Title: PYRIDINYL-SUBSTITUTED PIPERAZINYL OXOETHYL TETRAHYDROPYRAZOLOPYRIDINES

Abstract: Pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of the Formula: are provided, in which variables are as described herein. Such compounds may be used to modulate ligand binding to histamine H3 receptors in vivo or in vitro, and are particularly useful in the treatment of a variety of central nervous system (CNS) and other disorders in humans, domesticated companion animals and livestock animals. Compounds provided herein may be administered alone or in combination with one or more other CNS agents to potentiate the effects of the other CNS agents(s). Pharmaceutical compositions and methods for treating such disorders are provided, as are methods for using such ligands for detecting histamine H3 receptors (e.g., receptor localization studies).
PYRIDINYL-SUBSTITUTED PIPERAZINYL OXOETHYL TETRAHYDROPYRAZOLOPYRIDINES

FIELD OF THE INVENTION

This invention relates generally to pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines, and to the use of such compounds for treating conditions responsive to histamine H3 receptor modulation. The invention further relates to the use of such compounds as probes for the detection and localization of histamine H3 receptors.

BACKGROUND OF THE INVENTION

Hormones and neurotransmitters regulate a wide variety of biological functions, often via specific receptor proteins located on the surface of living cells. Many of these receptors carry out intracellular signaling via the activation of coupled guanosine triphosphate-binding proteins (G proteins); such receptors are collectively called G protein-coupled receptors or GPCRs. The important role of GPCRs in the regulation of cell and organ function has attracted attention to these receptors as targets for new pharmaceutical agents.

Histamine is a multifunctional chemical transmitter that signals through specific cell surface GPCRs. To date, four histamine receptor subtypes have been identified: H1, H2, H3 and H4. Histamine H3 receptor is a presynaptic GPCR that is found primarily in the central nervous system, although lower levels are also found in the peripheral nervous system. Genes encoding the H3 receptor have been reported in various organisms, including humans (see Lovenberg et al. (1999) Molecular Pharmacology 55:1101-07), and alternative splicing of this gene appears to result in multiple isoforms. The histamine H3 receptor is an auto- and hetero-receptor whose activation leads to a decreased release of neurotransmitters (including histamine, acetylcholine, norepinephrine and glutamate) from neurons in the brain. Histamine H3 receptor is involved in the regulation of processes such as sleep and wakefulness, feeding and memory.

Antagonists of histamine H3 receptor increase synthesis and release of cerebral histamine and other neurotransmitters, inducing an extended wakefulness, an improvement in cognitive processes, a reduction in food intake and a normalization of vestibular reflexes. Such antagonists are useful, for example, as therapeutics for central nervous system disorders such as Alzheimer's disease, Parkinson's disease, schizophrenia, mood and attention alterations including attention deficit hyperactivity disorder and attention deficit disorder, memory and learning disorders, cognitive disorders (such as mild cognitive impairment and cognitive deficits in psychiatric pathologies), epilepsy, migraine, and disorders associated with the regulation of sleep and wakefulness, as well as in the treatment and prevention of...
conditions such as obesity, eating disorders, diabetes, vertigo, motion sickness and allergic rhinitis.

Accordingly, there is a need for new H3 receptor modulators. The present invention fulfills this need, and provides further related advantages.

5 SUMMARY OF THE INVENTION

In certain aspects, the present invention provides pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula I:

\[
\text{Formula I}
\]

and pharmaceutically acceptable salts, solvates and esters of such compounds. Within Formula I:

n is 1, 2 or 3;

R_x and R_y independently represent d-C_{3-8}alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, (C_3-8cycloalkyl)C_0-C_2alkyl or (4- to 10-membered heterocycle)C_0-C_2alkyl, each of which is optionally substituted and each of which is preferably substituted with from 0 to 4 substituents independently chosen from oxo, nitro, halogen, amino, cyano, hydroxy, aminocarbonyl, d-C_{3-8}alkyl, C_2-C_4alkenyl, Ci-C_4haloalkyl, Ci-C_4alkoxy, Ci-C_4aloalkoxy, Ci-C_4alkylthio, C_2-C_4alkyl ether, Ci-C_4alkanoyl, Cs-C_4alkanone, mono- or di-(Cr C_4alkyl)amino, mono- or di-(Ci-C_4alkyl)aminocarbonyl, C_5-Cycloalkyl and 4- to 7-membered heterocycloalkyl;

or R_x and R_y are taken together to form a 5- or 6-membered heterocycloalkyl or a 10- to 12-membered bicyclic heterocycloalkyl, each of which is optionally substituted and each of which is preferably substituted with from 0 to 2 substituents independently chosen from oxo, Ci-C_4alkyl, C_2-C_4alkenyl, Cvc-C_4alkynyl, C_2-C_4alkyl ether, mono- or di-(Cr C_4alkyl)amino-Co-C_4alkyl, (C_3-C_8cycloalkyl)C_0-C_2alkyl, (4- to 8-membered heterocycloalkyl)C_0-C_2alkyl and phenylC_0-C_2alkyl, each of which is substituents is optionally further substituted and each of which is preferably substituted with from 0 to 4 secondary substituents independently chosen from oxo, nitro, halogen, amino, cyano, hydroxy, aminocarbonyl, Ci-C_4alkyl, C_2-C_4alkenyl, Ci-C_4haloalkyl, Ci-C_4alkoxy, C_1-C_4haloalkoxy, Ci-C_4alkylthio, C_2-C_4alkyl ether, Ci-C_4alkanoyl, Cs-C_4alkanone, mono- or di-(Ci-C_4alkyl)amino, mono- or di-(Ci-C_4alkyl)aminocarbonyl, (C_3-C_8cycloalkyl)C_0-C_2alkyl and (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl;

such that at least one of R_x or R_y comprises at least one basic nitrogen atom;

R_1 represents 0, 1, 2 or 3 substituents, preferably such substituent(s) if present are independently chosen from halogen, cyano, amino, aminocarbonyl, oxo, CrC_{3-8}alkyl, C_1-
C<sub>6</sub>alkoxy, C<sub>3</sub>hydroxyalkyl, C<sub>6</sub>haloalkyl, C<sub>3</sub>haloalkoxy, mono- or di-(C<sub>6</sub>
alkyl)amino, mono- or di-(C<sub>3</sub>alkyl)aminocarbonyl, (C<sub>3</sub>ycycloalkyl)Co-C<sub>6</sub>alkyl and
(4- to 7-membered heterocycloalkyl)C<sub>6</sub>C<sub>4</sub>alkyl;

Rio represents from 0 to 3 substituents independently chosen from d-C<sub>6</sub>alkyl, o xo, fluoro and
d-C<sub>6</sub>fluoroalkyl; and

R<sub>13</sub> is hydrogen, halogen, cyano, C<sub>6</sub>haloalkyl, C<sub>3</sub>alkoxy or C<sub>3</sub>fluoroalkoxy.

Within certain aspects, pyridinyl-substituted piperazinyl oxoethyl tetrahydropropyrazolopyridines provided herein are histamine H3 receptor modulators that
exhibit a K<sub>i</sub> at a histamine H3 receptor, preferably a human H3 receptor, that is no greater
than 4 micromolar, 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10
nanomolar, as determined using a histamine-induced H3 receptor GTP binding assay.

Within certain aspects, compounds provided herein are labeled with a detectable marker (e.g., radiolabeled or fluorescein conjugated).

The present invention further provides, within other aspects, pharmaceutical
compositions comprising at least one pyridinyl-substituted piperazinyl oxoethyl
tetrahydropropyrazolopyridine as provided herein in combination with a physiologically
acceptable carrier or excipient.

Within further aspects, methods are provided for modulating H3 receptor activity,
comprising contacting a cell (e.g., neuronal) expressing H3 receptor with at least one H3
receptor modulator as described herein. Such contact may occur in vivo or in vitro and is
generally performed using a concentration of compound that is sufficient to alter H3 receptor
GTP binding in vitro (e.g., using an assay provided in Example 7 or Example 8, herein).

The present invention further provides methods for treating a condition responsive to
H3 receptor modulation in a patient, comprising administering to the patient a therapeutically
effective amount of at least one H3 receptor modulator. Such conditions include, for
example, attention deficit disorder, attention deficit hyperactivity disorder, dementia,
schizophrenia, cognitive disorders (including mild cognitive impairment), epilepsy, migraine,
excessive daytime sleepiness (EDS) and related disorders such as shift work sleep disorder,
jet lag, narcolepsy, sleep apnea, allergic rhinitis, vertigo, motion sickness, memory disorders
such as Alzheimer's disease, Parkinson's disease, obesity, eating disorders and diabetes.

Within further aspects, the present invention provides methods for determining the
presence or absence of H3 receptor in a sample, comprising: (a) contacting a sample with a
H3 receptor modulator as described herein under conditions that permit binding of the H3
receptor modulator to H3 receptor; and (b) detecting a level of the H3 modulator bound to H3
receptor.

The present invention also provides packaged pharmaceutical preparations,
comprising: (a) a pharmaceutical composition as described herein in a container; and (b)
instructions for using the composition to treat one or more conditions responsive to H3 receptor modulation, such as the conditions recited herein.

In yet another aspect, the present invention provides methods of preparing the compounds disclosed herein, including the intermediates.

These and other aspects of the present invention will become apparent upon reference to the following detailed description.

DETAILS DESCRIPTION

As noted above, the present invention provides pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines. Such compounds may be used in vitro or in vivo, to modulate H3 receptor activity in a variety of contexts.

TERMINOLOGY

Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. Where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (e.g., R₁, X, n). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

The phrase "pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines," as used herein, encompasses all compounds of Formula I (as well as compounds of other Formulas provided herein), including any enantiomers, racemates and stereoisomers, and pharmaceutically acceptable salts thereof. In certain embodiments, substituted pyrimidinones provided herein are isolated so as to be substantially free of residual organic solvent (i.e., any such solvent in the preparation is present in an amount that is at or below the limit set for that solvent by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)).

A "pharmaceutically acceptable salt" of a compound recited herein is an acid or base salt that is suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic
acids. Specific pharmaceutically acceptable anions for use in salt formation include, but are not limited to, acetate, 2-acetoxybenzoate, ascorbate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carbonate, chloride, citrate, dihydrochloride, diphosphate, edetate, estolate (ethylsuccinate), formate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, hydroxymaleate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phenylacetate, phosphate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulfamate, sulfanilate, sulfate, sulfonates including besylate (benzenesulfonate), camsylate (camphorsulfonate), edisylate (ethane-1,2-disulfonate), esylate (ethanesulfonate) 2-hydroxyethylsulfonate, mesylate (methanesulfonate), triflate (trifluoromethanesulfonate) and tosylate (p-toluenesulfonate), tannate, tartrate, teoclate and triethiodide. Similarly, pharmaceutically acceptable cations for use in salt formation include, but are not limited to ammonium, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, and metals such as aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein. In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, methanol, isopropanol or acetonitrile, is preferred.

It will be apparent that compounds and salts thereof provided herein may, but need not, be formulated as a hydrate, and that such hydrates are encompassed by the formulas, names and structures recited herein. In addition, the various non-hydrate solvates, non-covalent complexes, crystal forms and polymorphs of the compounds provided herein are within the scope of the present invention. Also provided herein are prodrugs of the compounds of the recited Formulas. A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified in vivo, following administration to a patient, to produce a compound a formula provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying
functional groups present in the compounds in such a way that the modifications are cleaved in vivo to yield the parent compounds.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include groups having from 1 to 8 carbon atoms (C1-C8alkyl), from 1 to 6 carbon atoms (C1-C6alkyl) and from 1 to 4 carbon atoms (C1-C4alkyl), such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. "C0-C4alkyl" refers to a single covalent bond (C0) or an alkylene group having from 1 to 4 carbon atoms.

"Alkylene" refers to a divalent alkyl group. C1-C4alkylene is an alkylene group having from 1 to 4 carbon atoms. Co-C4alkylene is a single covalent bond or an alkylene group having from 1 to 4 carbon atoms.

"Alkenyl" refers to straight or branched chain alkene groups, which comprise at least one unsaturated carbon-carbon double bond. Alkenyl groups include C2-C8alkenyl, C2-C6alkenyl and C2-C4alkenyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have one or more unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include C2-C8alkynyl, C2-C6alkynyl and C2-C4alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

A "cycloalkyl" is a group that comprises one or more saturated and/or partially saturated rings in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of the foregoing, such as cyclohexenyl. Cycloalkyl groups do not comprise an aromatic ring or a heterocyclic ring. A "(C3-C6cycloalkyl)Co-C2alkyl" is a Cs-Cg(cycloalkyl) group linked via a single covalent bond or a methylene or ethylene group.

By "alkoxy," as used herein, is meant an alkyl group attached via an oxygen bridge. Alkoxyl groups include Ci-Cgalkoxy and Ci-QalkOxy groups, which have from 1 to 8 or 1 to 4 carbon atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentxy are specific alkoxy groups. Similarly, "alkylthio" refers to an alkyl group attached via a sulfur bridge.

The term "oxo" is used herein to refer to an oxygen substituent of a carbon atom that results in the formation of a carbonyl group (C=O) or an oxygen substituent of a nitrogen atom that results in the formation of a N=O (or N*-O*) group. An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of -CHX to -C(=O)-. Preferably, an oxo substituent of an aromatic ring results in a substituted ring that retains aromaticity.
The term "alkanoyl" refers to an acyl group (e.g., -(C=O)-alkyl), in which carbon atoms are in a linear or branched alkyl arrangement and where attachment is through the carbonyl of the carbonyl group. Alkanoyl groups have the indicated number of carbon atoms, with the carbonyl carbon being included in the numbered carbon atoms. For example a C₂alkanoyl group is an acetyl group having the formula -(C=O)CH₃; "Cialkanoyl" refers to -(C=O)H. Alkanoyl groups include, for example, Ci-Cgalkanoyl, Ci-C₈alkanoyl and Ci-C₉alkanoyl groups, which have from 1 to 8, from 1 to 6 or from 1 to 4 carbon atoms, respectively.

An "alkanone" is a ketone group in which carbon atoms are in a linear or branched alkyl arrangement. "Cs-Cgalkanone," "C₃-C₈alkanone" and "C₃-C₉alkanone" refer to an alkanone having from 3 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C₃alkanone group has the structure -CH₂-(C=O)-CH₃.

Similarly, "alkyl ether" refers to a linear or branched ether substituent (i.e., an alkyl group that is substituted with an alkoxy group). Alkyl ether groups include C₂-C₈alkyl ether, C₂-C₆alkyl ether and C₂-C₄alkyl ether groups, which have 2 to 8, 6 or 4 carbon atoms, respectively. A C₆alkyl ether has the structure -CH₂O-CH₃.

The term "aminocarbonyl" refers to an amide group (i.e., -(C=O)NH₂). The term "mono- or di-(C₁-C₆alkyl)aminocarbonyl" refers to groups of the formula -(C=O)-N(R)₂, in which the carbonyl is the point of attachment, one R is Ci-C₆alkyl and the other R is hydrogen or an independently chosen Ci-C₆alkyl.

"Alkylamino" refers to a secondary or tertiary amine that has the general structure -NH-alkyl or -N(alkyl) (alkyl), wherein each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Such groups include, for example, mono- and di-(C₁-C₆alkyl)amino groups, in which each Ci-Cgalkyl may be the same or different, as well as mono- and di-(Ci-C₆alkyl)amino groups and mono- and di-(Ci-C₈alkyl)amino groups.

"Alkylaminoalkyl" refers to an alkylamino group linked via an alkylene group (i.e., a group having the general structure -alkylene-NH-alkyl or -alkylene-N(alkyl) (alkyl)) in which each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Alkylaminoalkyl groups include, for example, mono- and di-(Ci-C₆alkyl)aminoCi-C₄alkyl.

"Mono- or di-(Ci-C₆alkyl)aminoCo-C₄alkyl" refers to a mono- or di-(Ci-C₆alkyl)amino group linked via a single covalent bond or a d-C₄alkylene group. The following are representative alkylaminoalkyl groups:

It will be apparent that the definition of "alkyl" as used in the terms "alkylamino" and "alkylaminoalkyl" differs from the definition of "alkyl" used for all other alkyl-containing...
groups, in the inclusion of cycloalkyl and (cycloalkyl)alkyl groups (e.g., (C₃-C₇ cycloalkyl)Co-
alkyl).

