] calc'd 463.2 obs. 463.4

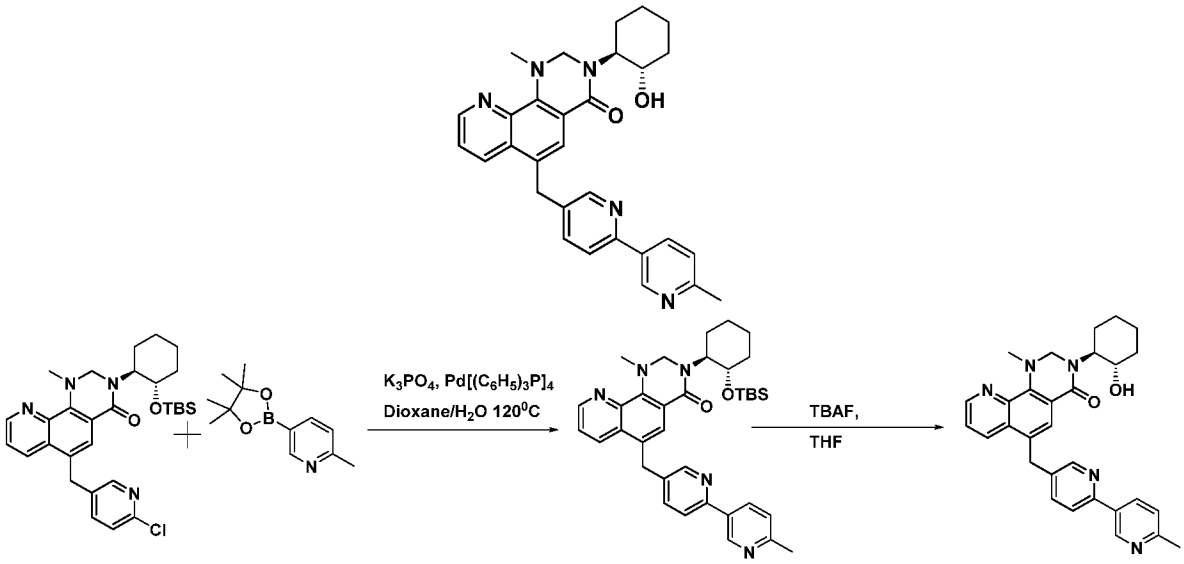
Example 13: 3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((5'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one



Step 1: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((5'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a stirred solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (80 mg, 0.145 mmol) in *n*-butanol (2 mL) and water (0.5 mL) under an atmosphere of nitrogen was added potassium phosphate tribasic (612 mg, 0.29 mmol), (5-methylpyridin-3-yl)boronic acid (23 mg, 0.17 mmol), tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 7.26 μmol), and 2-dicyclohexylphosphino-2,6-dimethoxybiphenyl (5.9 mg, 0.015 mmol). The mixture was heated at 120°C for 30 minutes, cooled to room temperature and treated with water (2 mL). The mixture was extracted twice with ethyl acetate and the combined organic extracts were dried with sodium sulfate, filtered, concentrated *in vacuo*. The residue was purified via silica gel chromatography (90 – 100% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 608.2 $[M+H]^+$ [Calc'd for $C_{36}H_{46}N_5O_2Si$ $[M+H]^+$= 608.3].

Step 2: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-6-((5'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((5'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (40 mg, 0.066 mmol) in 2 mL of tetrahydrofuran at 0°C was added tetra-n-butyl ammonium fluoride (1.0 M in tetahydrofuran, 0.329 mL, 0.329 mmol). The mixture was stirred at room temperature for 5 hours and then diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 - 5% methanol in dichloromethane) to provide the titled compound. ^{1}H NMR (400MHz, CD_3OD): δ 8.96 -8.94 (m, 1H), 8.91-8.90 (m, 1H), 8.64 (s, 1H), 8.56 (d, *J* = 8.6 Hz, 1H), 8.43 (s, 1H), 8.23 (s, 1H), 8.01 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.65-7.61 (m, 1H), 4.80 (s, 2H), 4.58 (s, 2H), 4.28-4.23 (m, 1H), 3.79-3.70 (m, 1H), 3.23 (s, 3H), 2.45 (s, 3H), 2.19-2.10 (m, 1H), 1.89-1.75 (m, 4H), 1.46-1.42 (m, 3H) ppm. LRMS $C_{30}H_{32}N_5O_2$: calc'd 494.2, obs 494.3 $(M+H)^+$.

Example 14: 3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one

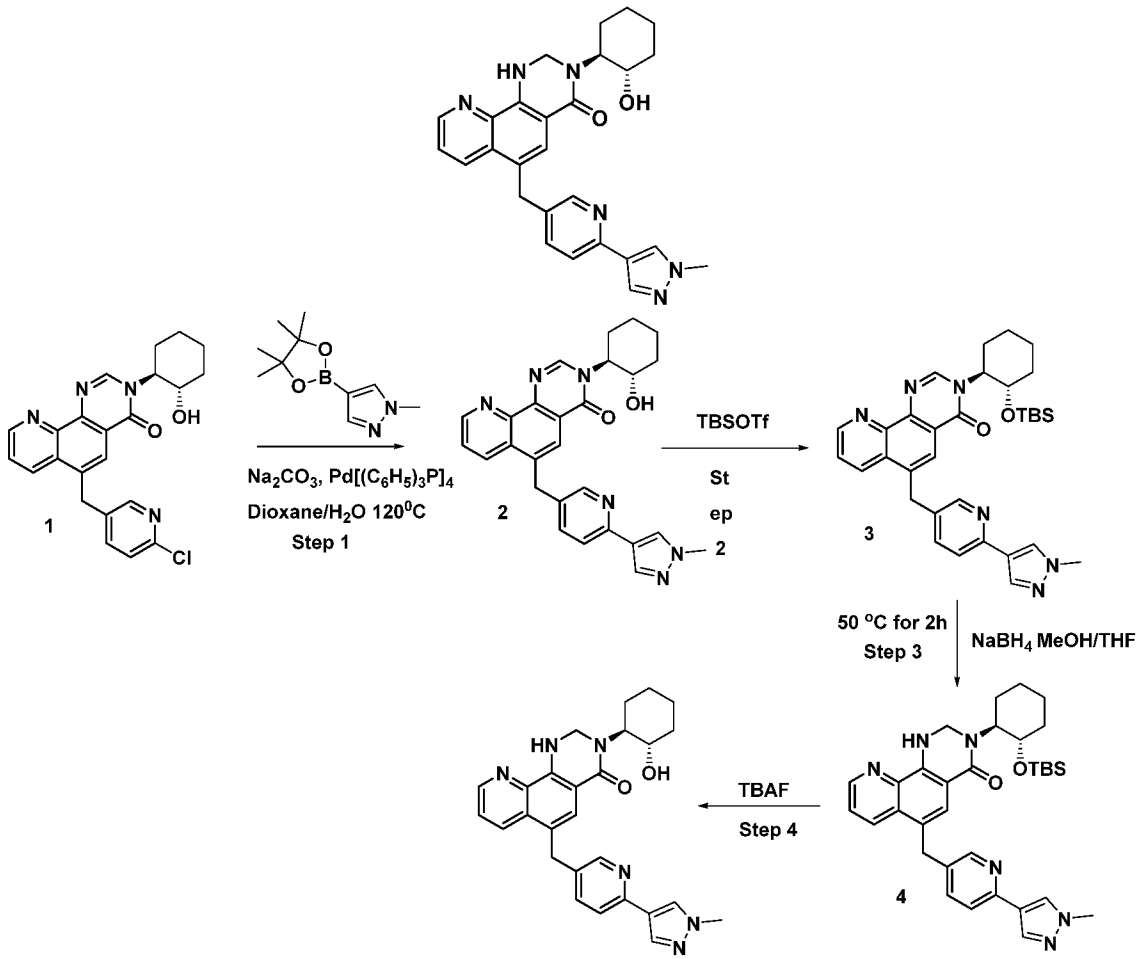


Step 1: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((6'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a stirred solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (80 mg, 0.14 mmol) in n-butanol (2 mL) and water (0.5 mL) under an atmosphere of nitrogen was added potassium phosphate tribasic (62 mg, 0.29 mmol), (5-methylpyridin-3-yl)boronic acid (23 mg, 0.174 mmol), tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 7.2 μmol), and 2-dicyclohexylphosphino-2,6 dimethoxy biphenyl (5.9 mg, 0.015 mmol). The mixture was heated at 120°C for 30 minutes, cooled to room temperature and treated with water (2 mL). The mixture was extracted twice with ethyl acetate and the combined organic ectracts were dried with sodium sulfate, filtered, concentrated *in vacuo*. The residue was purified via silica gel chromatography (90 – 100% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 608.4 $[M+H]^+$ [Calc'd for $C_{36}H_{46}N_5O_2Si$ $[M+H]^+$= 608.3].