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

A "haloalkyl" is an alkyl group that is substituted with 1 or more halogen atoms (e.g.,
"Ci-C₆ haloalkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups
include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl;
mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and
1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are Ci-C₆ fluoroalkyl
groups (i.e., all halogens are fluoro) such as trifluoromethyl and difluoromethyl. The term
"haloalkoxy" refers to a haloalkyl group as defined above attached via an oxygen bridge. "Ci-
C₆ haloalkoxy" groups have 1 to 6 carbon atoms.

A dash ("-" ) that is not between two letters or symbols is used to indicate a point of
attachment for a substituent. For example, -COOH is attached through the carbon atom.

A "heteroatom," as used herein, is oxygen, sulfur or nitrogen.

A "heterocycle" or "heterocyclic group" has from 1 to 3 fused, pendant or spiro rings,
least one of which is a heterocyclic ring (i.e., one or more ring atoms is a heteroatom
independently chosen from O, S and N, with the remaining ring atoms being carbon).
Additional rings, if present, may be heterocyclic or carbocyclic. Typically, a heterocyclic
ring comprises 1, 2, 3 or 4 heteroatoms; within certain embodiments each heterocyclic ring
has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 4 to 8 ring
members (rings having from 4 or 5 to 7 ring members are recited in certain embodiments) and
heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring
members. Certain heterocycles comprise a sulfur atom as a ring member; in certain
embodiments, the sulfur atom is oxidized to SO or SO₂. Heterocycles may be optionally
substituted with a variety of substituents, as indicated. Unless otherwise specified, a
heterocycle may be a heterocycloalkyl group (i.e., each ring is saturated or partially saturated)
or a heteroaryl group (i.e., at least one ring within the group is aromatic), and may be linked
via any ring atom, provided that a stable compound results. A nitrogen-containing (or N-
containing) heterocycle comprises at least one nitrogen ring atom; preferably such N-
containing heterocycle comprises at least one basic nitrogen atom (i.e., pKₐ ≥ 6). Additional
ring heteroatoms may, but need not, be present.

Certain heterocyclic groups include, for example, acridinyl, azepanyl, azocinyl,
benzimidazolyl, benzimidazolinyl, benzothiazolyl, benzisoxazolyl, benzofuranyl,
benzothiofuranyl, benzo thiophenyl, benzoxazolyl, benzothiazolyl, benzotriazoly lacarbazolyl,
benztetrazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl,
decahydroquinolinyl, dihydrofuro[2,3-b]tetrahydrofuran, dihydroisoquinolinyl,
dihydrotetrahydrofuranyl, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, dithiazinyl, furanyl, furazanyl,
imidazolinyl, imidazolidinyl, imidazolyl, indazolyl, indolenyl, indoliny1, indolizinyl, indolyl, isobenzofuranyl, isochroman yl, isoindazolyl, isoindoliny1, isoindolyl, isothiazolyl, isoxazolyl, isoquinolinyl, morpholinyl, naphthyridiny1, octahydroisoquinolinyl, oxadiazolyl, oxazolidinyl, oxazolyl, phenanthridiny1, phenanthroliny1, phenothiazinyl, phenoxathiinyl, phenoxazinyl, piperaziny1, piperidiny1, piperidony1, pteridiny1, puriny1, pyrany1, pyraziny1, pyrazolidiny1, pyrazoliny1, pyrazolyl, pyridaziny1, pyridimidazolyl, pyridooxazolyl, pyridothiazolyl, pyr idyl, pyrimidiny1, pyrrolidy1, pyrrolidony1, pyrroly1, quinazoliny1, quinoxalinyl, quinuclidiny1, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiadiaziny1, thia diazolyl, thianthrenyl, thiazolyl, thienothiazolyl, thieno oxazolyl, thienoimidazolyl, thienyl, thiopheny1, thiomorpholinyl and variants thereof in which the sulfur atom is oxidized, triazinyl, xanth enyl and any of the foregoing that are substituted with from 1 to 4 substituents as described above.

Certain heterocycles are 5- to 12-membered heteroaryl groups, or 5- or 6-membered heteroaryl rings (e.g., pyridyl, pyrimidy1 and pyridaziny1), each of which may be substituted as indicated. Other heterocycles are 9- or 10-membered heteroaryl groups, which may be substituted as indicated, and comprise two fused rings, at least one of which comprises a heteroatom and at least one of which is aromatic. Representative such groups include, for example, quinoliny1, quinoxaliny1, isoquinolinyl, pyridoimidazolyl and pyridopyraziny1. It will be apparent that the aromatic ring and the heterocycle may, but need not, be the same; for example, the term "heteroaryl" encompasses groups that comprise a phenyl ring and a heterocycloalkyl ring, such as 2,3-dihydro-1,4-benzodioxiny1 and 1,3-benzodioxol-5-yl. Other heterocycles are 4- to 8-membered heterocycloalkyl groups, which are saturated or partially saturate heterocyclic rings as described above, containing 4, 5, 6, 7 or 8 ring members.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described above, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound (i.e., a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

Groups that are "optionally substituted" are unsubstituted or substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4, 5 or 6 positions, by one or more suitable groups (which may be the same or different). Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of permissible substituents. Certain optionally substituted groups are substituted with
from 0 to 2, 3 or 4 independently selected substituents (i.e., are unsubstituted or substituted with up to the recited maximum number of substituents). Other optionally substituted groups are substituted with at least one substituent (e.g., substituted with from 1 to 2, 3 or 4 independently selected substituents).

Unless otherwise specified, the term "H3 receptor" is used herein to refer to any histamine H3 subtype receptor, including human H3 receptor (see, e.g., U.S. Patent No. 6,136,559), H3 receptor found in other mammals and chimeric receptors retaining H3 function, including the chimeric H3 receptor provided herein as SEQ ID NO:8.

A "H3 receptor modulator" is a compound that modulates H3 receptor GTP binding. A H3 receptor modulator may be a H3 receptor agonist or antagonist. A H3 receptor modulator binds with "high affinity" if the Kᵢ at H3 receptor is less than 4 micromolar, preferably less than 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar. Representative assays for evaluating an effect on H3 receptor GTP binding are provided in Examples 7 and 8, herein.

Unless otherwise specified, the terms "IC₅₀" and "EC₅₀" as used herein, refer to values obtained using the assay as described in Example 7.

A H3 receptor modulator is considered an "antagonist" if it detectably inhibits H3 receptor agonist-stimulated GTP binding (using, for example, the representative assay provided in Example 7); in general, such an antagonist inhibits such GTP binding with a IC₅₀ value of less than 4 micromolar, preferably less than 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar. H3 receptor antagonists include neutral antagonists and inverse agonists.

An "inverse agonist" of H3 receptor is a compound that reduces the GTP binding activity of H3 receptor below its basal activity level in the absence of added agonist. Inverse agonists of H3 receptor may also inhibit the activity in the presence of agonist. The basal activity of H3 receptor, as well as the reduction in H3 receptor GTP binding activity due to the presence of H3 receptor antagonist, may be determined using an assay provided in Example 7 or Example 8.

A "neutral antagonist" of H3 receptor is a compound that inhibits the activity of H3 receptor agonist, but does not significantly change the basal activity of the receptor (i.e., within the assay of Example 7 or Example 8 performed in the absence of agonist, H3 receptor activity is reduced by no more than 10%, preferably by no more than 5%, and more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). The basal activity is the level of GTP binding observed in the assay in the absence of added histamine or any other agonist, and in the further absence of any test compound. Neutral antagonists of H3 receptor may, but need not, inhibit the binding of agonist to H3 receptor.
As used herein a "H3 receptor agonist" is a compound that elevates the activity of the receptor above the basal activity level of the receptor. H3 receptor agonist activity may be identified using the representative assays provided in Example 7 and Example 8. In general, such an agonist has an EC₅₀ value of less than 4 micromolar, preferably less than 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar within the assay provided in Example 7. If the GTP binding activity brought about by a test compound attains the same level to that of histamine, it is defined as a full agonist. If the level of GTP binding activity brought about by a test compound is above baseline but below the level attained by histamine, it is defined as a partial agonist. Preferred antagonist compounds provided herein do not elevate GTP binding activity under such conditions more than 10% above baseline, preferably not more than 5% above baseline, and most preferably not more than 2% above baseline.

A "therapeutically effective amount" (or dose) is an amount that, upon administration to a patient, results in a discernible patient benefit (e.g., provides detectable relief from a condition being treated). Such relief may be detected using any appropriate criteria, including alleviation of one or more symptoms characteristic of the condition. A therapeutically effective amount or dose generally results in a concentration of compound in a body fluid (such as blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine) that is sufficient to alter H3 receptor GTP binding in vitro.

A "patient" is any individual treated with a compound or pharmaceutically acceptable salt thereof provided herein. Patients include humans, as well as other animals such as companion animals (e.g., dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to H3 receptor modulation, or may be free of such symptom(s) (e.g., treatment may be prophylactic).

**PYRIDINYL-SUBSTITUTED PIPERAZINYL OXOETHYL TETRAHYDROPYRAZOLOPYRIDINES**

As noted above, the present invention provides pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula 1. Within certain aspects, such compounds are H3 receptor modulators that may be used in a variety of contexts, including in the therapeutic treatment of human and animal patients as discussed below. H3 receptor modulators may also be used within in vitro assays (e.g., assays for receptor activity), and as probes for detection and localization of H3 receptor.
Within certain embodiments, pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula I further satisfy Formula II or Formula III:

Within Formula II:

\[ p \text{ is } 0 \text{ or } 1; \]

\[ X \text{ is CH, CH}_2, \text{ N or NH, such that if } p \text{ is } 0 \text{ then } X \text{ is CH or CH}_2; \]

\[ R_2 \text{ represents } 0, \text{ or } 1 \text{ or } 2 \text{ substituents independently chosen from d-C}_6\text{-alkyl, C}_2\text{-C}_6\text{-alkenyl, C}_2\text{-C}_6\text{-alkynyl, mono- or di-} \right(\text{C}_1\text{-C}_6\text{-alkyl})\text{aminoC}_6\text{-alkyl, (C}_3\text{-C}_6\text{cycloalkyl})\text{C}_6\text{-alkyl, (4- to 8-membered heterocycloalkyl})\text{C}_6\text{-alkyl and phenylC}_6\text{-alkyl}, each of which is optionally substituted and each of which is preferably substituted with from 0 to 4 substituents independently chosen from o xo, nitro, halogen, amino, cyano, hydroxy, aminocarbonyl, C_i\text{-alkyl, C}_2\text{-C}_6\text{-alkenyl, C}_1\text{-C}_6\text{-alkoxy, C}_1\text{-C}_6\text{haloalkyl, C}_1\text{-C}_6\text{haloalkoxy, C}_1\text{-C}_6\text{alkylthio, C}_2\text{-C}_6\text{alkyl ether, C}_i\text{-C}_6\text{alkanoyl, C}_6\text{-C}_6\text{alkylamine, mono- or di-} \right(\text{C}_1\text{-C}_6\text{-alkyl})\text{amino, mono- or di-} \right(\text{C}_1\text{-C}_6\text{-alkyl})\text{aminocarbonyl, (C}_3\text{-C}_6\text{cycloalkyl})\text{C}_6\text{-alkyl and (4- to 7-membered heterocycloalkyl})\text{C}_6\text{-alkyl; such that } R_2 \text{ represents at least one substituent that comprises at least one basic nitrogen if } X \text{ is CH or CH}_2; \]

and the remaining variables are as described for Formula I.

Within Formula III, R_3 and R_4 are independently chosen from hydrogen, halogen, cyano, C_i\text{-alkyl, C}_2\text{-C}_6\text{-alkoxy, C}_1\text{-C}_6\text{hydroxyalkyl, (C}_3\text{-C}_6\text{cycloalkyl})\text{C}_6\text{-alkyl and (4- to 7-membered heterocycloalkyl})\text{C}_6\text{-alkyl, and the remaining variables are as described for Formula I.} \]

In certain pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula II, the carbon or nitrogen atom at the X position is substituted with one or two substituents represented by R_2. For example, in certain compounds, X is N and R_2 represents an oxo substituent and (optionally) a second different substituent. It will be apparent that both the oxo substituent and the optional second substituent may, but need not, be covalently bonded to the N at the X position.

Certain pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula II further satisfy one of Formulas IIa-IDi:
Within Formulas Ila-IDi:

\( R_5 \) is \( \text{Ci-C}_6\text{alkyl}, \) \((\text{C}_3\text{-C}_7\text{cycloalkyl})\text{Co-C}_4\text{alkyl}, \) \( (4\text{- to 8-membered heterocycloalkyl})\text{Co-C}_4\text{alkyl} \) or \( \text{phenylCo-C}_4\text{alkyl} \), each of which is substituted with from 0 to 2 substituents independently chosen from halogen and \( \text{CVC}_6\text{alkyl} \);

\( R_6 \) is \( \text{Ci-C}_6\text{alkyl}, \) mono- or di-(\( \text{Ci-C}_6\text{alkyl})\text{aminoCo-C}_4\text{alkyl}, \) \( (\text{C}_3\text{-C}_7\text{cycloalkyl})\text{Co-C}_4\text{alkyl} \), or \( (4\text{- to 8-membered heterocycloalkyl})\text{Co-C}_4\text{alkyl} \) or \( \text{phenylCo-C}_4\text{alkyl} \), each of which is substituted with from 0 to 2 substituents independently chosen from amino, \( \text{d-C}_6\text{alkyl} \) and mono- or di-(\( \text{Ci-C}_6\text{alkyl})\text{aminoCo-C}_6\text{alkyl} \); such that \( R_6 \) comprises at least one basic nitrogen atom;

\( R_7 \) is \( \text{Ci-C}_6\text{alkyl}, \) \( \text{d-C}_6\text{hydroxyalkyl} \) or \( \text{C}_2\text{-C}_6\text{alkyl} \) ether;

and the remaining variables are as described for Formula II.

In certain embodiments of the above subformulas, \( R_5 \) is \( \text{d-C}_6\text{alkyl}, \) \( \text{C}_3\text{-C}_7\text{cycloalkyl}, \) \( (4\text{- to 7-membered heterocycloalkyl})\text{Co-C}_2\text{alkyl} \) or \( \text{phenylCo-C}_2\text{alkyl} \), each of which is substituted with from 0 to 2 substituents independently chosen from halogen and \( \text{Ci-C}_6\text{alkyl} \); and \( R_6 \) is mono- or di-(\( \text{Ci-C}_6\text{alkyl})\text{aminoCo-C}_6\text{alkyl} \) or a \( \text{N}-\text{containing} \) \( (4\text{- to 7-membered heterocycloalkyl})\text{Co-C}_6\text{alkyl} \) that is substituted with from 0 to 2 substituents independently chosen from halogen and \( \text{Ci-C}_6\text{alkyl} \).

In certain embodiments of Formula II and subformulas thereof, \( R_1 \) represents 1 or 2 substituents independently chosen from halogen, cyano, \( \text{Ci-C}_4\text{alkyl}, \) \( \text{Ci-C}_4\text{alkoxy}, \) \( \text{C}_1\text{-C}_4\text{hydroxyalkyl}, \) \( \text{C}_4\text{alkanoyl}, \) \( \text{C}_5\text{-C}_9\text{alkyl} \) ether, mono- or di-(\( \text{Ci-C}_4\text{alkyl})\text{aminoCo-C}_2\text{alkyl}, \) \( \text{C}_3\text{-C}_7\text{cycloalkyl} \) and \( 4\text{- to 7-membered heterocycloalkyl} \). In further such embodiments, \( R_1 \) represents 1 or 2 substituents independently chosen from halogen, cyano, \( \text{C}_1\text{-C}_4\text{alkyl}, \) \( \text{C}_1\text{-C}_4\text{alkoxy}, \) \( \text{C}_1\text{-C}_4\text{hydroxyalkyl}, \) \( \text{C}_1\text{C}_4\text{alkanoyl} \), \( (\text{C}_3\text{-C}_7\text{cycloalkyl})\text{Co-C}_4\text{alkyl} \) and \( (4\text{- to 7-
membered heterocycloalkyl)Co-C_2alkyl. In other embodiments of Formula II and subformulas thereof, R_1 represents 0 substituents.