Step 2: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-6-((6'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((6'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (40 mg, 0.066 mmol) in 2 mL of tetrahydrofuran at 0°C and added tetra-n-butyl ammonium fluoride (1.0 M in tetrahydrofuran, 0.33 mL, 0.33 mmol). The mixture was stirred at room temperature for 5 hours and then diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 - 5 %

methanol in dichloromethane) to provide the titled compound. ^{1}H NMR (400MHz, CD_3OD): δ 8.98 (s, 1H), 8.9-8.94 (m, 1H), 8.62 (s, 1H), 8.55 (dd, *J* = 8.8, 1.4 Hz, 1H), 8.27 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.00 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.64-7.61 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 4.80 (s, 3H), 4.57 (s, 2H), 4.30-4.21 (m, 1H), 3.81-3.71 (m, 1H), 3.22 (s, 3H), 2.59 (s, 3H), 2.17-2.11 (m, 1H), 1.85-1.77 (m, 4H), 1.39-1.35 (m, 3H) ppm. LRMS $C_{30}H_{32}N_5O_2$: calc'd 494.2, obs 494.2 $(M+H)^+$.

Example 15: 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido [3,2-*h*]quinazolin-4(1*H*)-one



Step 1: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one: To a stirred solution of 6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl) pyrido[3,2-*h*]quinazolin-4(3*H*)-one (1.50 g, 3.56 mmol) in dioxane (20 mL) and water (6.6 mL) under an atmosphere of nitrogen was added Na_2CO_3 (1.13 g, 10.7 mmol), 1-methyl-4-(4,4,5-trimethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazol (0.692 g, 3.56 mmol) and tetrakis triphenylphosphine palladium(0) (0.206 g, 0.178

mmol). The mixture was heated at 120°C for 16 hours, cooled to room temperature, and treated with water (20 mL). The aqueous layer was extracted twice with ethyl acetate and the combined organic extracts were dried with Na_2SO_4, filtered, concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0 – 5 % methanol in dichloromethane) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 467.4 $[M+H]^+$ [Calc'd for $C_{27}H_{27}N_6O_2$ $[M+H]^+$= 467.5].

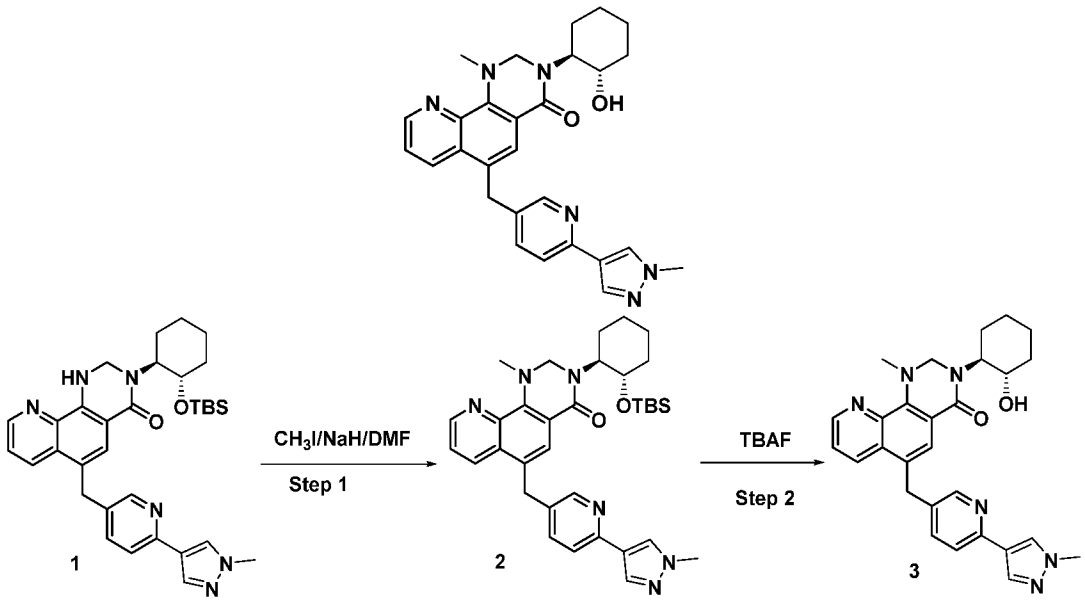
Step 2: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one: To a solution of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one (250 mg, 0.536 mmol) in dichloromethane (15 mL) at 0°C was added triethylamine (0.224 mL, 1.61 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (212 mg, 0.804 mmol). The mixture was warmed to room temperature and stirred for an additional 3 hours. The mixture was diluted with cold water and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 - 5% methanol in dichloromethane) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 581.1 $[M+H]^+$ [Calc'd for $C_{33}H_{41}N_6O_2Si$ $[M]^+$= 581.8].

Step 3: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one (350 mg, 0.603 mmol) in a mixture of methanol (10 mL) and tetrahydrofuran (10 mL) at 0°C was added sodium borohydride (228 mg, 6.03 mmol). The mixture was heated at 50°C for 2 hours, cooled to room temperature, and then treated with water. The mixture was extracted with dichloromethane and the combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 583.2 $[M+H]^+$ [Calc'd for $C_{33}H_{43}N_6O_2Si$ $[M+H]^+$= 583.8.

Step 4: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (40 mg, 0.069 mmol) in 3 mL of tetrahydrofuran at 0°C was added tetra-n-butyl ammonium fluoride (1.0 M in tetrahydrofuran,

0.17 mL, 0.17 mmol). The mixture was stirred at room temperature for 5 hours, diluted with ethyl acetate and the organic layer was washed with water and brine, dried with Na_2SO_4, 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 titled compound. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.84-8.83 (m, 1H), 8.52 (s, 1H), 8.45 (dd, J = 8.5, 1.3 Hz, 1H), 8.28 (s, 1H), 7.99 (s, 1H), 7.72 (s, 1H), 7.65-7.61 (m, 3H), 4.72 (s, 2H), 4.36 (s, 2H), 4.13-4.10 (m, 1H), 3.88 (s, 3H), 1.99-1.94 (m, 2H), 1.72-1.62 (m, 4H), 1.56-1.53 (m, 1H), 1.26-1.20 (m, 3H) ppm. LRMS $C_{27}H_{29}N_6O_2$: calc'd 469.2, obs 469.4 $(M+H)^+$.

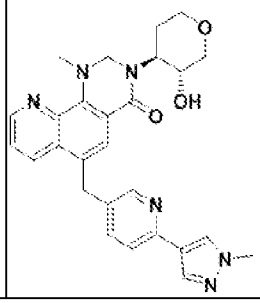
Example 16: 3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one

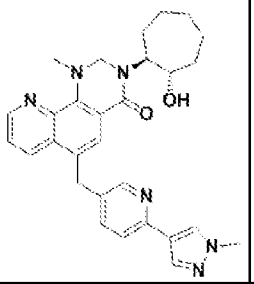
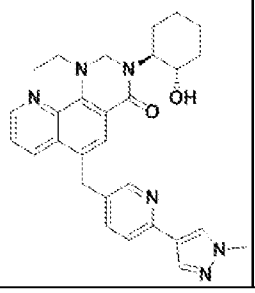


Step 1: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (90 mg, 0.15 mmol) in 2 mL of DMF at 0°C was added sodium hydride (7.4 mg, 0.18 mmol). After stirring for 10 minutes, iodomethane (0.019 mL, 0.31 mmol) was added. After stirring for 12 hours, the mixture was treated with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 597.2 $[M+H]^+$ [Calc'd for $C_{34}H_{45}N_6O_2Si$ $[M+H]^+$= 597.8].

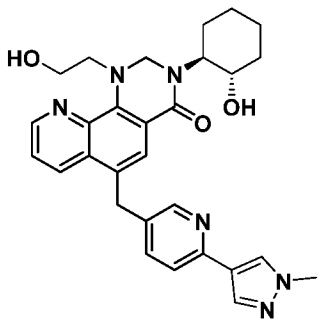
Step 2: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (60 mg, 0.10 mmol) in 5 mL of tetrahydrofuran at 0°C was added tetra-n-butyl ammonium fluoride (1.0 M in tetrahydrofuran, 0.12 mL, 0.25 mmol). The mixture was stirred at room temperature for 6 hours and then extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2 - 5 % methanol in dichloromethane) to provide the titled compound. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.93-8.92 (m, 1H), 8.53 (d, J = 7.2 Hz, 1H), 8.46 (s, 1H), 8.19 (s, 1H), 7.91 (s, 1H), 7.82 (s, 1H), 7.62-7.59 (m, 1H), 7.51 (s, 2H), 4.68-4.62 (m, 3H), 4.41 (s, 2H), 4.11-4.07 (m, 1H), 3.85 (s, 2H), 3.59-3.50 (m, 1H), 3.23 (s, 3H), 1.96-1.92 (m, 1H), 1.71-1.61 (m, 4H), 1.33-1.23 (m, 4H) ppm. LRMS $C_{28}H_{31}N_6O_2$: calc'd 483.2, obs 483.2 $(M+H)^+$.

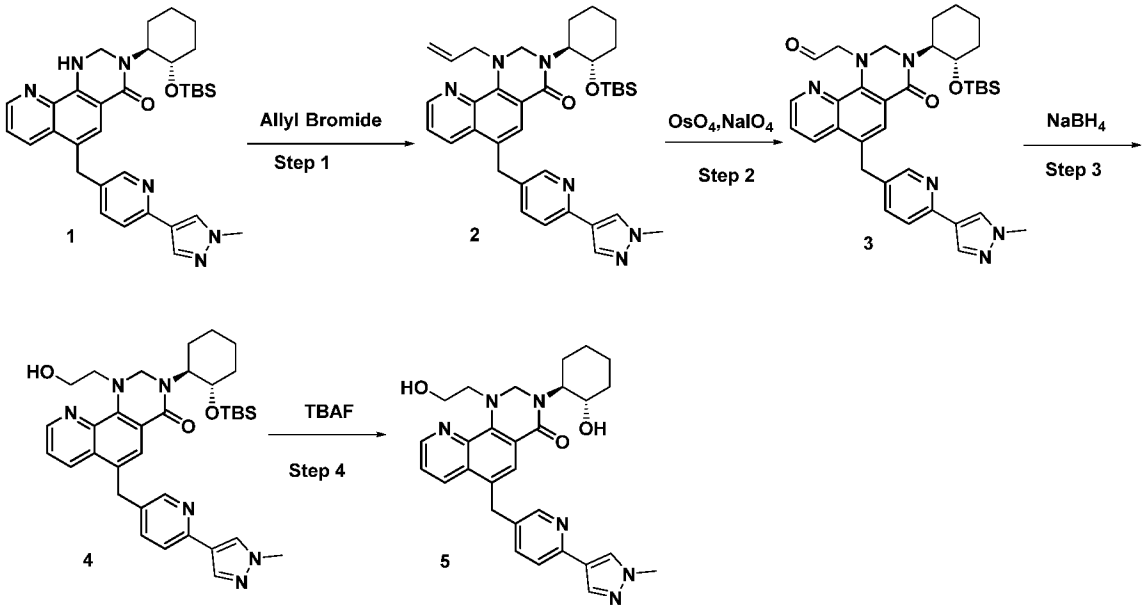
Utilizing the procedures described in Examples 15 and 16, the following compounds were prepared:

Ex #	Structure	1H-NMR (400MHz,CD3OD)	Chemical Name	MS (ES+), [M+H]+
17		8.96-8.95 (m, 1H), 8.55 (dd, J = 8.4, 1.6 Hz, 1H), 8.43 (s, 1H), 8.11 (s, 1H), 7.97 (s, 2H), 7.65-7.61 (m, 2H), 7.57-7.55 (m, 1H), 4.83 (s, 2H), 4.51 (s, 2H), 4.49-4.40 (m, 1H), 4.10-4.07 (m, 2H), 4.00-3.90 (m, 3H), 3.90-3.86 (m, 1H), 3.53-3.50 (m, 1H), 3.35-3.24 (m, 4H), 2.10-2.04 (m, 1H), 1.88-1.84 (m, 1H) ppm	3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-1-methyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one	$C_{27}H_{29}N_6O_3$ [M+H] calc'd 485.2 obs. 485.4

18		8.95 – 8.94 (m, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 8.14 (s, 1H), 7.63 - 7.62 (m, 1H), 7.49 - 7.48 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 4.75 (s, 3H), 4.45 (s, 2H), 4.29 - 4.27 (m, 1H), 3.97 - 3.94 (m, 1H), 3.22 (s, 4H), 1.97 - 1.82 (m, 3H), 1.80 - 1.72 (m, 5H), 1.65 - 1.57 (m, 3H) ppm	3-((1S,2S)-2-hydroxycyclohe ptyl)-1-methyl-6-((6-(methylthio)pyr idin-3-yl)methyl)-2,3-dihydropyrido[3 ,2-h]quinazolin-4(1H)-one	$C_{29}H_{33}N_6O_2$ [M+H] calc'd 497.3 obs. 497.4
19		DMSO: 8.93-8.91 (m, 1H), 8.52 (dd, J = 8.6, 1.6 Hz, 1H), 8.47 (s, 1H), 8.20 (s, 1H), 7.92 (s, 1H), 7.81 (s, 1H), 7.62-7.59 (m, 1H), 7.53 (s, 2H), 4.73-4.64 (m, 2H), 4.40 (s, 2H), 4.05-4.04 (m, 1H), 3.86 (s, 3H), 3.70-3.65 (m, 3H), 1.99-1.98 (m, 1H), 1.71-1.66 (m, 4H), 1.30-1.24 (m, 6H) ppm	1-ethyl-3-((1S,2S)-2-hydroxycyclohe xyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3 ,2-h]quinazolin-4(1H)-one	$C_{29}H_{33}N_6O_2$ [M+H] calc'd 497.3 obs. 497.4

Example 20: 3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-(2-hydroxyethyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one





Step 1: Preparation of 1-allyl-3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (80 mg, 0.14 mmol) in 5 mL of DMF at 0°C was added sodium hydride (3.9 mg, 0.16 mmol). After stirring for 10 minutes, 3-bromoprop-1-ene (25 mg, 0.21 mmol) was added. After stirring for 12 hours, the mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 623.4 $[M+H]^+$ [Calc'd for $C_{36}H_{47}N_6O_2Si$ $[M+H]^+$= 623.9].

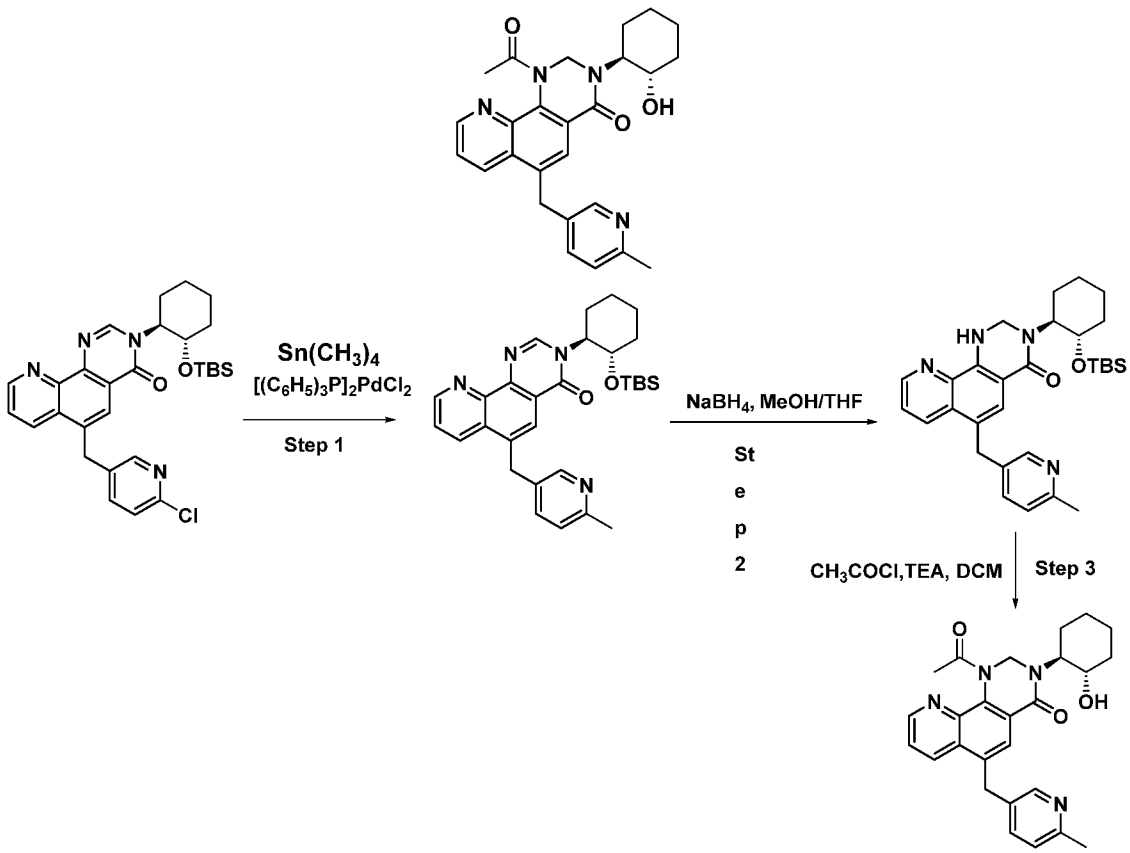
Step 2: Preparation of 2-(3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-4-oxo-3,4-dihydropyrido[3,2-*h*]quinazolin-1(2*H*)-yl)acetaldehyde: To a stirred solution of sodium periodate (82 mg, 0.38 mmol) in water (1 mL) at 0°C, osmium (VIII) oxide (0.98 mg, 3.8 µmol, 2.5 % solution in *tert*-butanol) was added. The mixture was stirred at 0°C for 15 minutes and then treated with 1-allyl-3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (80 mg, 0.13 mmol) in dichloromethane (4 mL) and methanol (2 mL). The mixture was warmed to room temperature and stirred for an additional 4 hours. The mixture was treated with water and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and

concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 624.4 $[M-H]^+$ [Calc'd for $C_{36}H_{46}N_6O_2Si$ $[M]^+$= 625.4].

Step 3: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-(2-hydroxyethyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 2-(3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-4-oxo-3,4-dihydropyrido[3,2-*h*]quinazolin-1(2*H*)-yl)acetaldehyde (80 mg, 0.13 mmol) in 5 mL of methanol at 0°C was added sodium borohydride (9.7 mg, 0.26 mmol). The mixture was warmed to room temperature and stirred for 16 hours. The mixture was diluted with water and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 628.2 $[M+H]^+$ [Calc'd for $C_{35}H_{47}N_6O_3Si$ $[M+H]^+$= 627.9].