Within certain pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula II, R_2 represents one substituent chosen from d-C_6alkyl, mono- or di-(C_1-C_4alkyl)amino-Co-C_4alkyl, C_3-C_7cycloalkyl, (4- to 7-membered heterocycloalkyl)C_0-C_2alkyl and phenyl-Co-C_2alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen and d-C_6alkyl. Within further such compounds, R_2 represents one substituent chosen from isopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Certain pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula III further satisfy one or more of Formulas IIa-IIIe:

![Chemical structures for Formulas IIa to IIIe](image)

Within Formulas IIa-IIIe:

- p is 0 or 1;
- X is CH, CH_2, N or NH, such that if p is 0 then X is CH or CH_2;
- R_7 is Ci-C_6alkyl or Ci-C_6hydroxyalkyl or C_2-C_4alkyl ether;
- R_8 and R_9 are independently chosen from Ci-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkyl ether, mono- or di-(Ci-C_6alkyl)aminoCo-C_4alkyl, (C_3-C_7cycloalkyl)Co-C_4alkyl and (4- to 7-membered heterocycloalkyl)Co-C_4alkyl; or R_8 and R_9 are taken together to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from Ci-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkyl ether, (C_3-C_7cycloalkyl)Co-C_4alkyl and (4- to 7-membered heterocycloalkyl)Co-C_4alkyl; such that at least one of R_8 and R_9 comprises at least one basic nitrogen atom;
- m is 2, 3 or 4;
- R_2 and R_5 are as described above; in certain embodiments R_5 is isopropyl, cyclobutyl, cyclopentyl or cyclohexyl;
- and the remaining variables are as described for Formula III.
In certain embodiments of Formula IHc, \( R_2 \) represents one substituent chosen from Ci-C\(_4\)alkyl, mono- or di-(Ci-C\(_4\)alkyl)aminoCo-C\(_4\)alkyl, C\(_3\)-C\(_4\)cycloalkyl, (4- to 7-membered heterocycloalkyl)C\(_0\)-C\(_2\)alkyl and phenylC\(_0\)-C\(_2\)alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen and d-C\(_4\)alkyl. In further embodiments, \( R_2 \) represents one substituent chosen from isopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Within certain embodiments of Formula III and subformulas thereof, neither \( R_3 \) nor \( R_4 \) is hydrogen; in other embodiments, exactly one of \( R_3 \) and \( R_4 \) is hydrogen; in still further embodiments, \( R_3 \) is halogen, cyano, Ci-C\(_4\)alkyl (e.g., methyl or ethyl), Ci-C\(_4\)alkoxy, d-Qhydroxyalkyl, cyclopropyl or morpholinyl; and \( R_4 \) is hydrogen.

Within certain embodiments, pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula I further satisfy Formula IV or Formula V:

![Formula IV](image)

![Formula V](image)

Within Formulas IV and V:

\( R_7, R_8 \) and \( R_9 \) are as described above;

\( m \) is 2, 3 or 4;

and the remaining variables are as described for Formula I.

Within certain embodiments of Formulas IV and V, \( R_1 \) represents 1 or 2 substituents independently chosen from halogen, cyano, Ci-C\(_4\)alkyl, Ci-C\(_4\)alkoxy, Ci-C\(_4\)hydroxyalkyl, d-C\(_4\)alkanoyl, C\(_2\)-C\(_4\)alkyl ether, mono- or di-(Ci-C\(_4\)alkyl)aminoC\(_0\)-C\(_2\)alkyl, C\(_3\)-C-cycloalkyl and 4- to 7-membered heterocycloalkyl. Within further embodiments, \( R_1 \) represents 1 or 2 substituents independently chosen from halogen, cyano, Ci-C\(_4\)alkyl, Ci-C\(_4\)alkoxy, Ci-C\(_4\)hydroxyalkyl, Ci-C\(_4\)alkanoyl, (C\(_3\)-C\(_2\)cycloalkyl)C\(_0\)-C\(_2\)alkyl and (4- to 7-membered heterocycloalkyl)C\(_0\)-C\(_2\)alkyl.

Certain pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula IV further satisfy the formula:

![Formula V](image)

wherein:

\( R_7 \) is Ci-C\(_4\)alkyl; and

\( R_8 \) and \( R_9 \) are independently chosen from Ci-C\(_0\)alkyl; or \( R_8 \) and \( R_9 \) are taken together to form

a 5- to 7-membered heterocycloalkyl.
Other pyridinyl-substituted piperazinyl oxoethyl tetrahydropyrazolopyridines of Formula IV further satisfy the formula:

![Chemical Structure]

wherein:

5  \( R_7 \) is \( \text{C}_{1-4}\)alkyl, \( \text{C}_{1-4}\)hydroxyalkyl or \( \text{C}_{2-4}\)alkyl ether;

R_8 and R_9 are taken together to form a 5- to 7-membered N-containing heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from \( \text{C}_{1-4}\)alkyl; and o is 0, 1 or 2.

Representative compounds provided herein include, but are not limited to, those specifically described in Examples 1-3. It will be apparent that the specific compounds recited herein are representative only, and are not intended to limit the scope of the present invention. Further, as noted above, all compounds of the present invention may be present as a free acid or base or as a pharmaceutically acceptable salt or solvate (e.g., hydrate).

In certain aspects, compounds provided are H3 receptor modulators, as determined using an assay for H3 receptor GTP binding. References herein to a "histamine-induced H3 receptor GTP binding assay" are intended to refer to either of the in vitro GTP binding assays provided in Examples 7 and 8, which may be performed in the presence or absence of added agonist. Briefly, to assess H3 receptor agonist-stimulated GTP binding, a H3 receptor preparation is incubated with a H3 receptor agonist (e.g., histamine or an analogue thereof such as R-alpha-methylhistamine), labeled (e.g., \( ^{35}\)S) GTP and unlabeled test compound.

Within the assays provided herein, the H3 receptor used is preferably mammalian H3 receptor (e.g., human or rat H3 receptor, and preferably human H3 receptor), and more preferably a chimeric human H3 receptor such as a receptor having the sequence provided in SEQ ID NO:8. The H3 receptor may be recombinantly expressed or naturally expressed. The H3 receptor preparation may be, for example, a membrane preparation from cells that recombinantly express H3 receptor. Incubation with a H3 receptor modulator results in a decrease or increase in the amount of label bound to the H3 receptor preparation, relative to the amount of label bound in the absence of the compound.

As noted above, compounds that are H3 receptor antagonists are preferred within certain embodiments. When agonist-contacted cells are contacted with a compound that is a H3 receptor antagonist, the response is preferably reduced by at least 20%, more preferably at least 50% and still more preferably at least 80%, as compared to cells that are contacted with the agonist in the absence of test compound. The IC_{50} for H3 receptor antagonists provided herein is preferably less than 4 micromolar, less than 1 micromolar, less than 500nM, less than 100 nM, less than 50 nM or less than 10 nM. In certain embodiments, H3 receptor
antagonists provided herein exhibit no detectable agonist activity in the assay of Example 7 at a concentration of compound equal to the IC_{50}. Certain preferred antagonists exhibit no detectable agonist activity in the assay at a concentration of compound that is 100-fold higher than the IC_{50}.

In certain embodiments, preferred H3 receptor modulators provided herein are non-sedating. In other words, a dose of H3 receptor modulator that is twice the minimum therapeutically effective dose causes only transient (i.e., lasting for no more than 1/4 the time that the therapeutic effect lasts) or preferably no statistically significant sedation in an animal model assay of sedation (using the method described by Fitzgerald et al. (1988) Toxicology 49(2-3):433-9). Preferably, a dose that is any of 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 times the minimum therapeutically effective dose does not produce statistically significant sedation.

If desired, H3 receptor modulators provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective concentrations of the compound to be achieved at oral doses of less than 140 mg/kg, preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, and still more preferably less than 1 mg/kg), toxicity (a preferred H3 receptor modulator is nontoxic when a therapeutically effective amount is administered to a subject), side effects (a preferred H3 receptor modulator produces side effects comparable to placebo when a therapeutically effective amount of the compound is administered to a subject), serum protein binding and in vitro and in vivo half-life (a preferred H3 receptor modulator exhibits an in vivo half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable for certain H3 receptor modulators. Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (e.g., intravenously). Serum protein binding may be predicted from albumin binding assays or whole serum binding assays. In vitro half-lives of compounds may be predicted from assays of microsomal half-life as described within Example 8 of PCT Publication Number WO 06/089076.

As noted above, preferred compounds provided herein are nontoxic. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established
criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, or (4) does not cause substantial release of liver enzymes.

As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that satisfies the criteria set forth in Example 9 of PCT Publication Number WO 06/089076. In other words, cells treated as described in Example 9 therein with 100 µM of such a compound exhibit ATP levels that are at least 50% of the ATP levels detected in untreated cells. In more highly preferred embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells.

A compound that does not significantly prolong heart QT intervals is a compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of a dose that yields a serum concentration equal to the EC$_{50}$ or IC$_{50}$ for the compound. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals. By "statistically significant" is meant results varying from control at the p<0.1 level or more preferably at the p<0.05 level of significance as measured using a standard parametric assay of statistical significance such as a student’s T test.

A compound does not cause substantial liver enlargement if daily treatment of laboratory rodents (e.g., mice or rats) for 5-10 days with a dose that yields a serum concentration equal to the EC$_{50}$ or IC$_{50}$ for the compound results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (e.g., dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

Similarly, a compound does not promote substantial release of liver enzymes if administration of twice the minimum dose that yields a serum concentration equal to the EC$_{50}$ or IC$_{50}$ for the compound does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more than 100% over matched mock-treated controls. In more highly preferred embodiments, such doses do not elevate such serum levels of ALT, LDH or AST by more than 75% or 50% over matched controls. Alternatively, a H3 receptor modulator does not promote substantial release of liver enzymes if, in an in vitro hepatocyte assay, concentrations
(in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) that are equal to the EC$_{50}$ or IC$_{50}$ for the compound do not cause detectable release of any such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In more highly preferred embodiments, there is no detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the EC$_{50}$ or IC$_{50}$ for the compound.

In other embodiments, certain preferred compounds do not substantially inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the EC$_{50}$ or IC$_{50}$ for the compound.

Certain preferred compounds are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral micronucleus assay or the like) at a concentration equal the EC$_{50}$ or IC$_{50}$ for the compound. In other embodiments, certain preferred H3 receptor modulators do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

For detection purposes, as discussed in more detail below, H3 receptor modulators provided herein may be isotopically-labeled or radiolabeled. For example, compounds may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as $^2$H, $^3$H, $^{11}$C, $^{12}$C, $^{13}$C, $^{15}$N, $^{16}$O, $^{17}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{19}$F and $^{35}$Cl. In addition, substitution with heavy isotopes such as deuterium (*i.e.*, $^2$H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

**PREPARATIONOF PYRIDINYL-SUBSTITUTED PIPERAZINYL OXOETHYL TETRAHYDROPYRAZOLOPYRIDINES**

Compounds provided herein may generally be prepared using standard synthetic methods. Starting materials illustrated in the schemes and in the examples are commercially available from suppliers such as Sigma-Aldrich Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that shown in any of the following Schemes may be used, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Each variable in the following schemes refers to any group consistent with the description of the compounds provided herein.
Certain abbreviations used in the following Schemes and elsewhere herein are:

- **Ac**: acetate
- **BOC**: *tert*-butyl carboxyl
- **BOP**: benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate
- **Bu**: butyl
- **CDCl₃**: deuterated chloroform
- **δ**: chemical shift
- **DCM**: dichloromethane
- **DMF**: N,N-dimethylformamide
- **DMFDMA**: N,N-dimethylformamide dimethylacetal
- **dppf**: 1,1'-bis(diphenylphosphino)ferrocene
- **Brederick reagent**: fert-butoxy bis(dimethylamino)methane
- **t-BuXPhos**: 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl
- **EtOAc**: ethyl acetate
- **Et**: ethyl
- **EtOH**: ethanol
- **Eq.**: equivalent(s)
- **¹H NMR**: proton nuclear magnetic resonance
- **HPLC**: high pressure liquid chromatography
- **h**: hour(s)
- **Hz**: hertz
- **LCMS**: liquid chromatography/mass spectrometry
- **MS**: mass spectrometry
- **mCPBA**: m-chloroperoxybenzoic acid
- **(M+1)**: mass + 1
- **Me**: methyl
- **MeOH**: methanol
- **min**: minute(s)
- **Pd₂(dba)₃**: tris(dibenzylideneacetone)dipalladium(O)
- **PPh₃**: triphenylphosphine
- **PTSA**: p-toluene sulfonic acid
- **TLC**: thin layer chromatography
- **rt**: room temperature
Preparation of compounds of formula 10 is shown in scheme 1. Reacting compound 1 with DMFDMA in DMF provides compound 2, which when heated with hydrazine affords pyrazole 3. Treatment of compound 3 with a suitable 4-pyridine halide under modified Buchwald conditions gives substituted pyrazole 4a. Alternatively, reacting 1 with a suitable hydrazine provides the hydrazone 5, which reacts with Brederick reagent at elevated temperature to furnish pyrazole 4a. Compounds 4b can also be prepared from compound 1 by treatment with a suitable amine, such as morpholine, to give enamine 6, which upon reaction with a suitable acid chloride gives compound 7. Condensation of 7 and a substituted hydrazine at elevated temperature provides pyrazole 4b.
Deprotection of 4 with HCl in a suitable solvent gives amine 8 as a dihydrochloride salt, which reacts with compound 9 to afford compound 10. Alternatively, reacting amine 8 with a suitable α-bromo acetate 11 gives ester 12, which when reacting with HCl affords acid 13 as the dihydrochloride salt. Finally, acid 13 can be converted to compound 10 by a standard amidation reaction.

Compounds of formula 16-21 can be prepared from the corresponding 2-chloropyridine 15, which can be prepared according to Scheme 1, by nucleophilic substitutions and by Pd catalyzed coupling reactions.

In certain embodiments, a compound provided herein may contain one or more asymmetric carbon atoms, so that the compound can exist in different stereoisomeric forms. Such forms can be, for example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single enantiomers (i.e., optically active forms). Standard methods for preparing single enantiomers include asymmetric synthesis and resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (e.g., $^{14}$C), hydrogen (e.g., $^3$H), sulfur (e.g., $^{35}$S) or iodine (e.g., $^{125}$I). Tritium labeled
compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising one or more compounds provided herein, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, water, buffers (e.g., neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione and/or preservatives. Preferred pharmaceutical compositions are formulated for oral delivery to humans or other animals (e.g., companion animals such as dogs or cats). In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, inhalation (e.g., nasal or oral), topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions in a form suitable for oral use are preferred. Such forms include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents to increase the bulk weight of the material to be tableted (e.g., calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents that modify the disintegration rate in the environment of use (e.g., corn starch, starch derivatives, alginic acid and salts of carboxymethylcellulose), binding agents that impart cohesive qualities to the powdered
material(s) (e.g., starch, gelatin, acacia and sugars such as sucrose, glucose, dextrose and lactose) and lubricating agents (e.g., magnesium stearate, calcium stearate, stearic acid or talc). Tablets may be formed using standard techniques, including dry granulation, direct compression and wet granulation. The tablets may be uncoated or they may be coated by known techniques.

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

Aqueous suspensions comprise the active material(s) in admixture with one or more suitable excipients, such as suspending agents (e.g., sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (e.g., naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also comprise one or more preservatives, such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil (e.g., arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents and/or flavoring agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The oily phase may be a vegetable oil (e.g., olive oil or arachis oil), a mineral oil (e.g., liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (e.g., gum acacia or gum tragacanth), naturally-occurring phosphatides (e.g., soy bean
lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (e.g., sorbitan monoleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (e.g., polyoxyethylene sorbitan monoleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

A pharmaceutical composition may be prepared as a sterile injectable aqueous or oleaginous suspension. The active ingredient(s), depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting agents and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectable compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Pharmaceutical compositions may also be prepared in the form of suppositories (e.g., for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the body temperature and will therefore melt in the body to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (e.g., dichlorodifluoromethane or trichlorofluoromethane).