Step 4: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-(2-hydroxyethyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-(2-hydroxyethyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (40 mg, 0.064 mmol) in 5 mL of tetrahydrofuran at 0°C was added tetra-n-butyl ammonium fluoride (1.0 M in tetrahydrofuran, 0.16 mL, 0.160 mmol). The mixture was warmed to room temperature, stirred for 5 hours and then diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, 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 titled compound. ^{1}H NMR (400MHz, CD_3OD): δ 8.93 (s, 1H), 8.62 (d, J = 9.0 Hz, 1H), 8.51 (s, 1H), 8.31 (s, 1H), 8.10 (s, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.96 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.71-7.68 (m, 1H), 4.60 (s, 2H), 4.24-4.21 (m, 1H), 3.99 (s, 6H), 3.84-3.79 (m, 2H), 3.69-3.66 (m, 1H), 2.31-2.13 (m, 1H), 1.96-1.82 (m, 4H), 1.46-1.42 (m, 4H) ppm. LRMS $C_{29}H_{33}N_6O_3$: calc'd 513.3, obs 513.4 $(M+H)^+$.

Example 21: 1-Acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one



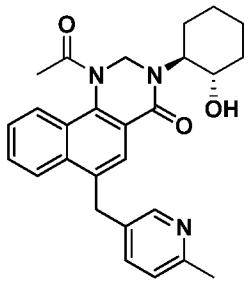
Step 1: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one**:** In a microwave vial containing a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl) oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one (900 mg, 1.68 mmol) in DMF (10 mL) under an atmosphere of nitrogen was added bis(triphenylphosphine)palladium(II)dichloride (59 mg, 0.084 mmol) and tetramethyltin (0.349 mL, 2.52 mmol) at room temperature. The vessel was sealed and heated at 120°C in microwave reactor for 1 hour. The mixture was cooled to room temperature, treated with water (5 mL), and extracted twice with ethyl acetate. The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (80 – 90 ethyl acetate in petroleum ether) to provide the titeld compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 515.2 $[M+H]^+$ [Calc'd for $C_{30}H_{39}N_4O_2Si$ $[M+H]^+$= 515.7].

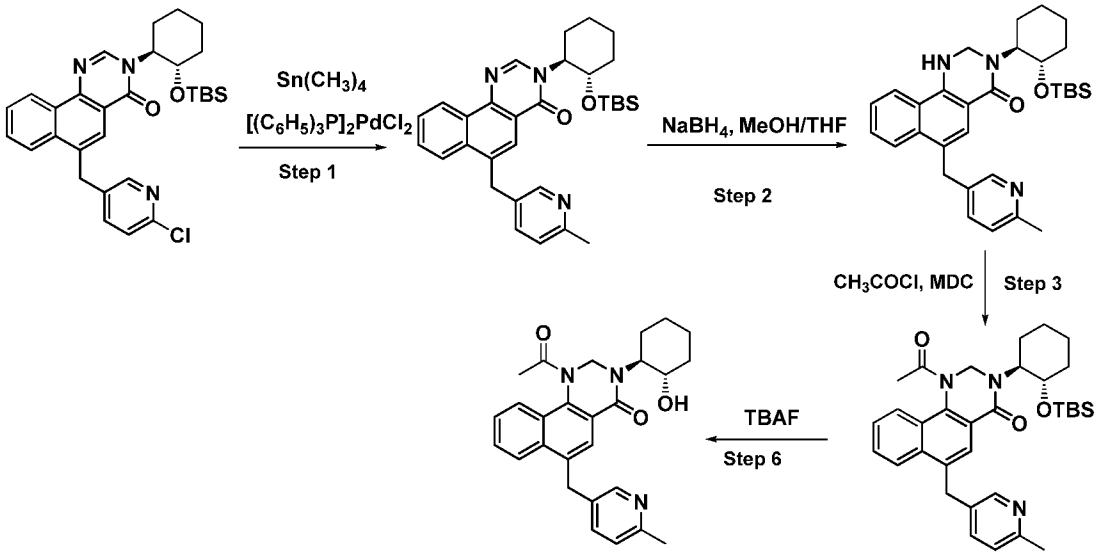
Step 2: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a stirred solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one (460 mg, 0.894 mmol) in methanol (10 mL) and tetrahydrofuran (10 mL) at 0°C, sodium borohydride (338 mg, 8.94 mmol) was added portion

wise. The mixture was stirred at room temperature for 16 hours and then concentrated under reduced pressure. The mixture was diluted with cold water (20 mL), extracted with ethyl acetate (2 x 20mL). The combined organic extracts were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (40 – 50% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 517.4 $[M+H]^+$ [Calc'd for $C_{30}H_{41}N_4O_2Si$ $[M+H]^+$= 517.8].

Step 3: Preparation of 1-acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one**:** To a stirred solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (60 mg, 0.12 mmol) in dichloromethane (2 mL) at 0°C under nitrogen atmosphere was added triethylamine (3.2 µL, 0.023 mmol) followed by acetyl chloride (8.3 µL, 0.12 mmol). The mixture was warmed to ambient temperature and stirred for an additional 1 hour. The mixture was diluted with water, extracted with ethyl acetate and the combined organic extraacts were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 – 15 % methanol in dichloromethane) to provide the titled compound. ^{1}H NMR (400MHz, CD_3OD): δ 9.01 - 9.00 (m, 1H), 8.63 - 8.61 (m, 1H), 8.37 (s, 1H), 7.98 (s, 1H), 7.68 - 7.67 (m, 1H), 7.59 (dd, *J* = 8.0, 2.0, Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.13 - 5.92 (m, 1H), 4.56 (s, 3H), 4.36 - 4.30 (m, 1H), 3.70 - 3.69 (m, 1H), 2.50 (s, 3H), 2.13 - 2.11 (m, 4H), 1.95 - 1.88 (m, 4H), 1.48 - 1.44 (m, 3 H) ppm. LRMS $C_{26}H_{29}N_4O_3$: calc'd 445.2, obs 445.2 $(M+H)^+$.

Example 22: 1-Acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one





Step 1: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinazolin-4(3*H*)-one**:** In a microwave vial containing a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl) oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)benzo[*h*]quinazolin-4(3*H*)-one (250 mg, 0.468 mmol) in DMF (5 mL) at room temperature under an atmosphere of nitrogen was added bis(triphenylphosphine)palladium(II)dichloride (16.4 mg, 0.023 mmol) and tetramethyltin (126 mg, 0.702 mmol). The vessel was sealed heated at 120°C in a microwave reactor for 1 hour. cooled to ambient temperature, and the mixture was diluted with cold water and extracted twice with ethyl acetate. The combined organic extracts were dried with sodium sulfate, filtered, concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 – 50 % ethyl acetate in petroleum ether) to provide the tittle compound that gave a mass ion (ES+) of 514.2 $[M+H]^+$ [Calc'd for $C_{31}H_{40}N_3O_2Si[M+H]^+$= 514.7].

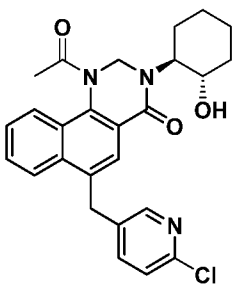
Step 2: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one**:** To a stirred solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)benzo[*h*]quinazolin-4(3*H*)-one (150 mg, 0.292 mmol) in methanol (5 mL) and tetrahydrofuran (5 mL) at 0°C, sodium borohydride (11.0 mg, 0.292 mmol) was added portion wise. The mixture was stirred at room temperature for 16 hours and then concentrated under reduced pressure. The mixture was diluted with cold water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel

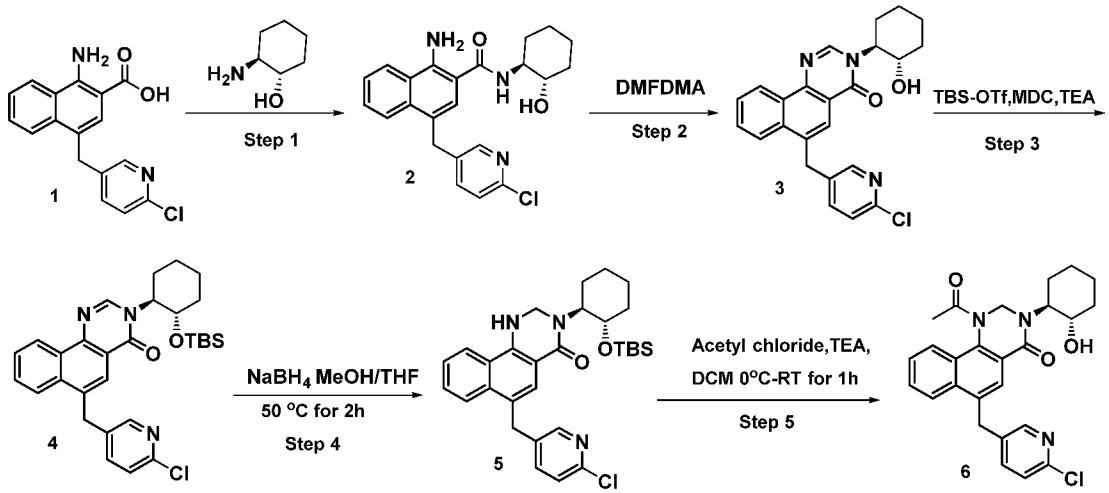
chromatography (45 – 50 % ethyl acetate in petroleum ether) to provide the tittle compound that gave a mass ion (ES+) of 516.4 $[M+H]^+$ [Calc'd for $C_{31}H_{42}N_3O_2Si[M+H]^+$= 516.8].

Step 3: Preparation of 1-acetyl-3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one: To a stirred solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one (90 mg, 0.17 mmol) in dichloromethane (2 mL) at 0°C under nitrogen atmosphere was added acetyl chloride (0.037 ml, 0.523 mmol). The mixture was stirred for 16 hours at room temperature, diluted with water, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure to provide the titled compound that gave a mass ion consistent with theory (ES+) of 558.4$[M+H]^+$ [Calc'd for $C_{33}H_{44}N_3O_3Si$ $[M+H]^+$ = 558.8].

Step 4: Preparation of 1-acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one**:** To a stirred solution of 1-acetyl-3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one (90 mg, 0.16 mmol) in tetrahydrofuran (2 mL) at 0°C, tetra-n-butyl ammonium fluoride (1.0 M in tetrahydrofuran, 0.81 mL, 0.81 mmol) was added. The mixture was warmed to ambient temperature and stirred for an additional 16 hours. The mixture was diluted with ice water and extracted with dichloromethane. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5 - 8 % methanol in dichloromethane) to provide the tittled compound. ^{1}H NMR (400MHz, CD_3OD): δ 8.37 – 8.36 (m, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 7.93 – 7.91 (m, 1H), 7.70 – 7.60 (m, 3H), 7.25 (d, *J* = 8.8 Hz, 1H), 4.56 (s, 3H), 4.22 – 4.18 (m, 1H), 3.65 – 3.80 (m, 1H), 2.50 (s, 4H), 2.24 – 2.12 (m, 1H), 1.92 – 1.88 (m, 4H), 1.86 – 1.78 (m, 3H), 1.44 – 1.39 (m, 3 H) ppm. LRMS $C_{27}H_{30}N_3O_3$: calc'd 444.2, obs 444.2 $(M+H)^+$.

Example 23: 1-Acetyl-6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one





Step 1: Preparation of 1-amino-4-((6-chloropyridin-3-yl)methyl)-*N*-((1*S*,2*S*)-2-hydroxycyclohexyl)-2-naphthamide**:** To a stirred solution of 1-amino-4-((6-chloropyridin-3-yl)methyl)-2-naphthoic acid (800 mg, 2.56 mmol) in DMF (10 mL) at room temperature was added BOP (1.13 g, 2.56 mmol), (1*S*,2*S*)-2-aminocyclohexanol (295 mg, 2.56 mmol) and triethylamine (0.357 mL, 2.56 mmol). The mixture was stirred for 3 hours at room temperature, diluted with cold water and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 - 50% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 410.4 $[M+H]^+$ [Calc'd for $C_{23}H_{25}ClN_3O_2$ $[M+H]^+$= 410.9].

Step 2: Preparation of 6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)benzo[*h*]quinazolin-4(3*H*)-one: To a solution of 1-amino-4-((6-chloropyridin-3-yl)methyl)-*N*-((1*S*,2*S*)-2-hydroxycyclohexyl)-2-naphthamide (800 mg, 1.95 mmol) in DMF (5 mL), was added *N*,*N*-dimethyl formamide dimethyl acetal (0.261 mL, 1.952 mmol). The mixture was heated at 80°C for 3 hours, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60 – 65v% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 420.2 $[M+H]^+$ [Calc'd for $C_{24}H_{23}ClN_3O_2$ $(M+H)^+$ = 420.1].

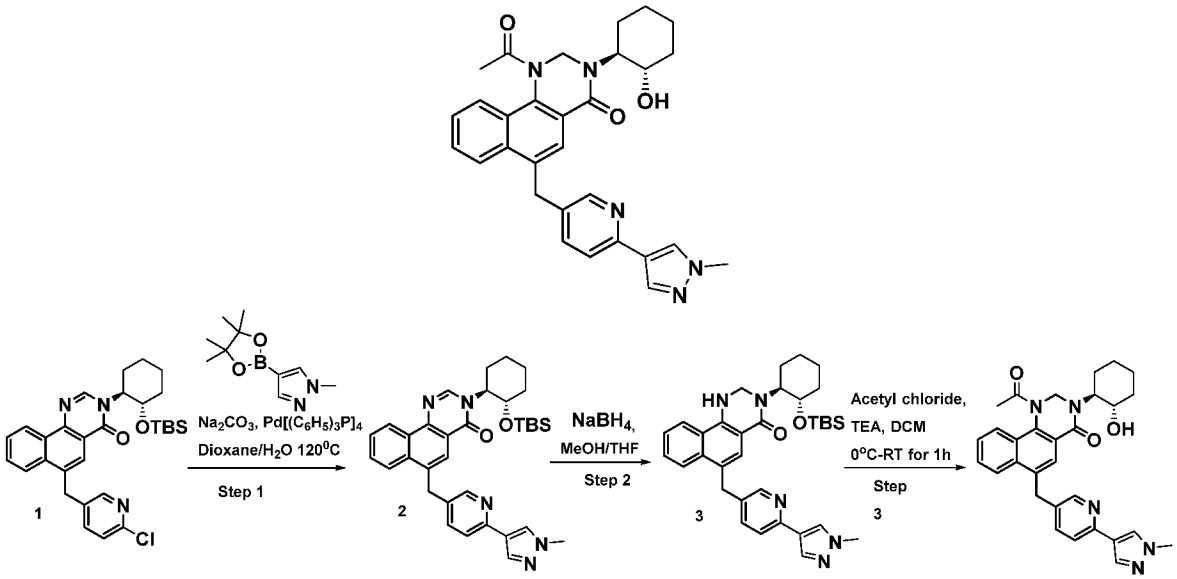
Step 3: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)benzo[*h*]quinazolin-4(3*H*)-one**:** To a solution of 6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)benzo[*h*] quinazolin-4(3*H*)-one (600 mg, 1.43 mmol) in dichloromethane (15 mL) at 0°C was added triethylamine (0.398 mL, 2.86 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (567 mg, 2.14 mmol). The mixture was

warmed to room temperature, stirred for 1 hour, and then diluted with cold water and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (10 - 15% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 534.2 $[M+H]^+$ [Calc'd for $C_{30}H_{37}ClN_3O_2Si$ $[M+H]^+$= 534.2].

Step 4: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one**:** To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl) methyl) benzo[*h*]quinazolin-4(3*H*)-one (200 mg, 0.374 mmol) in a mixture of methanol (5 mL) and tetrahydrofuran (5 mL) at 0°C was added sodium borohydride (70.8 mg, 1.87 mmol). The mixture was heated at 50°C for 16 hours, cooled to room temperature, and diluted with water. The mixture was extracted twice with dichloromethane and the combined organic extracts were washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 – 50% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 537.2 $[M+H]^+$ [Calc'd for $C_{30}H_{40}ClN_3O_2Si$ $[M]^+$= 537.2].

Step 5: Preparation of 1-acetyl-6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one: To a stirred solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one (80 mg, 0.15 mmol) in dichloromethane (3 mL) at 0°C under nitrogen atmosphere was added triethylamine (10 µL, 0.075 mmol) followed by acetyl chloride (11 µL, 0.15 mmol). The mixture was warmed to ambient temperature and stirred for 1 hour. The mixture was diluted with water, extracted with dichloromethane, and the combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative reverse phase prep HPLC (90:10 to 0:100; water containing 0.1% formic acid: acetonitrile containing 0.1% formic acid) to provide the titled compound. ^{1}H NMR (400MHz, CD_3OD): δ 8.34 (s, 1H), 8.17 - 8.06 (m, 2H), 7.91 (s, 1H), 7.69 - 7.63 (m, 3H), 7.39 - 7.33 (m, 1H), 4.63 (s, 2H), 4.29 - 4.23 (m, 2H), 3.93 - 3.91 (m, 1H), 3.74 - 3.71 (m, 1H), 2.17 - 2.13 (m, 1H), 1.90-1.70 (m, 7H), 1.43-1.35 (m, 3H) ppm. LRMS $C_{26}H_{27}ClN_3O_3$: calc'd 464.2, obs 464.2 $(M+H)^+$.

Example 24: 1-Acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one



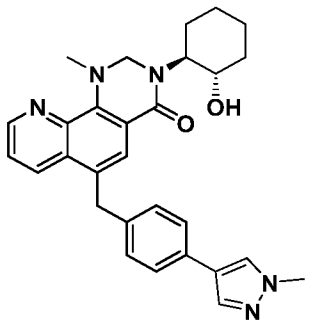
Step 1: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)benzo[*h*]quinazolin-4(3*H*)-one**:** To a microwave vial charged with 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-chloropyridin-3-yl)methyl)benzo[*h*]quinazolin-4(3*H*)-one (200 mg, 0.476 mmol), dioxane (5 mL) and water (1 mL) under an atmosphere of nitrogen was added Na_2CO_3 (151 mg, 1.43 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (99 mg, 0.48 mmol) and tetrakis(triphenylphosphine)palladium(0) (27 mg, 0.024 mmol). The vessel was sealed and heated at 120°C for 1 hour in a microwave reactor. The mixture was cooled to room temperature, treated with water (2 mL), and extracted twice with ethyl acetate. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0 – 65 % ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 466.2 $[M+H]^+$ [Calc'd for $C_{28}H_{28}N_5O_2$ $[M+H]^+$= 466.2].