Pharmaceutical compositions may be formulated for release at a pre-determined rate. Instantaneous release may be achieved, for example, via sublingual administration (i.e., administration by mouth in such a way that the active ingredient(s) are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract). Controlled release formulations (i.e., formulations such as a capsule, tablet or coated tablet that slows and/or delays release of active ingredient(s) following administration) may be administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at a target site. In general, a controlled release formulation comprises a matrix and/or coating that delays disintegration and absorption in the gastrointestinal tract (or implantation site) and thereby provides a delayed action or a sustained action over a longer period. One type of controlled-release formulation is a sustained-release formulation, in which at least one active ingredient
is continuously released over a period of time at a constant rate. Preferably, the therapeutic
agent is released at such a rate that blood (e.g., plasma) concentrations are maintained within
the therapeutic range, but below toxic levels, over a period of time that is at least 4 hours,
preferably at least 8 hours, and more preferably at least 12 hours. Such formulations may
generally be prepared using well known technology and administered by, for example, oral,
rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for
use within such formulations are biocompatible, and may also be biodegradable; preferably
the formulation provides a relatively constant level of H3 receptor modulator release. The
amount of H3 receptor modulator contained within a sustained release formulation depends
upon, for example, the site of implantation, the rate and expected duration of release and the
nature of the condition to be treated or prevented.

Controlled release may be achieved by combining the active ingredient(s) with a
matrix material that itself alters release rate and/or through the use of a controlled-release
coating. The release rate can be varied using methods well known in the art, including (a)
varying the thickness or composition of coating, (b) altering the amount or manner of addition
of plasticizer in a coating, (c) including additional ingredients, such as release-modifying
agents, (d) altering the composition, particle size or particle shape of the matrix, and (e)
providing one or more passageways through the coating. The amount of H3 receptor
modulator contained within a sustained release formulation depends upon, for example, the
method of administration (e.g., the site of implantation), the rate and expected duration of
release and the nature of the condition to be treated or prevented.

The matrix material, which itself may or may not serve a controlled-release function,
is generally any material that supports the active ingredient(s). For example, a time delay
material such as glyceryl monostearate or glyceryl distearate may be employed. Active
ingredient(s) may be combined with matrix material prior to formation of the dosage form
(e.g., a tablet). Alternatively, or in addition, active ingredient(s) may be coated on the surface
of a particle, granule, sphere, microsphere, bead or pellet that comprises the matrix material.
Such coating may be achieved by conventional means, such as by dissolving the active
ingredient(s) in water or other suitable solvent and spraying. Optionally, additional
ingredients are added prior to coating (e.g., to assist binding of the active ingredient(s) to the
matrix material or to color the solution). The matrix may then be coated with a barrier agent
prior to application of controlled-release coating. Multiple coated matrix units may, if
desired, be encapsulated to generate the final dosage form.

In certain embodiments, a controlled release is achieved through the use of a
controlled release coating (i.e., a coating that permits release of active ingredient(s) at a
controlled rate in aqueous medium). The controlled release coating should be a strong,
continuous film that is smooth, capable of supporting pigments and other additives, non-toxic,
Coatings that regulate release of the H3 receptor modulator include pH-independent coatings, pH-dependent coatings (which may be used to release H3 receptor modulator in the stomach) and enteric coatings (which allow the formulation to pass intact through the stomach and into the small intestine, where the coating dissolves and the contents are absorbed by the body). It will be apparent that multiple coatings may be employed (e.g., to allow release of a portion of the dose in the stomach and a portion further along the gastrointestinal tract). For example, a portion of active ingredient(s) may be coated over an enteric coating, and thereby released in the stomach, while the remainder of active ingredient(s) in the matrix core is protected by the enteric coating and released further down the GI tract. pH dependent coatings include, for example, shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, methacrylic acid ester copolymers and zein.

In certain embodiments, the coating is a hydrophobic material, preferably used in an amount effective to slow the hydration of the gelling agent following administration. Suitable hydrophobic materials include alkyl celluloses (e.g., ethylcellulose or carboxymethylcellulose), cellulose ethers, cellulose esters, acrylic polymers (e.g., poly(acrylic acid), poly(methacrylic acid), acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxy ethyl methacrylates, cyanoethyl methacrylate, methacrylic acid alkamide copolymer, poly(methyl methacrylate), polyacrylamide, ammonio methacrylate copolymers, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride) and glycidyl methacrylate copolymers) and mixtures of the foregoing. Representative aqueous dispersions of ethylcellulose include, for example, AQUACOAT® (FMC Corp., Philadelphia, PA) and SURELEASE® (Colorcon, Inc., West Point, PA), both of which can be applied to the substrate according to the manufacturer's instructions. Representative acrylic polymers include, for example, the various EUDRAGIT® (Rohm America, Piscataway, NJ) polymers, which may be used singly or in combination depending on the desired release profile, according to the manufacturer's instructions.

The physical properties of coatings that comprise an aqueous dispersion of a hydrophobic material may be improved by the addition or one or more plasticizers. Suitable plasticizers for alkyl celluloses include, for example, dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate and triacetin. Suitable plasticizers for acrylic polymers include, for example, citric acid esters such as triethyl citrate and tributyl citrate, dibutyl phthalate, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil and triacetin.

Controlled-release coatings are generally applied using conventional techniques, such as by spraying in the form of an aqueous dispersion. If desired, the coating may comprise pores or channels or to facilitate release of active ingredient. Pores and channels may be generated by well known methods, including the addition of organic or inorganic material that
is dissolved, extracted or leached from the coating in the environment of use. Certain such pore-forming materials include hydrophilic polymers, such as hydroxyalkylcelluloses (e.g., hydroxypropylmethylcellulose), cellulose ethers, synthetic water-soluble polymers (e.g., polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone and polyethylene oxide), watersoluble polydextrose, saccharides and polyasaccharides and alkali metal salts. Alternatively, or in addition, a controlled release coating may include one or more orifices, which may be formed by methods such as those described in US Patent Nos. 3,845,770; 4,034,758; 4,077,407; 4,088,864; 4,783,337 and 5,071,607. Controlled-release may also be achieved through the use of transdermal patches, using conventional technology (see, e.g., US Patent No. 4,668,232).

Further examples of controlled release formulations, and components thereof, may be found, for example, in US Patent Nos. 4,572,833; 4,587,117; 4,606,909; 4,610,870; 4,684,516; 4,777,049; 4,994,276; 4,996,058; 5,128,143; 5,202,128; 5,276,384; 5,384,133; 5,445,829; 5,510,119; 5,618,560; 5,643,604; 5,891,474; 5,958,456; 6,039,980; 6,143,353; 6,126,969; 6,156,342; 6,197,347; 6,387,394; 6,399,096; 6,437,000; 6,447,796; 6,475,493; 6,491,950; 6,524,615; 6,838,094; 6,905,709; 6,923,984; 6,923,988; and 6,911,217; each of which is hereby incorporated by reference for its teaching of the preparation of controlled release dosage forms.

In addition to or together with the above modes of administration, a compound provided herein may be conveniently added to food or drinking water (e.g., for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Compounds provided herein are generally present within a pharmaceutical composition at levels providing a therapeutically effective amount upon administration, as described above. Dosage forms providing dosage levels ranging from about 0.1 mg to about 140 mg per kilogram of body weight per day are preferred (about 0.5 mg to about 7 g per human patient 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. Dosage unit forms generally contain between from about 0.1 mg to about 2 g, preferably 0.5 mg to 1 g, and more preferably 1 mg to 500 mg, of an active ingredient. It will be understood, however, that the optimal dose for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time and route of administration; the rate of excretion; any simultaneous treatment, such as a drug combination; and the type and severity of the particular disease undergoing treatment.
Optimal dosages may be established using routine testing and procedures that are well known in the art.

Pharmaceutical compositions may be packaged for treating conditions responsive to H3 receptor modulation, including those specifically recited herein (e.g., attention deficit disorder, attention deficit hyperactivity disorder, schizophrenia, a cognitive disorder (such as mild cognitive impairment), epilepsy, migraine, narcolepsy, allergic rhinitis, vertigo, motion sickness, a memory disorder such as Alzheimer's disease, Parkinson's disease, obesity, an eating disorder or diabetes). Packaged pharmaceutical preparations comprise a container holding one or more dosage units comprising a therapeutically effective amount of at least one H3 receptor modulator as described herein and instructions (e.g., labeling) indicating that the contained composition is to be used for treating a condition responsive to H3 receptor modulation in the patient.

METHODS OF USE

H3 receptor modulators provided herein may be used to alter activity and/or activation of H3 receptors in a variety of contexts, both in vitro and in vivo. Within certain aspects, H3 receptor modulators may be used to inhibit or enhance (preferably to inhibit) H3 receptor activity in vitro or in vivo. In general, such methods comprise the step of contacting a H3 receptor with one or more H3 receptor modulators provided herein, in aqueous solution and under conditions otherwise suitable for binding of the H3 receptor modulator(s) to H3 receptor. The H3 receptor modulator(s) are generally present at a concentration that is sufficient to alter H3 receptor GTP binding activity in vitro (using the assay provided in Example 7). The H3 receptor may be present in solution or suspension (e.g., in an isolated membrane or cell preparation), or in a cultured or isolated cell. Within certain embodiments, the H3 receptor is present in a patient (e.g., expressed by a neuronal cell), and the aqueous solution is a body fluid. Preferably, one or more H3 receptor modulators are administered to a patient in an amount such that each H3 receptor modulator is present in at least one body fluid of the patient at a therapeutically effective concentration that is 1 micromolar or less; preferably 500 nanomolar or less; more preferably 100 nanomolar or less, 50 nanomolar or less, 20 nanomolar or less, or 10 nanomolar or less. For example, such compounds may be administered at a dose that is less than 20 mg/kg body weight, preferably less than 5 mg/kg and, in some instances, less than 1 mg/kg. In vivo, modulation of H3 receptor activity may be assessed by detecting an alteration of a symptom (e.g., memory or attention) in a patient being treated with one or more H3 receptor modulators provided herein.

The present invention further provides methods for treating conditions responsive to H3 receptor modulation. Within the context of the present invention, the term "treatment" encompasses both disease-modifying treatment and symptomatic treatment, either of which
may be prophylactic (i.e., before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms) or therapeutic (i.e., after the onset of symptoms, in order to reduce the severity and/or duration of symptoms). A condition is "responsive to H3 receptor modulation" if it is characterized by inappropriate activity of H3 receptor, regardless of the amount of H3 receptor ligand present locally, and/or if modulation of H3 receptor activity results in alleviation of the condition or a symptom thereof. Such conditions may be diagnosed and monitored using criteria that have been established in the art. Patients may include humans, domesticated companion animals and livestock, with dosages as described above.

Conditions that are responsive to H3 receptor modulation include, for example:

Cardiovascular disorders, including atherosclerosis, hypertension, myocardial infarction, coronary heart disease and stroke; Cancer (e.g., endometrial, breast, prostate and colon cancer, cutaneous carcinoma, medullary thyroid carcinoma and melanoma);

Metabolic disorders including impaired glucose tolerance, dyslipidaemia, and diabetes (e.g., non-insulin dependent diabetes mellitus);

Immune conditions and disorders including osteoarthritis, allergy (e.g., allergic rhinitis), and inflammation;

Respiratory conditions including nasal congestion, upper airway allergic response, asthma and chronic obstructive pulmonary disease;

Disorders associated with the regulation of sleep and wakefulness, or arousal and vigilance, including narcolepsy, jet lag, sleep apnea, and sleep disorders, such as excessive daytime sleepiness (EDS) (e.g., shift work sleep disorder), insomnia (e.g., primary insomnia), idiopathic hypersomnia, circadian rhythm sleep disorder, dyssomnia NOS, parasomnias including nightmare disorder, sleep terror disorder, sleep disorders secondary to depression, anxiety and/or other mental disorders and substance-induced sleep disorder;

Eating disorders (e.g., bulimia, binge eating and anorexia) and obesity;

Digestive system and gastrointestinal disorders including gallbladder disease, ulcer, hyper- and hypo-motility of the gastrointestinal tract and irritable bowel syndrome;

CNS disorders including hyper- and hypo-activity of the central nervous system, migraine, epilepsy, seizures, convulsions, mood disorders, attention deficit disorder, attention deficit hyperactivity disorder, bipolar disorder, depression, manic disorders, obsessive compulsive disorder, schizophrenia, migraine, vertigo, motion sickness, dementia, cognitive deficit (e.g., in psychiatric disorder, such as mild cognitive impairment), learning deficit, memory deficit (e.g., age-related memory dysfunction), multiple sclerosis, Parkinson's disease, Alzheimer's disease and other neurodegenerative disorders,
addiction (e.g., resulting from drug abuse), neurogenic inflammation and Tourette's syndrome;
Vestibular dysfunction (e.g., Meniere's disease, dizziness and motion sickness);
Pain (e.g., inflammatory pain or neuropathic pain) and itch;
Septic shock; and
Glaucma.

H3 receptor modulators may further be used to enhance a patient's cognitive ability.

In certain embodiments, compounds provided herein are used to treat attention deficit disorder, attention deficit hyperactivity disorder, schizophrenia, a cognitive disorder (such as mild cognitive impairment), epilepsy, migraine, narcolepsy, allergic rhinitis, vertigo, motion sickness, a memory disorder such as Alzheimer's disease, Parkinson's disease, obesity, an eating disorder or diabetes. Treatment regimens may vary depending on the compound used and the particular condition to be treated. However, for treatment of most disorders, a frequency of administration of 4 times daily or less is preferred. In general, a dosage regimen of 2 times daily is more preferred, with once a day dosing particularly preferred. It will be understood, however, that the specific dose level and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy. In general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

Within other aspects, H3 receptor modulators provided herein may be used within combination therapy for the treatment of conditions that are responsive to H3 receptor modulation, as described above. Within such combination therapy, a H3 receptor modulator is administered to a patient along with a second therapeutic agent that is not a H3 receptor modulator. The H3 receptor modulator and second therapeutic agent may be present in the same pharmaceutical composition, or may be administered separately in either order. It will be apparent that additional therapeutic agents may, but need not, also be administered.

Second therapeutic agents suitable for use in such combination therapy include, for example, antiobesity agents, antidiabetics, antihypertensive agents, antidepressants, antipsychotic agents and anti-inflammatory agents. In certain combinations, the second therapeutic agent is a compound for the treatment of attention deficit disorder or attention deficit hyperactivity disorder, an antipsychotic agent or an anti-obesity agent.

Histamine H1 receptor modulators represent one class of second therapeutic agents. Combination with H1 receptor modulators may be used, for example, in the treatment of
Alzheimer's disease, inflammatory diseases and allergic conditions. Representative H1 receptor antagonists include, for example, loratadine (CLARITIN™), desloratadine (CLARINEX™), fexofenadine (ALLEGRA™) and cetirizine (ZYRTEC™). Other H1 receptor antagonists include ebastine, mizolastine, acrivastine, astemizole, azatadine, azelastine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, diphenhydramine, hydroxyzine, levocabastine, promethazine and tripelennamine.

Antibesity therapeutic agents for use in combination therapy include, for example, leptin, leptin receptor agonists, melanin concentrating hormone (MCH) receptor antagonists, melanocortin receptor 3 (MC3) agonists, melanocortin receptor 4 (MC4) agonists, melanocyte stimulating hormone (MSH) agonists, cocaine and amphetamine regulated transcript (CART) agonists, dipeptidyl aminopeptidase inhibitors, a growth hormone secretagogue, beta-3 adrenergic agonists, 5HT-2 agonists, orexin antagonists, neuropeptide Y1 or Y5 antagonists, tumor necrosis factor (TNF) agonists, galanin antagonists, urocortin agonists, cholecystokinin (CCK) agonists, GLP-I agonists, serotonin (5HT) agonists, bombesin agonists, CB1 antagonists such as rimonabant, growth hormone, growth factors such as prolactin or placental lactogen, growth hormone releasing compounds, thyrotropin (TRH) agonists, uncoupling protein 2 or 3 (UCP 2 or 3) modulators, dopamine agonists, agents that modify lipid metabolism such as antilipidemic agents (e.g., cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine), lipase/amylase inhibitors, peroxisome proliferator-activated receptor (PPAR) modulators, retinoid X receptor (RXR) modulators, TR-beta agonists, agouti-related protein (AGRP) inhibitors, opioid antagonists such as naltrexone, exendin-4, GLP-I, ciliary neurotrophic factor, corticotropin-releasing factor binding protein (CRF BP) antagonists and/or corticotropin-releasing factor (CRF) agonists. Representative such agents include, for example, sibutramine, dexfenfluramine, dextroamphetamine, amphetamine, orlistat, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate and ecopipam.