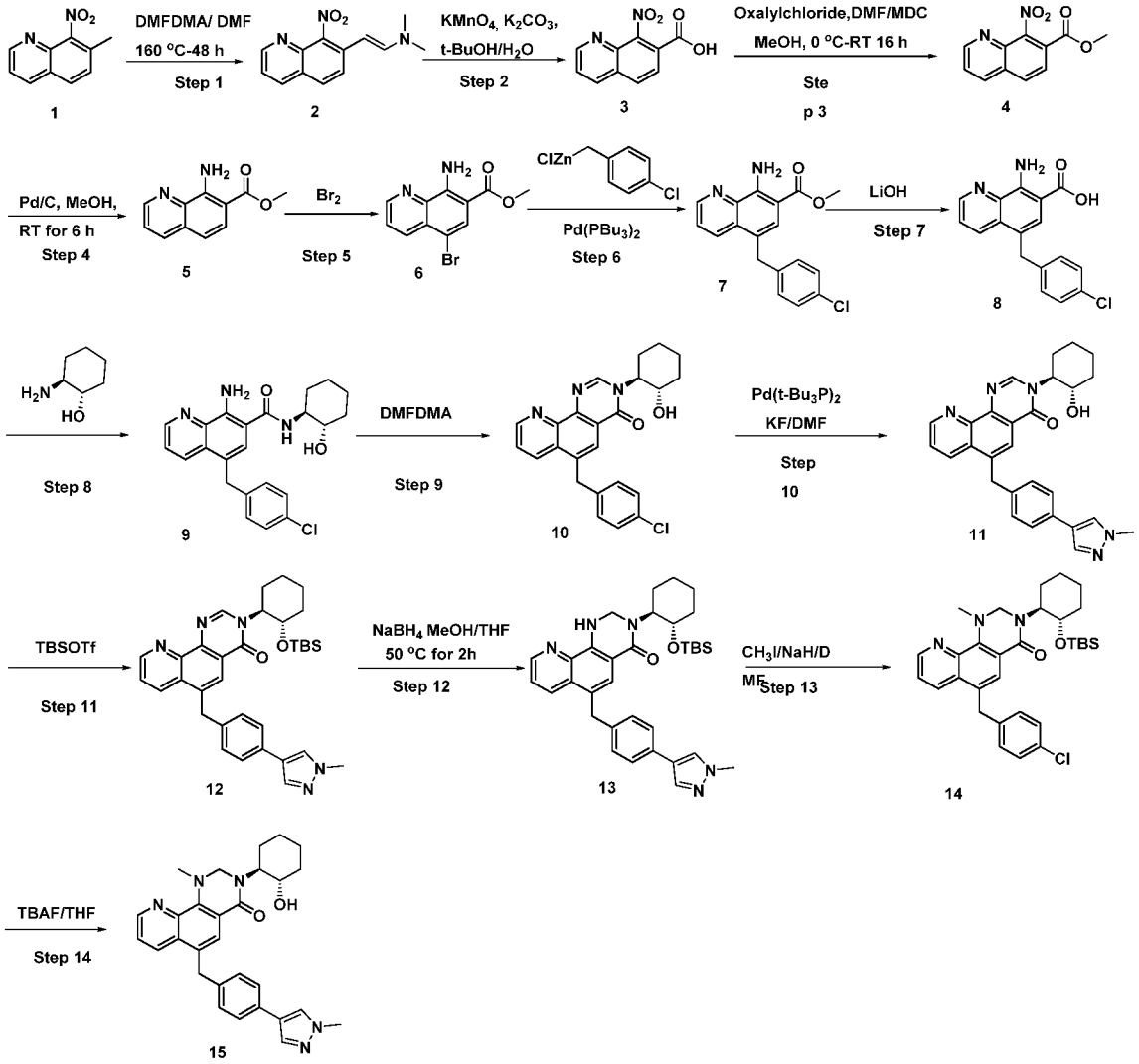
Step 2: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)benzo[*h*]quinazolin-4(3*H*)-one (130 mg, 0.224 mmol) in a mixture of methanol (3 mL) and tetrahydrofuran (3 mL) at 0°C was added sodium borohydride (85 mg, 2.24 mmol). The mixture was stirred at room temperature for 16 hours, cooled to room temperature, diluted with water and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 – 80 % ethyl acetate in petroleum

ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 582.4 $[M+H]^+$ [Calc'd for $C_{34}H_{44}N_5O_2Si$ $[M+H]^+$= 582.3].

Step 3: Preparation of 1-acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one**:** To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one (90 mg, 0.15 mmol) in dichloromethane (3 mL) at 0°C under an atmosphere of nitrogen was added triethylamine (11 µl, 0.077 mmol) followed by acetyl chloride (0.013 mL, 0.19 mmol). The mixture was warmed to ambient teperature and stirred for an additional 16 hours. The mixture was diluted with water and extracted with dichloromethane. The organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase prep HPLC (90:10 to 0:100; water containing 0.1% formic acid: acetonitrile containing 0.1% formic acid) to provide the titled compound. ^{1}H NMR (400MHz, CD_3OD): δ 8.44 (s, 1H), 8.22 – 8.20 (m, 1H), 8.11 (s, 2H), 7.98 (s, 1H), 7.94 (s, 1H), 7.70 – 7.66 (m, 3H), 7.58 (d, J = 8.1 Hz, 1H), 4.61 (s, 3H), 4.32 – 4.30 (m, 1H), 3.91 (s, 3H), 3.50 – 3.49 (m, 1H), 2.83 – 2.53 (m, 1H), 2.13 – 2.11 (m, 1H), 1.90 – 1.81 (m, 6H), 1.43 – 1.31 (m, 3H) ppm. LRMS $C_{30}H_{32}N_5O_3$: calc'd 510.3, obs 510.2 $(M+H)^+$.

Example 25: 3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one





Step 1: Preparation of (*E*)-*N*,*N*-dimethyl-2-(8-nitroquinolin-7-yl)ethen-1-amine: A solution of 7-methyl-8-nitroquinoline (25.0 g, 133 mmol) and *N*,*N*-dimethyl formamide dimethyl acetal (35.6 mL, 266 mmol) in anhydrous DMF (10 mL) was refluxed at 160°C for 48 hours. The mixture was cooled to room temperature and 50 mL of hexane was added. After vigorously stirring for 30 min, a brick red solid was collected, washed with additional hexane, and dried to provide the titled compound that gave proton NMR spectra consistent with theory.

Step 2: Preparation of 8-nitroquinoline-7-carboxylic acid: To a solution of (*E*)-*N*,*N*-dimethyl-2-(8-nitroquinolin-7-yl)ethen-1-amine (25.0 g, 103 mmol) and potassium carbonate (34.1 g, 247 mmol) in 300 mL of 1:1 *t*-BuOH:H_2O at 0°C was added potassium permanganate (39.0 g, 247 mmol) slowly over 20 minutes. The mixture was stirred at room temperature for 4 hours, afterwhich a black precipitate was formed, which was filtered and washed twice with 100 mL water. The filtrate was concentrated to 40 mL in volume, and acidified with 6 N HCl pH ~2.

The solid obtained, which was filtered, washed with 100 mL of water, and dried to provide the titled compound that gave proton NMR spectra consistent with theory.

Step 3: Preparation of methyl 8-nitroquinoline-7-carboxylate: To a solution of 8-nitroquinoline-7-carboxylic acid (16.0 g, 73.3 mmol) in dichloromethane (150 mL) at 0°C was added DMF (0.284 mL, 3.67 mmol) followed by oxalylchloride (6.42 mL, 73.3 mmol) drop wise. After stirring for 1 hour, the mixture was concentrated *in vacuo* under nitrogen atmosphere and then dissolved in MeOH (200 mL). After stirring for 15 hours, the mixture was concentrated *in vacuo,* diluted with 10% aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo.* The residue was washed with hexanes, filtered, and dried to provide the titled compound that gave proton NMR spectra consistent with theory.

Step 4: Preparation of methyl 8-aminoquinoline-7-carboxylate: To a solution of methyl 8-nitroquinoline-7-carboxylate (15.0 g, 64.6 mmol) in MeOH (300 mL) and THF (10 mL) was added palladium on carbon (1.50 g, 14.1 mmol). The mixture was sparged under an atmosphere of hydrogen and stirred for 6 hours at ambient temperature. The mixture was sparged under an atmosphere of nitrogen, filtered, and the solids were washed with additional methanol and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5 - 10% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory.

Step 5: Preparation of methyl 8-amino-5-bromoquinoline-7-carboxylate: To a stirred solution of methyl 8-aminoquinoline-7-carboxylate (10.0 g, 49.5 mmol) in mixture of 1:1 Dioxane : CCl_4 (100 mL) at 0°C was added a solution of bromine (2.55 mL, 49.5 mmol) in mixture of 1:1 dioxane: CCl_4 (30 mL) dropwise. The mixture was stirred at 0°C for 2 hours. The mixture was filtered and the resulting solid was washed with hexane and dried to provide the titled compound that gave proton NMR spectra consistent with theory.