Antihypertensive therapeutic agents for use in combination therapy include, for example, beta-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nifedipine, diltiazem and verapamil, alpha-blockers such as doxazosin, urapidil, prazosin and terazosin, and angiotensin receptor blockers such as losartan.

CNS-active agents for use in combination therapy include, but are not limited to the following: for anxiety, depression, mood disorders or schizophrenia - serotonin receptor (e.g.,
5-HT\textsubscript{1A} agonists and antagonists, neurokinin receptor antagonists, GABAergic agents, and corticotropin releasing factor receptor (CRF\textsubscript{1}) antagonists; for sleep disorders - melatonin receptor agonists, GABAergic agents, 5-HT\textsubscript{2A} antagonists and inverse agonists and orexin antagonists; and for neurodegenerative disorders - such as Alzheimer's dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. For example, such combination therapy may include a selective serotonin reuptake inhibitor (SSRI) or a non-selective serotonin, dopamine and/or norepinephrine reuptake inhibitor. Such agents include, for example, fluoxetine, sertraline, paroxetine, amitriptyline, seroxat and citalopram. For cognitive disorders, representative agents for use in combination therapy include GABAergic agents.

Other therapeutic agents suitable for combination therapy include, for example, agents that modify cholinergic transmission (e.g., 5-HT\textsubscript{6} antagonists), M1 muscarinic agonists, M2 muscarinic antagonists and acetylcholinesterase inhibitors.

Suitable doses for H3 receptor modulator within such combination therapy are generally as described above. Doses and methods of administration of other therapeutic agents can be found, for example, in the manufacturer's instructions in the *Physician's Desk Reference*. In certain embodiments, the combination administration of a H3 receptor modulator with the second therapeutic agent results in a reduction of the dosage of the second therapeutic agent required to produce a therapeutic effect (i.e., a decrease in the minimum therapeutically effective amount). Thus, preferably, the dosage of second therapeutic agent in a combination or combination treatment method is less than the maximum dose advised by the manufacturer for administration of the second therapeutic agent without combination administration of a H3 receptor modulator. More preferably this dosage is less than \(\frac{2}{3}\), even more preferably less than \(\frac{1}{6}\), and highly preferably, less than \(\frac{1}{8}\) of the maximum dose, while most preferably the dose is less than 10\% of the maximum dose advised by the manufacturer for the second therapeutic agent when administered without combination administration of a H3 receptor modulator. It will be apparent that the dosage amount of H3 receptor modulator component(s) of the combination needed to achieve the desired effect may similarly be affected by the dosage amount and potency of the other therapeutic component(s) of the combination.

In certain preferred embodiments, the combination administration of a H3 receptor modulator with other therapeutic agent(s) is accomplished by packaging one or more H3 receptor modulators and one or more other therapeutic agents in the same package, either in separate containers within the package or in the same contained as a mixture of one or more H3 receptor modulators and one or more other therapeutic agents. Preferred mixtures are formulated for oral administration (e.g., as pills, capsules, tablets or the like). In certain embodiments, the package comprises a label bearing indicia indicating that the one or more
H3 receptor modulators and one or more other therapeutic agents are to be taken together for the treatment of attention deficit disorder, attention deficit hyperactivity disorder, schizophrenia, a cognitive disorder (such as mild cognitive impairment), epilepsy, migraine, narcolepsy, allergic rhinitis, vertigo, motion sickness, a memory disorder such as Alzheimer's disease, Parkinson's disease, obesity, an eating disorder or diabetes.

Within separate aspects, the present invention provides a variety of non-pharmaceutical in vitro and in vivo uses for the compounds provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of H3 receptor (in samples such as cell preparations or tissue sections, preparations or fractions thereof). In addition, compounds provided herein that comprise a suitable reactive group (such as an aryl carbonyl, nitro or azide group) may be used in photoaffinity labeling studies of receptor binding sites. In addition, compounds provided herein may be used as positive controls in assays for receptor activity, as standards for determining the ability of a candidate agent to bind to H3 receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize H3 receptors in living subjects. For example, a H3 receptor modulator may be labeled using any of a variety of well known techniques (e.g., radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable incubation time (e.g., determined by first assaying a time course of binding). Following incubation, unbound compound is removed (e.g., by washing), and bound compound detected using any method suitable for the label employed (e.g., autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (e.g., 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of H3 receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of H3 receptor in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

Compounds provided herein may also be used within a variety of well known cell separation methods. For example, H3 receptor modulators may be linked to the interior surface of a tissue culture plate or other support, for use as affinity ligands for immobilizing and thereby isolating, H3 receptors (e.g., isolating receptor-expressing cells) in vitro. Within one preferred embodiment, a H3 receptor modulator linked to a fluorescent marker, such as fluorescein, is contacted with the cells, which are then analyzed (or isolated) by fluorescence activated cell sorting (FACS).
H3 receptor modulators provided herein may further be used within assays for the identification of other agents that bind to H3 receptor. In general, such assays are standard competition binding assays, in which bound, labeled H3 receptor modulator is displaced by a test compound. Briefly, such assays are performed by: (a) contacting H3 receptor with a radiolabeled H3 receptor modulator as described herein, under conditions that permit binding of the H3 receptor modulator to H3 receptor, thereby generating bound, labeled H3 receptor modulator; (b) detecting a signal that corresponds to the amount of bound, labeled H3 receptor modulator in the absence of test agent; (c) contacting the bound, labeled H3 receptor modulator with a test agent; (d) detecting a signal that corresponds to the amount of bound labeled H3 receptor modulator in the presence of test agent; and (e) detecting a decrease in signal detected in step (d), as compared to the signal detected in step (b).

The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification. Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein.

EXAMPLES

Mass spectroscopy data in the following Examples is Electrospray MS, obtained in positive ion mode using a Micromass Time-of-Flight LCT (Waters Corp.; Milford, MA), equipped with a Waters 600 pump (Waters Corp.; Milford, MA), Waters 996 photodiode array detector (Waters Corp.; Milford, MA), and a Gilson 215 autosampler (Gilson, Inc.; Middleton, WI). MassLynx™ (Waters Corp.; Milford, MA) version 4.0 software with OpenLynx Global Server™, OpenLynx™ and AutoLynx™ processing is used for data collection and analysis. MS conditions are as follows: capillary voltage = 3.5 kV; cone voltage = 30 V, desolvation and source temperature = 350°C and 120°C, respectively; mass range = 181-750 with a scan time of 0.22 seconds and an interscan delay of 0.05 seconds.

Analyses are performed using one of the following procedures:

Method 1: Sample volume of 1 microliter is injected onto a 50x4.6mm Chromolith SpeedROD RP-18e column (Merck KGaA, Darmstadt, Germany), and eluted using a 2-phase linear gradient at a flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% MeOH with 0.05% TFA; Mobile Phase B - 5% water, 95% MeOH with 0.025% TFA. The following gradient is used: 0-0.5 min 10-100%B, hold at 100%B to 1.2 min, return to 10%B at 1.21 min. Inject to inject cycle is 2.15 min.

Method 2: Sample volume of 1 microliter is injected onto a 30x4.6mm XBridge™ C18, 5µ, column (Waters Corp.; Milford, MA), and eluted using a 2-phase linear gradient at a
flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% MeOH with 0.025% Ammonium Hydroxide; Mobile Phase B - 5% water, 95% MeOH with 0.025% Ammonium Hydroxide. The following gradient is used: 0-0.5 min 5-100%B, hold at 100%B to 1.2 min, return to 5%B at 1.21 min. Inject to inject cycle is 2.15 min.

EXAMPLE 1
Preparation of Representative Compounds

1. 5-[(4-CYCLOBUTYLPIPERAZIN-1-YL)-2-OXOETHYL]-2-(2-METHYLPIRIDIN-4-YL)-4,5,6,7-TETRAHYDRO-2H-PYRAZOLO[4,3-C]PYRIDINE

![Compound 1](image)

Step 1. tert-Butyl-3-[(dimethylamino)methylene]-4-oxopiperidine-1-carboxylate

A mixture of N-Boc-piperidone (75 g, 0.377 mol), DMF (350 mL) and DMFDMA (49.4 g, 0.414 mol) is heated at 100 °C under N₂ for 16 h. The volatiles are evaporated under vacuum and the thick yellow oil obtained is dissolved in EtOAc (500 mL) and washed with water (300 mL), brine (300 mL), and then dried. Evaporation of solvents affords the title compound as a yellow oil, which is used in the next step without further purification.

Step 2. tert-Butyl 4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carboxylate

To a solution of tert-butyl-3-[(dimethylamino)methylene]-4-oxopiperidine-1-carboxylate (63.6 g, 250 mmol) in EtOH (200 mL) is added hydrazine (9.6 mL, 305 mmol) and the mixture is heated at reflux for 8 h. Solvent is evaporated in vacuo and the residue is purified by flash column chromatography (5% MeOH in CH₂Cl₂) to give the title compound as a white solid.

Step 3. tert-Butyl 2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carboxylate
A mixture of tert-butyl 4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carboxylate (10.0 g, 44.79 mmol), 4-bromo-2-methylpyridine (7.94 g, 46.13 mmol), Pd\(_2\)(dba)_3 (657 mg, 0.72 mmol), t-BuXPhos (1.22 mg, 2.87 mmol) and tBuONa (4.74 g, 49.27 mmol) in toluene (150 mL) is degassed by argon then heated at 120 °C in a sealed tube overnight. EtOAc (200 mL) and water (250 mL) are added and the layers are separated. The organic layer is washed with water (200 mL), brine (200 mL), dried and evaporated. Purification of the residue by flash column chromatography (1:1 hexane: EtOAc) gives a white solid as the mixture of 2 regio isomers. Recrystallization of the solid from 1:1 hexane: EtOAc gives the title compound as white needles.

Step 4. 2-(2-Methylpyridazin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine dihydrochloride

To a solution of tert-butyl 2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.38 g, 7.57 mmol) in dioxane (20 ml) is added 4N HCl in dioxane (20 mL, 80 mmol) and the mixture is stirred at rt overnight. The solvent is removed and the residue is washed with ether to give the title compound as a white solid.

Step 5. 5-[(4-Cyclobutylpiperazin-1-yl)-2-oxoethyl]-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine

A mixture of 2-(2-methylpyridazin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine dihydrochloride (920 mg, 3.2 mmol), 1-(chloroacetyl)-4-cyclobutylpiperazine (prepared essentially as described in PCT International Application Publication No. WO 2007/106349; 694 mg, 3.2 mmol), K\(_2\)CO\(_3\) (2.2 g, 16 mmol) and KI (132 mg, 0.8 mmol) in CH\(_3\)CN (20 ml) is stirred at rt overnight. The solvent is removed in vacuo and the residue is partitioned between water (20 mL) and EtOAc (20 mL). The layers are separated and the aqueous layer is extracted with EtOAc (3 x 20 mL). The combined extracts are washed with brine (30 mL), dried and evaporated. The resultant oil is purified by flash column chromatography (100:5:0.5 CH\(_2\)Cl\(_2\): MeOH: NH\(_4\)OH) to give a light yellow solid. MS (M+) 395.28; retention time: 1.07 min (method 2); \(^1\)H NMR (δ, ppm): 8.47 (d, 1H), 7.70 (s,
2. 2-(2-CHLOROPYRIDIN-4-YL)-5-[(4-CYCLOBUTYLPIPERAZIN-1-YL)-2-OXOETHYL]-4,5,6,7-TETRAHYDRO-2H-PYRAZOLO[4,3-C]PYRIDINE

![Compound 2](image)

**Step 1. 2-Chloro-4-hydrazino-pyridine**

At 0 °C, to a solution of 4-amino-2-chloro-pyridine (6.6 g, 51.3 mmol) in HCl (6N, 50 mL) is added NaNC(O)₂ (4.43 g, 64.2 mmol) in water (10 mL) dropwise while maintaining the internal temperature below 10 °C. The mixture is stirred at 0 °C to about 10 °C for 1 h, then SnCl₂ hydrate (29 g, 128.3 mmol) in 6N HCl (50 mL) is added dropwise. The mixture is stirred at 0 °C to rt overnight. ION NaOH solution is added until pH > 8 and the mixture is extracted with CH₂Cl₂ (200 mL x 4). The combined extracts are washed with brine (300 mL), dried and solvent evaporated under vacuum. The semi-solid obtained is used in the next step without further purification.

**Step 2. tert-Butyl 4-[(2-chloropyridin-4-yl)hydrazono]-piperidine-1-carboxylate**

A mixture of 2-chloro-4-hydrazino-pyridine (587 mg, 4.09 mmol), Boc-4-piperidone (819 g, 4.09 mmol) in EtOH (20 mL) is heated at reflux for 3 h. The mixture is concentrated and the resultant oil is purified by column chromatography (1:1 EtOAc : hexane) to give a light yellow solid.

**Step 3. tert-Butyl 2-(2-chloropyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carboxylate**
A mixture of tert-butyl 4-[(2-chloropyridin-4-yl)hydrazono]-piperidine-1-carboxylate (610 mg, 1.88 mol) and Bredereck's reagent (4 ml) is heated at 120 °C overnight. Excess solvent is removed under high vacuum and the oil is partitioned between EtOAc (30 mL) and water (25 mL). The layers are separated and the aqueous layer is extracted with EtOAc (20 mL). The combined organic extracts are washed with brine (20 mL), dried, and solvent evaporated. Purification of the residue by flash column chromatography (2:1 hexane: EtOAc) gives the title compound as a white solid.

Step 4. 2-(2-Chloropyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine dihydrochloride

To a solution of tert-butyl 2-(2-chloropyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carboxylate (580 g, 1.73 mmol) in dioxane (5 mL) is added 4N HCl in dioxane (5 mL, 20 mmol) and the mixture is stirred at rt overnight. The solvent is removed and the residue is washed with ether to give the title compound as a white solid.

Step 5. 2-(2-Chloropyridin-4-yl)-5-[(4-cyclobutylpiperazin-1-yl)-2-oxoethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine

A mixture of 2-(2-chloropyridin-4-yl)-4,5,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine dihydrochloride (143 mg, 0.45 mmol), l-(chloroacetyl)-4-cyclobutylpiperazine (98 mg, 0.45 mmol), K$_2$CO$_3$ (311 mg, 2.25 mmol) and KI (15 mg, 0.09 mmol) in CH$_3$CN (10 mL) is stirred at rt overnight. The solvent is removed in vacuo and the residue is partitioned between water (10 mL) and EtOAc (10 mL). The layers are separated and the aqueous layer is extracted with EtOAc (3 x 10 mL) and the combined extracts are washed with brine (20 mL), dried, and solvent evaporated. The resultant oil is purified by flash column (100:5:0.5 CH$_2$Cl$_2$: MeOH: NH$_4$OH) to give a light yellow solid; MS (M+I): 415.25; retention time: 0.56 min (method 1).
3. 5-[(4-CYCLOBUTYLPIPERAZIN-1-YL)-2-OXOETHYL]-2-(2-MORPHOLIN-4YLPIRIDIN-4-YL)-4,5,6,7-TETRAHYDRO-2H-PYRAZOLO[4,3-C]PYRIDINE

Compound 3

A solution of 2-(2-chloropyridin-4-yl)-5-[(4-cyclobutylpiperazin-1-yl)-2-oxoethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (100 mg 0.24 mmol) in morpholine (3 mL) is heated at 180 °C in microwave (150 w) for 1 h. The solvent is evaporated and to the residue is added NaHCO₃ solution (10 mL) and EtOAc (20 mL). The layers are separated and the organic layer is washed with brine (10 mL), dried, and solvent evaporated. The residue is purified by preparative TLC (100:5:0.5 CH₂Cl₂:MeOH: NH₄OH) to give a light yellow solid.

MS (M+1): 466.33; retention time: 1.1 min (method 2).