Step 6: Preparation of methyl 8-amino-5-(4-chlorobenzyl)quinoline-7-carboxylate**:** To a solution of methyl 8-amino-5-bromoquinoline-7-carboxylate (100 mg, 0.356 mmol) in tetrahydrofuran (2 mL) at 0°C was added solution of (4-chlorobenzyl)zinc(II) chloride (2.13 ml, 1.07 mmol), followed bis(tri-*tert*-butylphosphino)palladium(0) (18 mg, 0.036 mmol). The mixture was warmed to room temperature and stirred for an additional 4 hours. The mixture was cooled to 0°C, treated with water (5 mL), and diluted with DCM/water. The resulting solid was filtered through a pad of celite and the filtrate was extracted with dichloromethane (2x 50 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo. The

residue was purified by silica gel column chromatography (80 - 90% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 327.2 $[M+H]^+$ [Calc'd for $C_{18}H_{16}ClN_2O_2$ $[M+H]^+$= 327.1].

Step 7: Preparation of 8-amino-5-(4-chlorobenzyl)quinoline-7-carboxylic acid: To a stirred solution of methyl 8-amino-5-(4-chlorobenzyl)quinoline-7-carboxylate (60 mg, 0.18 mmol) in methanol (1 mL), tetrahydrofuran (1 mL) and water (0.5 mL) at 0°C, was added lithium hydroxide (22 mg, 0.92 mmol). After stirring at 0°C for 5 minutes, the mixture was stirred at room temperature for 24 hours. The solvents were concentrated in vacuo and acidified with hydrochloric acid to pH ~3. The resulting solid was collected via filtration, washed twice with water and dried to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 313.0 $[M+H]^+$ [Calc'd for $C_{17}H_{14}ClN_2O_2$ $[M+H]^+$= 313.1].

Step 8: Preparation of 8-amino-5-(4-chlorobenzyl)-*N*-((1*S*,2*S*)-2-hydroxycyclohexyl)quinoline-7-carboxamide: To a stirred solution of 8-amino-5-(4-chlorobenzyl)quinoline-7-carboxylic acid (40 mg, 0.13 mmol) in a mixture of dichloromethane (2 mL) and DMF (0.5 mL) at room temperature was added BOP (85 mg, 0.19 mmol), (1*S*,2*S*)-2-aminocycloheptanol (16 mg, 0.14 mmol) and triethylamine (0.052 mL, 0.38 mmol) respectively. The mixture was stirred for 3 hours at room temperature, treated with cold water, and then extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 - 30% ethyl acetate in petroleum ether) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 410.4 $[M+H]^+$ [Calc'd for $C_{23}H_{25}ClN_3O_2$ $[M+H]^+$= 410.2.

Step 9: Preparation of 6-(4-chlorobenzyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one**:** To a solution of 8-amino-5-(4-chlorobenzyl)-*N*-((1*S*,2*S*)-2-hydroxycyclohexyl)quinoline-7-carboxamide (40 mg, 0.098 mmol) in DMF (1 mL), was added *N*,*N*-dimethyl formamide dimethyl acetal (0.065 mL, 0.49 mmol). The reaction mixture was heated at 140°C for 16 hours, cooled to room temperature, and concentrated under reduced pressure. The solid obtained was washed with 10 mL of water and dried 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 titled compoud that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 420.2 $[M+H]^+$ [Calc'd for $C_{24}H_{23}ClN_3O_2$ = 420.2].

Step 10: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one**:** To a stirred solution of 6-(4-chlorobenzyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one (380 mg, 0.905 mmol) in DMF (2 mL) under an atmosphere of nitrogen was added KF (116 mg, 1.99 mmol), 1-methyl-4-(4,4,5-trimethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole (351 mg, 1.81 mmol) and bis(tri-*tert*-butylphosphine)palladium(0) (23.1 mg, 0.045 mmol). The mixture was heated at 100°C for 16 hours, cooled to room temperature, and treated with water (20 mL). The mixture was extracted twice with ethyl acetate and the combined organic extracts were dried with Na_2SO_4, filtered, concentrated *in vacuo*. The residue was purified via silica gel column chromatography (30 – 35% methanol in dichloromethane) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 466.2 $[M+H]^+$ [Calc'd for $C_{28}H_{28}N_5O_2$ $[M+H]^+$= 466.2].

Step 11: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one: To a solution of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl) pyrido[3,2-*h*]quinazolin-4(3*H*)-one (280 mg, 0.601 mmol) in dichloromethane (10 mL) at 0°C was added triethylamine (0.251 mL, 1.80 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (238 mg, 0.902 mmol). The mixture was warmed to room temperature and stirred for an additional 3 hours. The mixture was diluted with dichloromethane, which was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 - 5% methanol in dichloromethane) to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 580.2 $[M+H]^+$ [Calc'd for $C_{34}H_{42}N_5O_2Si$ $[M+H]^+$= 580.3].

Step 12: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)-1,2,3,4-tetrahydropyrido[3,2-*h*]quinazoline**:** To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)pyrido[3,2-*h*]quinazolin-4(3*H*)-one (300 mg, 0.530 mmol) in a mixture methanol (10 mL) and THF (10 mL) at 0°C was added sodium borohydride (100 mg, 2.65 mmol). The mixture was heated at 50°C for 4 hours, cooled to room temperature, and diluted with water. The mixture was extracted twice with dichloromethane and the combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 582.4 $[M+H]^+$ [Calc'd for $C_{34}H_{44}N_5O_2Si$ $[M+H]^+$= 582.3].

Step 13: Preparation of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)-1,2,3,4-tetrahydropyrido[3,2-*h*]quinazoline (100 mg, 0.176 mmol) in DMF (5 mL) at 0°C was added sodium hydride (8.45 mg, 0.211 mmol). After stirring for 10 minutes, iodomethane (0.022 ml, 0.35 mmol) was added. The mixture was stirred for 12 hours and then treated with water. The mixture was extracted thrice with ethyl acetate and the combined organic extracts were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to provide the titled compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 596.4 $[M+H]^+$ [Calc'd for $C_{35}H_{46}N_5O_2Si$ $[M+H]^+$= 596.3].

Step 14: Preparation of 3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one: To a solution of 3-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one (50 mg, 0.084 mmol) in 5 mL of THF at 0°C was added tetra-n-butyl ammonium fluoride (1.0 M in THF, 0.21 mL, 0.210 mmol). The reaction mixture was warmed to room temperature and stirred for 5 hours. The mixture was concentrated *in vacuo* and the residue was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried with Na_2SO_4, 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 titled compound ^{1}H NMR (400MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.51 (d, J = 7.2 Hz, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.77 (s, 1H), 7.61-7.58 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 4.70-4.63 (m, 2H), 4.38 (s, 2H), 4.10-4.05 (m, 1H), 3.83 (s, 3H), 3.21 (s, 3H), 2.08-1.96 (m, 1H), 1.73-1.59 (m, 4H), 1.27-1.23 (m, 4H) ppm. LRMS $C_{29}H_{32}N_5O_2$: calc'd 482.3, obs 482.2 $(M+H)^+$.

Biological Utility

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 FLIPR^{384} Fluorometric Imaging Plate Reader System. The assay studies the effect of one or several concentrations of test compounds on basal or acetylcholine-stimulated Ca^{2+} levels using FLIPR.

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

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

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

Buffers: Assay Buffer: Flanks 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) Concentration of 2 µM in buffer for a final concentration of 1 µM in Assay. 20% Pluronic Acid Solution stock, with concentration of 0.04% in Buffer, 0.02% in Assay.

65 µL of 2 mM Fluo-4AM are mixed with 130 µL of 20% Pluronic Acid. The resulting solution and 650 µL FBS is added to the assay buffer for a total volume of 65 mL. Positive Controls: 4-Br-A23187: 10 mM in DMSO; final concentration 10 µM. Acetylcholine: 10 mM in water, working stock at both 20 µM and 30 µM in assay buffer, final concentration of 10 µM. This is used to check the maximum stimulation of the CHOK1/hM1 cells. 20 µM (2×) acetylcholine is added in the preincubation part of the assay, and the 30 µM (3×) stock is added in the second part. (EC20) Acetylcholine: 10 mM in water, working stock of 9 nM (3×), and final concentration in assay is 3 nM. This is used after the preincubation with test compounds. Addition of the EC20 Acetylcholine to each well with a test compound will ascertain any modulator activity. 24 wells contain 3 nM Acetylcholine alone as a control.

Determining Activity of Putative Compounds:

Screening Plate Compounds are titrated in 96-well plates (columns 2-11), 100% DMSO, started at a concentration of 15 mM (150× stock concentration), and 3-fold serial dilutions using Genesis Freedom200 System. Four 96-well plates are combined into a 384-well plate using

Mosquito Nanolitre Pipetting System by transferring 1 µl of serial diluted compounds to each well, and 1 mM acetylcholine (100× stock concentration) were added as a control. Using Temo, 49 µl 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×) is pipetted into wells corresponding to the screening compounds, and into control wells. The 30 µM acetylcholine control (3×) is added into control wells, and the 3× agonist plate is transferred into a 384 well plate.

Cells are washed three times with 100 µL of buffer, leaving 30 µL of buffer in each well. Using Multimek, 30 µL of Dye Loading Buffer is added into each well and incubated at 37°C, 5% CO_2 for up to one hour.

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

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 EC_{20} value of acetylcholine (3 nM final) is added to determine any modulator activity.