4. 2-(2-CYANOPYRIDIN-4-YL)-5-[(4-CYCLOBUTYLPIPERAZIN-1-YL)-2-OXOETHYL]-4,5,6,7-TETRAHYDRO-2H-PYRAZOLO[4,3-C]PYRIDINE

Compound 4

A mixture of 2-(2-chloropyridin-4-yl)-5-[(4-cyclobutylpiperazin-1-yl)-2-oxoethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (100 mg 0.24 mmol), Zn(CN)₂ (32 mg, 0.24 mmol), Pd₂(dba)₃ (9 mg, 0.01 mmol) and dppf (11 mg, 0.02 mmol) in DMF (2 mL) is degassed with argon and then heated at 110 °C in a sealed tube overnight. The solvent is evaporated and to the residue is added water (10 mL) and CH₂Cl₂ (20 mL). The layers are separated and the organic layer is washed with brine (10 mL), dried, and solvent evaporated. The residue is purified by preparative TLC (100:5:0.5 CH₂Cl₂:MeOH: NH₄OH) to give a light yellow solid. MS (M+1): 406.29; retention time: 0.36 min (method 1).

5. 5-[(4-CYCLOBUTYLPIPERAZIN-1-YL)-2-OXOETHYL]-2-(2-CYCLOPROPYLPIRIDIN-4-YL)-4,5,6,7-TETRAHYDRO-2H-PYRAZOLO[4,3-C]PYRIDINE

Compound 5
A mixture of 2-(2-chloropyridin-4-yl)-5-[(4-cyclobutylpiperazin-1-yl)-2-oxoethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (135 mg, 0.33 mmol), cyclopropylboronic acid (86 mg, 1 mmol), Pd(OAc)$_2$ (5 mg, 0.02 mmol), tricyclohexylphosphine (11 mg, 0.04 mmol) and K$_3$PO$_4$ (425 mg, 2 mmol) in toluene (5 ml) and water (2 ml) is degassed with argon, and then heated at 110 °C in a sealed tube overnight. The solvent is evaporated and to the residue is added water (10 mL) and CH$_2$Cl$_2$ (20 mL). The layers are separated and the organic layer is washed with brine (10 mL), dried, and solvent evaporated. The residue is purified by preparative TLC (100:5:0.5 CH$_2$Cl$_2$: MeOH: NH$_4$OH) to give a light yellow solid. MS (M+1): 421.27; retention time: 1.13 min (method 2); $^1$H NMR (δ, ppm): 8.41 (d, 1H), 7.70 (s, 1H), 7.44 (d, 1H), 7.24 (dd, 1H), 3.65 (s, broad, 6H), 3.41 (s, 2H), 2.89 (s, 4H), 2.66-2.72 (m, 1H), 2.28-2.31 (m, 4H), 1.63-2.10 (m, 7H), 0.98-1.10 (m, 4H).

6. 5-[(4-CYCLOBUTYLPIPERAZIN-1-YL)-2-OXOETHYL]-2-(2-METHOXYPYRIDIN-4-YL)-4,5,6,7-TETRAHYDRO-2H-PYRAZOLO[4,3-C]PYRIDINE

A mixture of 2-(2-chloropyridin-4-yl)-5-[(4-cyclobutylpiperazin-1-yl)-2-oxoethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (300 mg, 0.72 mmol), NaOMe (100 mg, 1.85 mmol) in DMF (3 mL) is heated at 100 °C overnight. The solvent is evaporated and to the residue is added water (20 mL) and CH$_2$Cl$_2$ (25 mL). The layers are separated and the organic layer is washed with brine (20 mL), dried, and solvent evaporated. The residue is purified by preparative TLC (100:5:0.5 CH$_2$Cl$_2$: MeOH: NH$_4$OH) to give a light yellow solid. MS (M+1): 411.29; retention time: 1.09 min (method 2); $^1$H NMR (δ, ppm): 8.14 (d, 1H), 7.66 (s, 1H), 7.18 (dd, 1H), 6.96 (d, 1H), 3.95 (s, 3H), 3.65 (s, broad, 6H), 3.40 (s, 2H), 2.88 (s, 4H), 2.67-2.73 (m, 1H), 2.28-2.32 (m, 4H), 1.64-2.05 (m, 6H).

7. 2-(2-ACETILPYRIDIN-4-YL)-5-[(4-CYCLOBUTYLPIPERAZIN-1-YL)-2-OXOETHYL]-4,5,6,7-TETRAHYDRO-2H-PYRAZOLO[4,3-C]PYRIDINE

A mixture of 2-(2-chloropyridin-4-yl)-5-[(4-cyclobutylpiperazin-1-yl)-2-oxoethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (415 mg, 1 mmol), tributyl(l-ethoxyvinyl)tin
(542 mg, 1.5 mmol) and Pd(PPh₃)₃ (58 mg, 0.05 mmol) in toluene (10 ml) is degassed with argon, and then heated at 110 °C in a sealed tube overnight. The solvent is evaporated and to the residue is added THF (10 mL) and 2N HCl (10 mL). The mixture is stirred at rt for 3 h and the solvent is removed. To the residue is added CH₂Cl₂ (25 mL) and NaHCO₃ solution (20 mL). The layers are separated and the organic layer is washed with brine (20 mL), dried, and solvent evaporated. The residue is purified by preparative TLC (100:5:0.5 CH₂Cl₂: MeOH: NH₄OH) to give a light yellow solid. MS (M+l): 423.29; retention time: 1.09 min (method 2).

8. 5-[(4-CYCLOBUTYLPIPERAZIN-1-YL)-2-OXOETHYL]-2-[2-(1-HYDROXY-1-METHLETHYL)PYRIDIN-4-YL]-4,5,6,7-TETRAHYDRO-2H-PYRAZOLO[4,3-C]PYRIDINE

At 0 °C, to a solution of 2-(2-acetylpyridin-4-yl)-5-[(4-cyclobutylpiperazin-1-yl)-2-oxoethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (283 mg, 0.67 mmol) in THF (10 mL) is added MeMgCl (3N in THF, 0.28 ml, 0.84 mmol) dropwise and the mixture is stirred at 0 °C for 2 h. 0.5N NaOH (5 mL) is added and the mixture is evaporated to dryness. To the residue is added CH₂Cl₂ (25 mL) and water (10 mL). The layers are separated and the organic layer is washed with brine (10 mL), dried, and solvent evaporated. The residue is purified by preparative TLC (100:5:0.5 CH₂Cl₂: MeOH: NH₄OH) to give a light yellow solid; MS (M+l): 439.33; retention time: 1.07 min (method 2).

9. 5-[(4-CYCLOPENTYLPIPERAZIN-1-YL)-2-OXOETHYL]-2-(2-METHYL)PYRIDIN-4-YL)-4,5,6,7TETRAHYDRO-2H-PYRAZOLO[4,3-C]PYRIDINE

Step 1. [2-(2-Methyl-pyridin-4-yl)-2,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-yl]-acetic acid t-butyl ester
To a mixture of 2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine hydrochloride (3.0 g, 10.45 mmol) and t-butyl bromoacetate (2.04 g, 10.45 mmol) in 50 mL of acetonitrile is added solid K$_2$CO$_3$ (8.67 g, 62.7 mmol). The resultant mixture is stirred at rt overnight. The mixture is then diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined extracts are washed with brine (100 mL), dried over Na$_2$SO$_4$, filtered and concentrated to give dark brown oil. The resulting residue is purified by column chromatography (EtOAc/hexanes : 1/2) to afford the product as a light-brown oil.

Step 2. [2-(2-Methyl-pyridin-4-yl)-2,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-yl]-acetic acid dihydrochloride

\[ \text{HO-} \begin{array}{c} \text{N} \\ \text{N} \\ \text{N} \\ \text{N} \end{array} \text{C=O} \begin{array}{c} \text{N} \\ \text{N} \\ \text{N} \\ \text{N} \end{array} \text{2HCl} \]

To a solution of tert-butyl [2-(2-methyl-pyridin-4-yl)-2,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-yl]-acetic acid t-butyl ester (3.1 g, 9.43 mmol) in dioxane (80 mL) is added 4N HCl in dioxane (20 mL, 80 mmol) and the mixture is stirred at rt overnight. The solvent is removed and the residue is washed with ether to give the title compound as a white solid.

Step 3. 5-[(4-Cyclopentylpiperazin-1-yl)-2-oxoethyl]-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine

\[ \text{N-} \begin{array}{c} \text{N} \\ \text{N} \\ \text{N} \\ \text{N} \end{array} \text{C=O} \begin{array}{c} \text{N} \\ \text{N} \\ \text{N} \\ \text{N} \end{array} \]

To a solution of 2-(2-methyl-pyridin-4-yl)-2,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-S-ylJ-acetic acid dihydrochloride (70 mg, 0.2 mmol), Et$_3$N (0.14 ml, 1 mmol), and cyclopentylpiperazine (47 mg, 0.3 mmol) in CH$_2$Cl$_2$ is added BOP (107 mg, 0.24 mmol) and the mixture is stirred at rt overnight. Solvent is removed under vacuum and water (6 mL) and EtOAc (15 mL) is added. The layers are separated and the organic layer is washed with brine (6 mL), dried over Na$_2$SO$_4$ and solvent evaporated under vacuum. The residue is purified by preparative TLC (100:5:0.5 CH$_2$Cl$_2$; MeOH: NH$_4$OH) to afford the product as a light yellow solid. MS (M+): 409.28; retention time: 1.12 min (method 2).
EXAMPLE 2

Preparation of 5-(4-Cyclobutyl-4-oxidopiperazin-1-yl)-2-oxoethyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine

5

Step 1. 4-(Chloroacetyl)-1-cyclobutylpiperazine 1-oxide

At 0 °C, to a solution of 1-(chloroacetyl)-4-cyclobutylpiperazine (1.25 g, 5.77 mmol) in CH₂Cl₂ (40 mL) is added mCPBA (77%, 1.62 g, 7.21 mmol) and the mixture is stirred at 0 °C to rt overnight. Excess NH₃ gas is bubbled through and the mixture is filtered. The filtrate is concentrated under vacuum and the residue is purified by flash column chromatography (100:10:1 CH₂Cl₂:MeOH: NH₄OH) to give the title compound as a white solid.

Step 2. 5-[(4-Cyclobutyl-4-oxidopiperazin-1-yl)-2-oxoethyl]-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine

A mixture of 2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine dihydrochloride (370 mg, 1.29 mmol), 4-(chloroacetyl)-1-cyclobutylpiperazine 1-oxide (300 mg, 1.29 mmol), K₂CO₃ (1.07 g, 7.71 mmol) and KI (107 mg, 0.65 mmol) in CH₃CN (20 mL) is stirred at ambient temperature overnight. The solvent is removed in vacuo and the residue is partitioned between water (10 mL) and CH₂Cl₂ (20 mL). The layers are separated and the aqueous layer is extracted with CH₂Cl₂ (3 x 20 mL). The combined organic extracts are washed with brine (20 mL), dried and solvent evaporated. The resultant oil is purified by flash column chromatography (100:10:1 CH₂Cl₂: MeOH: NH₄OH) to give a light yellow solid. MS (M+1): 411.24; retention time: 0.38 min (method 2).
EXAMPLE 3

Additional Representative Compounds

Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein. Compounds listed in Table I are prepared using such methods. All compounds in Table I exhibit a percent inhibition of the signal obtained with 1 µM histamine using 4 µM of the compound, determined as described in Example 8, of at least 75%. The molecular weight (presented as M+I) obtained as described above is shown in the column headed "MS". The retention time is provided in the column headed "R.T." and is given in minutes, along with a number indicating the mass spectroscopy method used.

Table I

<table>
<thead>
<tr>
<th>Compound</th>
<th>Name</th>
<th>R.T.</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>2-(2-methylpyridin-4-yl)-5-[[2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>0.94 (1)</td>
<td>417.21</td>
</tr>
<tr>
<td>12</td>
<td>5-[[2-[4-(3-fluorophenyl)piperazin-1-yl]-2-oxoethyl]-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.03 (1)</td>
<td>435.21</td>
</tr>
<tr>
<td>13</td>
<td>5-[[2-[4-(3-chlorophenyl)piperazin-1-yl]-2-oxoethyl]-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.08 (1)</td>
<td>451.15</td>
</tr>
<tr>
<td>14</td>
<td>N,N-dimethyl-2-[[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetyl]piperidin-4-yl</td>
<td>1.09 (2)</td>
<td>411.30</td>
</tr>
<tr>
<td>Compound</td>
<td>Name</td>
<td>R.T.</td>
<td>MS</td>
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</tr>
<tr>
<td>15</td>
<td>2-(2-methylpyridin-4-yl)-5-[[2-oxo-2-[3-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethoxy]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.11 (2)</td>
<td>423.30</td>
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<tr>
<td>16</td>
<td>2-(2-methylpyridin-4-yl)-5-[[2-[3-(morpholin-4-ylmethyl)piperidin-1-yl]ethoxy]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.06 (2)</td>
<td>439.28</td>
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<tr>
<td>17</td>
<td>2-(2-methylpyridin-4-yl)-5-[[2-oxo-2-[2-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethoxy]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.13 (2)</td>
<td>423.26</td>
</tr>
<tr>
<td></td>
<td>Chiral</td>
<td></td>
<td></td>
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<td>18</td>
<td>2-(2-methylpyridin-4-yl)-5-[[2-oxo-2-[2S]-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethoxy]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.08 (2)</td>
<td>409.26</td>
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<td>19</td>
<td>1'-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetyl]-1,3'-bipyrolidine</td>
<td>1.04 (2)</td>
<td>395.26</td>
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<tr>
<td></td>
<td>Chiral</td>
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<td>2-methyl-8-[[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetyl]-2,8-diazaspiro[5.5]undecane</td>
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<td>29</td>
<td>N-ethyl-N-[(ethylmethylamino)ethyl]-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.08</td>
<td>385.27</td>
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<tr>
<td>30</td>
<td>5-[2-(4-butylpiperazin-1-yl)-2-oxoethyl]-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.12</td>
<td>397.29</td>
</tr>
<tr>
<td>31</td>
<td>N,N-diethyl-1-[(2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetetyl]pyrrolidin-3-amine</td>
<td>1.06</td>
<td>397.29</td>
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<td>32</td>
<td>N-[2-(diethylamino)ethyl]-N-ethyl-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
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<td>399.28</td>
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<td>33</td>
<td>5-[2-(4-isobutylpiperazin-1-yl)-2-oxoethyl]-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.13</td>
<td>397.28</td>
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<tr>
<td>34</td>
<td>2-(2-methylpyridin-4-yl)-5-[2-(4-morpholin-4-yl)piperidin-1-yl]-2-oxoethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.00</td>
<td>425.28</td>
</tr>
<tr>
<td>35</td>
<td>4-methyl-1'-'[(2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetetyl]-1,4'-bipiperidine</td>
<td>1.14</td>
<td>437.31</td>
</tr>
<tr>
<td>36</td>
<td>5-[2-(4-azepan-1-yl)piperidin-1-yl]-2-oxoethyl]-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.13</td>
<td>437.31</td>
</tr>
<tr>
<td>Compound</td>
<td>Name</td>
<td>R.T.</td>
<td>MS</td>
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<tr>
<td>37</td>
<td>1-{(2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)acetyl}-N,N-dipropylpiperidin-4-amine</td>
<td>1.17 ( (2) )</td>
<td>439.32</td>
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<tr>
<td>38</td>
<td>2-(2-methylpyridin-4-yl)-5-[2-oxo-2-(4-pyrrolidin-1-yl)piperidin-1-yl]ethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.07 ( (2) )</td>
<td>409.28</td>
</tr>
<tr>
<td>39</td>
<td>1'-{(2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)acetyl}-1',4'-bipiperidine</td>
<td>1.10 ( (2) )</td>
<td>423.31</td>
</tr>
<tr>
<td>40</td>
<td>N-(2-methoxyethyl)-N-(1-methylpiperidin-4-yl)-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.05 ( (2) )</td>
<td>427.30</td>
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<tr>
<td>41</td>
<td>2-(2-methylpyridin-4-yl)-5-[2-[4-(3-morpholin-4-yl)propyl]piperazin-1-yl]-2-oxoethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.02 ( (2) )</td>
<td>468.33</td>
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<tr>
<td>42</td>
<td>N,N-dimethyl-3-[4-{(2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)acetyl}piperazin-1-yl]propan-1-amine</td>
<td>1.03 ( (2) )</td>
<td>426.32</td>
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<td>43</td>
<td>N,N-diethyl-2-[4-{(2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)acetyl}piperazin-1-y1]ethanamine</td>
<td>1.06 ( (2) )</td>
<td>440.33</td>
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<td>44</td>
<td>2-(2-methylpyridin-4-yl)-5-[2-oxo-2-[4-(3-pyrrolidin-1-yl)propyl]piperazin-1-yl]ethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.09 ( (2) )</td>
<td>452.34</td>
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<tr>
<td>Compound</td>
<td>Name</td>
<td>R.T.</td>
<td>MS</td>
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<td>45</td>
<td>2-(2-methylpyridin-4-yl)-5-{2-oxo-2-[4-(2-piperidin-1-yl)ethyl]piperazin-1-yl}ethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.08</td>
<td>452.32</td>
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<tr>
<td>46</td>
<td>2-(2-methylpyridin-4-yl)-5-{2-oxo-2-[4-(3-piperidin-1-ylpropyl)piperazin-1-yl]ethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.10</td>
<td>466.34</td>
</tr>
<tr>
<td>47</td>
<td>N,N-diethyl-3-(4-{2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl}acetyl)piperazin-1-ylpropan-1-amine</td>
<td>1.08</td>
<td>454.33</td>
</tr>
<tr>
<td>48</td>
<td>5-[2-[(1-methylpiperidin-3-yl)methyl]piperazin-1-yl]ethyl]-2-oxoethyl)-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.09</td>
<td>452.32</td>
</tr>
<tr>
<td>49</td>
<td>2-(2-methylpyridin-4-yl)-5-{2-oxo-2-[4-(2-pyrrolidin-1-yl)ethyl]piperazin-1-yl}ethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.07</td>
<td>438.31</td>
</tr>
<tr>
<td>50</td>
<td>2-(2-methylpyridin-4-yl)-5-{2-oxo-2-[4-(1-phenylethyl)piperazin-1-yl]ethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine</td>
<td>1.16</td>
<td>445.30</td>
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<td>N-isopropyl-N-(1-methylpiperidin-4-yl)-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.11</td>
<td>411.30</td>
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<td>52</td>
<td>N-isobutyl-N-(1-methylpiperidin-4-yl)-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.12</td>
<td>425.32</td>
</tr>
<tr>
<td>Compound</td>
<td>Name</td>
<td>R.T.</td>
<td>MS</td>
</tr>
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<tr>
<td>53</td>
<td>N-butyl-N-(1-methylpiperidin-4-yl)-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.13</td>
<td>425.32</td>
</tr>
<tr>
<td>54</td>
<td>N-ethyl-N-(1-methylpiperidin-4-yl)-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.06</td>
<td>397.29</td>
</tr>
<tr>
<td>55</td>
<td>N-methyl-N-[2-(1-methylpiperidin-2-yl)ethyl]-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.08</td>
<td>411.30</td>
</tr>
<tr>
<td>56</td>
<td>N-methyl-N-[2-(1-methylpiperidin-3-yl)ethyl]-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.09</td>
<td>411.31</td>
</tr>
<tr>
<td>57</td>
<td>N-methyl-N-[2-(1-methylpiperidin-4-yl)ethyl]-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.06</td>
<td>397.29</td>
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<tr>
<td>58</td>
<td>N-methyl-N-[1-methylpiperidin-3-yl]methyl]-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.08</td>
<td>397.29</td>
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<tr>
<td>59</td>
<td>N-methyl-N-[1-methylpiperidin-2-yl]methyl]-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]acetamide</td>
<td>1.10</td>
<td>397.29</td>
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<td>N-methyl-2-[2-(2-methylpyridin-4-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]-N-(2-pyrrolidin-1-ylethyl) acetamide</td>
<td>1.07</td>
<td>393.28</td>
</tr>
<tr>
<td>Compound</td>
<td>Name</td>
<td>R.T.</td>
<td>MS</td>
</tr>
<tr>
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<td>51</td>
<td>5-[(2-(4-cyclobutylpiperazin-1-yl)-2-oxoethyl][2-(2-isopropylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.14</td>
<td>423.36</td>
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<td>5-[(2-(4-cyclobutylpiperazin-1-yl)-2-oxoethyl][2-pyridin-4-yl]-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.05</td>
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<td>53</td>
<td>5-[(2-(4-cyclobutylpiperazin-1-yl)-2-oxoethyl][2-(3-fluoropyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
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<td>5-[(2-(4-cyclobutylpiperazin-1-yl)-2-oxoethyl][2-(3-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.07</td>
<td>395.24</td>
</tr>
<tr>
<td>55</td>
<td>5-[(2-(4-cyclobutylpiperazin-1-yl)-2-oxoethyl][2-(2,6-dimethylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.12</td>
<td>409.29</td>
</tr>
<tr>
<td>56</td>
<td>2-(3-fluoropyridin-4-yl)-5-[(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl][4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.07</td>
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<td>57</td>
<td>2-(3-fluoropyridin-4-yl)-5-[(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl][4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.09</td>
<td>397.28</td>
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<tr>
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<td>Name</td>
<td>R.T.</td>
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<td>68</td>
<td>5-[(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl)-2-(3-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.04</td>
<td>383.25</td>
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<td>5-[(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl)-2-(2-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.06</td>
<td>383.24</td>
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<td>70</td>
<td>5-[(2-(4-cyclobutylpiperazin-1-yl)-2-oxoethyl)-2-(2,3-dimethylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.10</td>
<td>409.27</td>
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<tr>
<td>71</td>
<td>5-[(2-(4-cyclobutylpiperazin-1-yl)-2-oxoethyl)-2-(2,5-dimethylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>0.87</td>
<td>409.24</td>
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<td>5-[(2-(4-cyclobutylpiperazin-1-yl)-2-oxoethyl)-2-(2-methoxy-3-methylpyridin-4-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.12</td>
<td>425.18</td>
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<td>73</td>
<td>2-(2,3-dimethylpyridin-4-yl)-5-[(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine]</td>
<td>1.07</td>
<td>397.17</td>
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</table>
EXAMPLE 4
Preparation of Chimeric Human H3 Receptor

Chimeric H3 receptor cDNA from human H3 receptor is generated from three cDNA fragments: (1) a human H3 receptor cDNA 5' fragment; (2) a human H3 receptor cDNA 3' fragment; and (3) a rat Ga,c cDNA fragment, each containing appropriate, overlapping linker sequences, as described in Example 1 of US Patent Application Serial Number 11/355,711, which published as US 2006/0188960, and is hereby incorporated by reference for its teaching of the preparation of a chimeric human H3 receptor-rat Ga,c baculoviral expression construct that has the sequence provided in SEQ ID NO:7 of US 2006/0188960, and encodes a polypeptide that has the sequence provided in SEQ ID NO:8 of US 2006/0188960.

EXAMPLE 5
Chimeric Human H3 Receptor Baculovirus Preparation and Infection

The chimeric human H3 receptor-rat Ga,c baculoviral expression vector is co-transfected along with BACULOGOLD DNA (BD PHARMINGEN, San Diego, CA) into S9 cells. The S9 cell culture supernatant is harvested three days post-transfection. The recombinant virus-containing supernatant is serially diluted in Hink's TNM-FH insect medium (JRH Biosciences, Kansas City, KS) supplemented Grace's salts and with 4.1 mM L-Gln, 3.3 g/L LAH, 3.3 g/L ultrafiltered yeastolate and 10% heat-inactivated fetal bovine serum (hereinafter "insect medium") and plaque assayed for recombinant plaques. After four days, recombinant plaques are selected and harvested into 1 ml of insect medium for amplification. Each 1 ml volume of recombinant baculovirus (at passage 0) is used to infect a
separate T25 flask containing 2 x 10^6 S/9 cells in 5 ml of insect medium. After five days of incubation at 27°C, supernatant medium is harvested from each of the T25 infections for use as passage 1 inoculum.

Two of seven recombinant baculoviral clones are chosen for a second round of amplification, using 1 ml of passage 1 stock to infect 1 x 10^8 cells in 100 ml of insect medium divided into two T175 flasks. Forty-eight hours post infection, passage 2 medium from each 100 ml prep is harvested and plaque assayed to determine virus titer. The cell pellets from the second round of amplification are assayed by affinity binding as described below to verify recombinant receptor expression. A third round of amplification is then initiated using a multiplicity of infection of 0.1 to infect a liter of S/9 cells. Forty hours post-infection, the supernatant medium is harvested to yield passage 3 baculoviral stock.

The remaining cell pellet is assayed for affinity binding using the protocol of DeMartino et al. (1994) *J. Biol. Chem.* 269(20):14446-50 (which is incorporated herein by reference for its teaching of binding assays at page 14447), adapted as follows. Radioligand ranges from 0.40 - 40 nM [³H]-N-(a)methylhistamine (Perkin Elmer, Boston, MA) and assay buffer contains 50 mM Tris, 1 mM CaCl₂, 5 mM MgCl₂, 0.1% BSA, 0.1 mM bacitracin, and 100 KIU/ml aprotinin, pH 7.4. Filtration is carried out using GF/C WHATMAN filters (presoaked in 1.0% polyethyleneimine for 2 hr prior to use). Filters are washed three times with 5 ml cold assay buffer without BSA, bacitracin, or aprotinin and air dried for 12-16 hr. Radioactivity retained on filters is measured on a beta scintillation counter.

Titer of the passage 3 baculoviral stock is determined by plaque assay and a multiplicity of infection, incubation time course, binding assay experiment is carried out to determine conditions for optimal receptor expression. A multiplicity of infection of 0.5 and a 72-hr incubation period are preferred infection parameters for chimeric human H3 receptor-rat Gα₃ expression in up to 1-liter S/9 cell infection cultures.

Log-phase S/9 cells (INVITROGEN), are infected with one or more stocks of recombinant baculovirus followed by culturing in insect medium at 27°C. Infections are carried out with virus directing the expression of human H3 receptor-rat Gα₃ in combination with three G-protein subunit-expression virus stocks: 1) rat Gα₁ G-protein-encoding virus stock (BIOSIGNAL #V5J008), 2) bovine β1 G-protein-encoding virus stock (BIOSIGNAL #V5H012), and 3) human γ2 G-protein-encoding virus stock (BIOSIGNAL #V6B003), which may be obtained from BIOSIGNAL Inc., Montreal.

The infections are conveniently carried out at a multiplicity of infection of 0.5:1.0:0.5:0.5. At 72 hr post-infection, an aliquot of cell suspension is analyzed for viability by trypan blue dye exclusion. If no blue is detected by visual inspection, the S/9 cells are harvested via centrifugation (3000 rpm / 10 min / 4°C).
EXAMPLE 6

Chimeric Human H3 Receptor Cell Membrane Preparations

S/9 cell pellets obtained as described in Example 5 are resuspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 µg/ml leupeptin, 2 µg/ml Aprotinin, 200 µM PMSF, and 2.5 mM EDTA, pH 7.4) and homogenized using a POLYTRON PT10-35 homogenizer (KINEMATICA AG, Lucerne, Switzerland; setting 5 for 30 seconds). The homogenate is centrifuged (536 x g/ 10 min at 4°C) to pellet the nuclei and unbroken cells. The supernatant containing the membranes is decanted to a clean centrifuge tube, centrifuged (48,000 x g/ 30 min, 4°C) and the resulting pellet resuspended in 30 ml homogenization buffer. This centrifugation and resuspension step is repeated twice. The final pellet is resuspended in ice cold Dulbecco's PBS containing 5 mM EDTA and stored in frozen aliquots at -80°C until used for radioligand binding or functional response assays. The protein concentration of the resulting membrane preparation (hereinafter termed "P2 membranes") is conveniently measured using a Bradford protein assay (BIO-RAD LABORATORIES, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 100-150 mg of total membrane protein.

EXAMPLE 7

Chimeric Human H3 Receptor GTP Binding Assays

This Example illustrates a representative assay for evaluating agonist-stimulated GTP-gamma^35S binding ("GTP binding") activity. Such GTP binding activity can be used to identify H3 antagonists and to differentiate neutral antagonist compounds from those that possess inverse agonist activity. This agonist-stimulated GTP binding activity can also be used to detect partial agonism mediated by antagonist compounds. A compound analyzed in this assay is referred to herein as a "test compound."

Four independent baculoviral stocks (one directing the expression of the chimeric human H3 receptor and three directing the expression of each of the three subunits of a heterotrimeric G-protein) are used to infect a culture of S/9 cells as described above. P2 membranes are prepared as described above, and agonist-stimulated GTP binding on the P2 membranes is assessed using histamine (Sigma Chemical Co., St. Louis, MO) as agonist in order to ascertain that the receptor/G-protein-alpha-beta-gamma combination(s) yield a functional response as measured by GTP binding. P2 membranes are resuspended by Dounce homogenization (tight pestle) in GTP binding assay buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM MgCl2, 2 mM EGTA, 1 mg/ml BSA, 0.2 mg/ml bacitracin, 0.02 mg/ml aprotinin, 0.01 mg/ml saponin, 10 µM GDP) and added to assay tubes at a concentration of 35 µg protein/reaction tube. After adding increasing doses of histamine at concentrations
ranging from $10^{-12}$ M to $10^{-5}$ M, reactions are initiated by the addition of 125 pM GTP-
gamma S (PERKIN ELMER; Boston, MA) with a final assay volume of 0.20 ml. In
competition experiments, non-radiolabeled test compounds are added to separate reactions at
concentrations ranging from $10^{-10}$ M to $10^{-5}$ M along with 1 µM histamine to yield a final
volume of 0.20 ml.

Neutral antagonists are antagonists that are substantially free of inherent agonist
activity, and include those test compounds that reduce the histamine-stimulated GTP binding
activity towards, but not below, baseline levels. In contrast, in the absence of added
histamine, inverse agonists reduce the GTP binding activity of the receptor-containing
membranes below baseline. The elevation of GTP binding activity above baseline by a
compound in the absence of added histamine in this assay demonstrates agonist activity.

After a 60-min incubation at room temperature, reactions are terminated by vacuum
filtration over WHATMAN GF/C filters (pre-soaked in wash buffer, 0.1% BSA) followed by
washing with ice-cold wash buffer (50 mM Tris pH 7.4, 120mM NaCl). The amount of
receptor-bound (and thereby membrane-bound) GTP-gamma S is determined by measuring
the filter-bound radioactivity, preferably by liquid scintillation spectrometry of the washed
filters. Non-specific binding is determined in parallel assays including 10 µM unlabeled
GTP-gammaS and typically represents less than 5 percent of total binding. Data is expressed
as percent above basal (baseline). The results of GTP binding experiments are analyzed using
SIGMAPLOT software (SPSS Inc., Chicago, IL). IC$_{50}$ values are calculated by non-linear
regression analysis of dose-response curves using Kaleidograph (Synergy Software, Reading,
PA).

Alternatively the data is analyzed as follows. First, the average bound radioactivity
from negative control wells (no agonist) is subtracted from the bound radioactivity detected
for each of the other experimental wells. Second, average bound radioactivity is calculated
for the positive control wells (agonist wells). Then, percent inhibition for each compound
tested is calculated using the equation:

$$\text{Percent Inhibition} = 100 - \frac{100 \times (\text{Bound radioactivity in Test Wells})}{(\text{Bound radioactivity in Agonist Wells})}$$

The % inhibition data is plotted as a function of test compound concentration and test
compound IC$_{50}$ is determined using a linear regression in which x is ln(concentration of test
compound) and y is ln(percent inhibition/(100 - percent inhibition). Data with a percent
inhibition that is greater than 90% or less than 15% are rejected and are not used in the
regression. The IC$_{50}$ is

$$e^{(-\text{intercept/slope})}$$
Calculated IC_{50} values are converted to K_{i} values by the Cheng-Prusoff correction (Cheng and Prusoff (1973) Biochem. Pharmacol. 22(23):3099-3108). Accordingly, the following equation: \( K_{i} = \frac{IC_{50}}{1 + [L]/EC_{50}} \) is used, where [L] is the histamine concentration in the GTP binding assay, and EC_{50} is the concentration of histamine producing a 50% response, as determined by a dose-response analysis using concentrations of histamine ranging from 10^{-10} M to 10^{-6} M.

To assess agonist or inverse agonist activity of a test compound, this assay is performed in the absence of added histamine, and EC_{50} values are determined by analogous calculations, where the EC_{50} is the concentration of test compound producing a 50% response.