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

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

IP values from the aforementioned assay for representative exemplary compounds as described herein are provided in the table below:

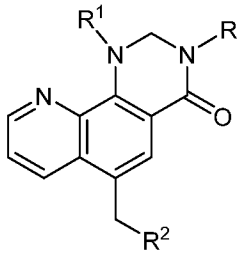
Ex. #	M1 Pot Nf Hu Ace V1 4p Ip Geo	M1 Pot Nf Hu Ace V3 4p Ip Geo
1		9.5
2		6.5
3		27.7
4		19.4
5		4.6
6		35.3
7		14.7
8		6.1

9		38.9
10		12.9
11		3.5
12		32.2
13		42.5
14		32.1
15	30000	
16	7.1	18.5
17		11.1
18		36.0
19		105.19.14
20	174.8	261.5
21		1531
22		1096
23		142.9
24		141.9
25	4.0	

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

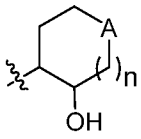
WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R is  ,

A is $-CH_2-$ or $-O-$ or $-S-$;

R^1 is selected from the group consisting of

(1) hydrogen, and

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

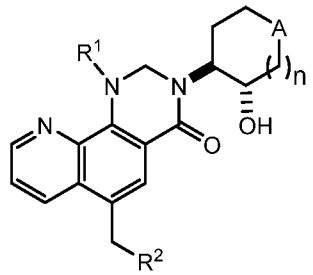
R^2 is selected from the group consisting of

(1) a C_{5-10}heterocyclyl, said heterocyclyl is optionally 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 optionally substituted with $-C_{1-6}$ alkyl; and

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

n is 0, 1 or 2.

2. The compound of claim 1 having formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof.

3. The compound of any of claims 1-2, wherein:

R^1 is hydrogen or $-C_{1-6}$ alkyl, said alkyl is optionally substituted with 1 to 3 groups independently selected from oxo and –OH;

R^2 is aryl or C_{5-10}heteroaryl, each of said aryl and heteroaryl is optionally 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 optionally substituted with C_{1-4}alkyl; and

n is 1 or 2.

4. The compound of any of claims 1-3, wherein:

R^1 is hydrogen, methyl, ethyl, propyl, $-CH_2CH_2$-OH, $-C(O)CH_3$, or $-CH_2C(O)H$;

R^2 is a phenyl or pyridyl, each of said phenyl and pyridyl is optionally substituted with halogen, methyl, ethyl, propyl, –O-methyl, –O-ethyl, –O-propyl, –S-methyl, –S-ethyl, –S-propyl, pyridyl or pyrazolyl; said substituent pyridyl and pyrazolyl is optionally substituted with methyl or ethyl; and

n is 1 or 2.

5. The compound of any of claims 1-4, wherein:

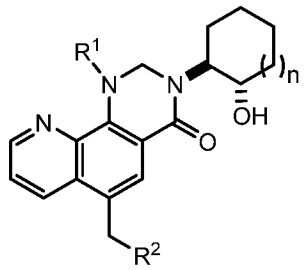
R^1 is methyl, ethyl, $-CH_2CH_2$-OH, $-C(O)CH_3$, or $-CH_2C(O)H$; and

R^2 is a phenyl or pyridyl, each of said phenyl and pyridyl is optionally substituted with halogen, methyl, ethyl, –O-methyl, –O-ethyl, –S-methyl, or –S-ethyl, pyridyl optionally substituted with methyl or pyrazolyl optionally substituted with methyl.

6. The compound of any of claims 1-5, wherein A is $-CH_2-$; and n is 1 or 2.

7. The compound of any of claims 1-5, wherein A is –O–; and n is 1.

8. The compound of claim 1 having formula (Ib):



(Ib),

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of

(1) hydrogen, and

(2) $-C_{1-4}$ alkyl, said alkyl is optionally substituted with oxo or –OH;

R^2 is selected from the group consisting of

(1) a C_{5-10} heteroaryl, said heteroaryl is optionally substituted with halogen, $-C_{1-4}$ alkyl, –O-C_{1-4} alkyl, –S-C_{1-4} alkyl, pyridyl or pyrazolyl, each of said pyridyl and pyrazolyl is optionally substituted with halogen or -C_{1-4} alkyl; and

(2) phenyl, said phenyl is optionally substituted with halogen, -C_{1-4} alkyl, pyridyl or pyrazolyl, each of said pyridyl and pyrazolyl is optionally substituted with halogen or -C_{1-4} alkyl; and

n is 1 or 2.

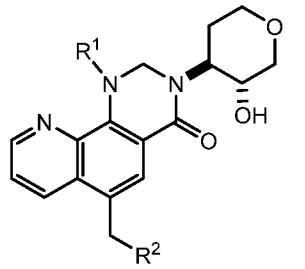
9. The compound of claim 8, wherein:

R^1 is hygrogen, methyl, ethyl, -CH_2CH_2-OH, -$C(O)CH_3$, or -$CH_2C(O)H$;

R^2 is phenyl or pyridyl; each of said phenyl and pyridyl is optionally substituted with halogen, methyl, ethyl, -O-methyl, -O-ethyl, -S-methyl, -S-ethyl, pyridyl optionally substituted with methyl, or pyrazolyl optionally substituted with methyl; and

n is 1 or 2.

10. The compound of claim 1 having formula (Ic):



(Ic),

or pharmaceutically acceptable salt thereof, wherein

R^1 is $-C_{1-4}$ alkyl, said alkyl is optionally substituted with oxo or –OH; and

R^2 is a C_{5-10} heteroaryl, said heteroaryl is optionally substituted with halogen, $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, $-S-C_{1-4}$ alkyl, pyridyl or pyrazolyl, each of said pyridyl and pyrazolyl is optionally substituted with $-C_{1-4}$ alkyl.

11. The compound of claim 10, wherein:
R^1 is hygrogen, methyl or ethyl; and
R^2 is pyridyl; said pyridyl is optionally substituted with halogen, methyl, ethyl, -O-methyl, -O-ethyl, -S-methyl, -S-ethyl, pyridyl optionally substituted with methyl, or pyrazolyl optionally substituted with methyl.

12. A compound which is selected from the group consisting of:
6-((6-Chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
6-((6-Chloropyridin-3-yl)methyl)-3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
6-((6-Chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycycloheptyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycycloheptyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,

3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((5'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido [3,2-*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((3*R*,4*S*)-3-hydroxytetrahydro-2*H*-pyran-4-yl)-1-methyl-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
1-ethyl-3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-(2-hydroxyethyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
1-Acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
1-Acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
1-Acetyl-6-((6-chloropyridin-3-yl)methyl)-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one,
1-Acetyl-3-((1*S*,2*S*)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[*h*]quinazolin-4(1*H*)-one,
3-((1*S*,2*S*)-2-Hydroxycyclohexyl)-1-methyl-6-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)-2,3-dihydropyrido[3,2-*h*]quinazolin-4(1*H*)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
1-acetyl-6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-2,3-dihydrobenzo[h]quinazolin-4(1H)-one,

3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((5'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((6'-methyl-[2,3'-bipyridin]-5-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
1-ethyl-3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-(2-hydroxyethyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
6-((6-chloropyridin-3-yl)methyl)-3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,

3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-6-((6-methoxypyridin-3-yl)methyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycycloheptyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((6-(methylthio)pyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
6-((6-chloropyridin-3-yl)methyl)-3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
3-((1S,2S)-2-hydroxycyclohexyl)-1-methyl-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydropyrido[3,2-h]quinazolin-4(1H)-one,
1-acetyl-3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-2,3-dihydrobenzo[h]quinazolin-4(1H)-one, and
1-acetyl-3-((1S,2S)-2-hydroxycyclohexyl)-6-((6-methylpyridin-3-yl)methyl)-2,3-dihydrobenzo[h]quinazolin-4(1H)-one;
or a pharmaceutically acceptable salt thereof.

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

14. 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 1-12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. Use of a pharmaceutical composition of any of claims 13-14 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.

16. Use of a compound of any of claims 1-12, 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.

17. 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 1-12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/12661

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 487/00, A61K 31/505, C07D 471/00 (2017.01)
CPC - C09B 57/00, C07D 215/24, C07D 471/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C07D 487/00, A61K 31/505, C07D 471/00 (2017.01)
CPC - C09B 57/00, C07D 215/24, C07D 471/04

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, Google Patent, Google Web
Search terms used - dihydropyrido quinazoline muscarinic M1 Alzheimer's disease positive allosteric modulators nabh4 reduction
Pubchem substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 8,664,234 B2 (Kuduk et al.) 04 March 2014 (04.03.2014); col 2, ln 27-30, col 23, scheme 1, col 27, scheme 3	1-3, 8-12
Y	US 2013/0116272 A1 (Kuduk et al.) 09 May 2013 (09.05.2013); para [0009]	1-3, 8-12
A	US 2015/0307497 A1 (Sugimoto et al.) 29 October 2015 (29.10.2015); entire document	1-3, 8-12
A	US 2014/0288084 A1 (Lindsley et al.) 25 September 2014 (25.09.2014); entire document	1-3, 8-12
A	US 2015/0141444 A1 (Kuduk et al.) 21 May 2015 (21.05.2015); entire document	1-3, 8-12

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 2017	30 MAR 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

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/12661

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.: 4-7, 13-17
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.