**EXAMPLE 8**

Chimeric Human H3 Receptor Screening: GTP Binding Assays

This Example illustrates a representative screening assay for evaluating inhibition of histamine-stimulated GTP-gamma^{35}S binding. Such GTP binding activity can be used to identify H3 antagonists and inverse agonists. A compound analyzed in this assay is referred to herein as a "test compound," and the initial identification of antagonists and inverse agonists is performed using a test compound concentration of 4 µM.

Four independent baculoviral stocks (one directing the expression of the chimeric human H3 receptor and three directing the expression of each of the three subunits of a heterotrimeric G-protein) are used to infect a culture of Sf9 cells as described above. P2 membranes are prepared as described above, and are resuspended by Dounce homogenization (tight pestle) in GTP binding assay buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM MgCl_{2}, 2 mM EGTA, 1 mg/ml BSA, 0.2 mg/ml bacitracin, 0.02 mg/ml aprotinin, 0.01 mg/ml saponin, 10 µM GDP) and added to assay tubes at a concentration of 35 µg protein/reaction tube. Non-radiolabeled test compounds are added to separate reactions at a concentration of 4 µM along with 1 µM histamine (agonist). Reactions are initiated by the addition of 125 pM GTP-gamma^{35}S with a final assay volume of 0.20 ml.

After a 60-min incubation at room temperature, reactions are terminated by vacuum filtration over GF/C filters (pre-soaked in 50 mM Tris pH 7.4, 120mM NaCl plus 0.1% BSA) followed by washing with ice-cold buffer (50 mM Tris pH 7.4, 120mM NaCl). The amount of receptor-bound (and thereby membrane-bound) GTP-gamma^{35}S is determined by measuring the bound radioactivity, preferably by liquid scintillation spectrometry of the washed filters. Non-specific binding is determined using 10 uM GTP-gammaS and typically represents less than 5 percent of total binding. After subtraction of non-specific binding, data is expressed as percent inhibition of 1 µM histamine signal.
Neutral antagonists are those test compounds that reduce the histamine-stimulated GTP binding activity towards, but not below, baseline levels. In contrast, in the absence of added histamine, inverse agonists reduce the GTP binding activity of the receptor-containing membranes below baseline. Any test compound that elevates GTP binding activity above baseline in the absence of added histamine in this assay is defined as having agonist activity.
What is claimed is:

1. A compound of the formula:

or a pharmaceutically acceptable salt thereof, wherein:

R₁ and R₂ independently represent C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₆cycloalkyl)C₆- C₂alkyl or (4- to 10-membered heterocycle)C₀-C₂alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from oxo, nitro, halogen, amino, cyano, hydroxy, aminocarbonyl, C₁-C₆alkyl, C₂-C₆alkenyl, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, C₁-C₆alkylthio, C₂-C₆alkyl ether, d-C₁-C₆alkanoyl, C₃-C₆alkanone, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₆alkyl)aminocarbonyl, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkyl ether, (C₃-C₆cycloalkyl)C₀-C₄alkyl and (4- to 7-membered heterocycloalkyl)C₀-C₆alkyl;

or Rₘ and Rₙ are taken together to form a 5- to 7-membered heterocycloalkyl or a 10- to 12-membered bicyclic heterocycloalkyl, each of which is substituted with from 0 to 2 substituents independently chosen from C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆alkyl ether, mono- or di-(C₁-C₆alkyl)amino C₁-C₆alkyl, (C₃-C₆cycloalkyl)C₀-C₂alkyl, (4- to 8-membered heterocycloalkyl)C₀-C₂alkyl and phenylC₀-C₂alkyl, each of which is substituents is further substituted with from 0 to 4 secondary substituents independently chosen from oxo, nitro, halogen, amino, cyano, hydroxy, aminocarbonyl, C₁-C₆alkyl, C₂-C₆alkenyl, d-C₁-C₆haloalkyl, C₁-C₆haloalkoxy, C₁-C₆alkylthio, C₂-C₆alkyl ether, C₁-C₆alkanoyl, C₃-C₆alkanone, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₆alkyl)aminocarbonyl, (C₃-C₆cycloalkyl)C₀-C₄alkyl and (4- to 7-membered heterocycloalkyl)C₀-C₆alkyl;

such that at least one of Rₘ and Rₙ comprises at least one basic nitrogen atom;

Rₜ represents 0, 1, 2 or 3 substituents independently chosen from halogen, cyano, amino, aminocarbonyl, oxo, C₁-C₆alkyl, d-C₁-C₆alkoxy, C₁-C₆hydroxyalkyl, C₁-C₆haloalkyl, C₁-C₆haloalkoxy, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₆alkyl)aminocarbonyl, (C₃-C₆cycloalkyl)C₀-C₄alkyl and (4- to 7-membered heterocycloalkyl)C₀-C₆alkyl;

R₁₀ represents from 0 to 3 substituents independently chosen from C₁-C₆alkyl, oxo, fluoro and C₁-C₆fluoroalkyl; and

R₁₃ is hydrogen, halogen, cyano, C₁-C₆haloalkyl, C₁-C₆haloalkoxy or C₁-C₆fluoroalkoxy.
2. A compound or salt thereof according to claim 1, wherein the compound further satisfies the formula:

![Chemical structure](image)

wherein:
- \( p \) is 0 or 1;
- \( X \) is \( \text{CH}, \text{CH}_2, \text{N} \) or \( \text{NH} \), such that if \( p = 0 \) then \( X \) is \( \text{CH} \) or \( \text{CH}_2 \); and
- \( R_2 \) represents 0, 1 or 2 substituents independently chosen from \( \text{Cl-C}_6\text{alkyl}, \text{C}_2\text{-C}_6\text{alkenyl}, \text{C}_2\text{-C}_6\text{alkynyl}, \text{mono-} \) or \( \text{di-(Cl-C}_6\text{alkyl)} \text{aminoC}_0\text{-C}_4\text{alkyl}, \text{(C}_3\text{-C}_6\text{cycloalkyl)} \text{C}_0\text{-C}_2\text{alkyl, (4- to 8-membered heterocycloalkyl)} \text{C}_0\text{-C}_2\text{alkyl and phenylC}_0\text{-C}_2\text{alkyl}, each of which is substituted with from 0 to 4 substituents independently chosen from oxo, nitro, halogen, amino, cyano, hydroxy, aminocarbonyl, \( \text{Cl-C}_6\text{alkyl}, \text{C}_2\text{-C}_6\text{alkenyl, Ci-C}_6\text{haloalkyl}, \text{Ci-C}_6\text{alkoxy, Ci-C}_6\text{haloalkoxy, Ci-C}_6\text{alkylthio, C}_2\text{-C}_6\text{alkyl ether, d-C}_6\text{alkanoyl, C}_3\text{-C}_6\text{alkanone, mono-} \) or \( \text{di-(Cl-C}_6\text{alkyl)} \text{amino, mono-} \) or \( \text{di-(Cl-C}_6\text{alkyl)} \text{aminocarbonyl, (C}_3\text{-C}_6\text{cycloalkyl)} \text{C}_0\text{-C}_4\text{alkyl and (4- to 7-membered heterocycloalkyl)} \text{C}_0\text{-C}_4\text{alkyl}; such that \( R_2 \) represents at least one substituents that comprises at least one basic nitrogen if \( X \) is \( \text{CH} \) or \( \text{CH}_2 \).

3. A compound or salt thereof according to claim 2, wherein the compound further satisfies one of the formulas:

![Chemical structures](image)

wherein:
R₅ is Ci-C₆alkyl, (C₅-C₇cycloalkyl)Co-C₄alkyl, (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl or phenylCo-C₄alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen and Ci-C₆alkyl;

R₆ is d-C₆alkyl, mono- or di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, (C₅-C₇cycloalkyl)C₀-C₄alkyl, or (4- to 8-membered heterocycloalkyl)C₀-C₄alkyl or phenylC₀-C₄alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from amino, halogen, Ci-C₆alkyl and mono- or di-(CrC₄alkyl)aminoCo-C₄alkyl; such that Re comprises at least one basic nitrogen atom; and

R₇ is C₁-C₆alkyl, Ci-C₇hydroxyalkyl or C₂-C₆alkyl ether.

4. A compound or salt thereof according to claim 3, wherein:

R₅ is Ci-C₆alkyl, C₅-C₇cycloalkyl, (4- to 7-membered heterocycloalkyl)Co-C₂alkyl or phenylCo-C₂alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen and CrC₂alkyl; and

R₆ is mono- or di-(Ci-C₆alkyl)aminoC₀-C₄alkyl or a N-containing (4- to 7-membered heterocycloalkyl)Co-C₂alkyl that is substituted with from 0 to 2 substituents independently chosen from halogen and Ci-C₆alkyl.

5. A compound or salt thereof according to any one of claims 1-4, wherein R₁ represents 1 or 2 substituents independently chosen from halogen, cyano, Ci-C₆alkyl, Ci-C₆alkoxy, C₁-C₆hydroxyalkyl, C₁-C₂alkanoyl, C₂-C₆alkyl ether, mono- or di-(Ci-C₆alkyl)aminoCo-C₂alkyl, C₅-C₆cycloalkyl and 4- to 7-membered heterocycloalkyl.

6. A compound or salt thereof according to claim 5, wherein R₁ represents 1 or 2 substituents independently chosen from halogen, cyano, Ci-C₆alkyl, CrC₂alkoxy, CrC₂hydroxyalkyl, C₁-C₂alkanoyl, (C₅-C₇cycloalkyl)Co-C₂alkyl and (4- to 7-membered heterocycloalkyl)C₀-C₂alkyl.

7. A compound or salt thereof according to any one of claims 1-4, wherein R₁ represents 0 substituents.

8. A compound or salt thereof according to claim 2, wherein R₂ represents one substituent chosen from CrC₆alkyl, mono- or di-(CrC₄alkyl)aminoC₀-C₄alkyl, C₅-C₇cycloalkyl, (4- to 7-membered heterocycloalkyl)Co-C₂alkyl and phenylCo-C₂alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen and Ci-C₆alkyl.

9. A compound or salt thereof according to claim 7, wherein R₂ represents one substituent chosen from isopropyl, cyclobutyl, cyclopentyl and cyclohexyl.
10. A compound or salt thereof according to claim 1, wherein the compound further satisfies the formula:

wherein $R_3$ and $R_4$ are independently chosen from hydrogen, halogen, cyano, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, $C_i$-$C_i$hydroxyalkyl, $C_i$-$C_i$alkanoyl, ($C_3$-$C_7$-cycloalkyl)$Co-C_2$alkyl and (4- to 7-membered heterocycloalkyl)$Co-C_i$alkyl.

11. A compound or salt thereof according to claim 10, wherein the compound further satisfies the formula:

wherein:

- $p$ is 0 or 1;
- $X$ is CH, CH$_2$, N or NH, such that if $p$ is 0 then $X$ is CH or CH$_2$; and
- $R_2$ represents 0, 1 or 2 substituents independently chosen from $d$-$C_i$alkyl, $C_2$-$C_4$alkenyln, mono- or di-($C_i$-$C_i$alkyl)amino$Co-C_i$alkyl, ($C_3$-$C_7$-cycloalkyl)$Co-C_2$alkyl, (4- to 8-membered heterocycloalkyl)$Co-C_2$alkyl and phenyl$C_i$-$C_4$alkyl, each of which is optionally substituted and each of which is preferably substituted with from 0 to 4 substituents independently chosen from oxo, nitro, halogen, amino, cyano, hydroxy, aminocarbonyl, $d$-$C_i$alkyl, $C_2$-$C_4$alkenyln, $C_i$-$C_i$haloalkoxy, $C_i$-$C_i$alkynylthio, $C_2$-$C_4$alkyl ether, $C_i$-$C_i$alkanoyln, $C_3$-$C_7$-alkanone, mono- or di-($C_i$-$C_i$alkyl)amino, mono- or di-($C_i$-$C_i$alkyl)aminocarbonyl, ($C_3$-$C_7$-cycloalkyl)$Co-C_i$alkyl and (4- to 7-membered heterocycloalkyl)$Co-C_i$alkyl; such that $R_2$ represents at least one substituent that comprises at least one basic nitrogen if $X$ is CH or CH$_2$.

12. A compound or salt thereof according to claim 11, wherein $R_2$ represents one substituent chosen from $C_i$-$C_i$alkyl, mono- or di-($C_4$-$C_4$alkyl)amino$C_i$-$C_i$alkyl, $C_3$-$C_7$-cycloalkyl, (4- to 7-membered heterocycloalkyl)$Co-C_2$alkyl and phenyl$Co-C_2$alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen and $C_i$-$C_i$alkyl.

13. A compound or salt thereof according to claim 12, wherein $R_2$ represents one substituent chosen from isopropyl, cyclobutyl, cyclopentyl and cyclohexyl.
14. A compound or salt thereof according to claim 11, wherein the compound further satisfies the formula:

wherein \( R_5 \) is \( \text{d-C}_6 \text{alkyl} \), \( \text{C}_3 \text{-C}_7 \text{cycloalkyl} \), \( (\text{4- to 7-membered heterocycloalkyl})\text{C}_0 \text{-C}_4 \text{alkyl} \) or phenyl\( \text{C}_0 \text{-C}_2 \text{alkyl} \), each of which is substituted with from 0 to 2 substituents independently chosen from halogen and \( \text{Ci-C}_6 \text{alkyl} \).

15. A compound or salt thereof according to claim 14, wherein \( R_5 \) is isopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

16. A compound or salt thereof according to any one of claims 10-15, wherein neither \( R_3 \) nor \( R_4 \) is hydrogen.

17. A compound or salt thereof according to any one of claims 10-15, wherein exactly one of \( R_3 \) and \( R_4 \) is hydrogen.

18. A compound or salt thereof according to claim 17, wherein \( R_3 \) is halogen, cyano, \( \text{d-C}_4 \text{alkyl} \), \( \text{C}_1 \text{-C}_4 \text{alkoxy} \), \( \text{C}_1 \text{-C}_4 \text{hydroxyalkyl} \), cyclopropyl or morpholinyl; and \( R_4 \) is hydrogen.

19. A compound or salt thereof according to claim 18, wherein \( R_3 \) is methyl or ethyl.

20. A compound or salt thereof according to claim 1, wherein the compound further satisfies the formula:

wherein:

- \( R_7 \) is \( \text{C}_x \text{C}_6 \text{alkyl} \), \( \text{d-C}_6 \text{hydroxyalkyl} \) or \( \text{C}_2 \text{-C}_6 \text{alkyl ether} \);
- \( R_8 \) and \( R_9 \) are independently chosen from \( \text{Ci-C}_6 \text{alkyl} \), \( \text{C}_2 \text{-C}_6 \text{alkenyl} \), \( \text{C}_2 \text{-C}_6 \text{alkyl ether} \), mono- or di-(\( \text{C}_1 \text{-C}_6 \text{alkyl}) \)amino\( \text{C}_0 \text{-C}_4 \text{alkyl} \), \( (\text{C}_3 \text{-C}_7 \text{cycloalkyl})\text{C}_0 \text{-C}_4 \text{alkyl} \) and \( (\text{4- to 7-membered heterocycloalkyl})\text{C}_0 \text{-C}_4 \text{alkyl} \); or \( R_8 \) and \( R_9 \) are taken together to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from \( \text{Ci-C}_6 \text{alkyl} \), \( \text{C}_2 \text{-C}_6 \text{alkenyl} \), \( \text{C}_2 \text{-C}_6 \text{alkyl ether} \), \( (\text{C}_1 \text{-C}_7 \text{cycloalkyl})\text{C}_0 \text{-C}_4 \text{alkyl} \) and \( (\text{4- to 7-membered heterocycloalkyl})\text{C}_0 \text{-C}_4 \text{alkyl} \); such that at least one of \( R_8 \) and \( R_9 \) comprises at least one basic nitrogen atom;
- \( m \) is 2, 3 or 4; and
- \( o \) is 0, 1, 2, 3 or 4.
21. A compound or salt thereof according to claim 20, wherein R₇ represents 1 or 2 substituents independently chosen from halogen, cyano, C₃₋₄ alkyl, C₃₋₄ alkoxy, C₃₋₄ hydroxyalkyl, C₃₋₄ alkanoyl, C₂₋₄ alky ether, mono- or di-(C₋₄ alky)aminoC₋₂ alky, C₃₋₄ cycloalkyl and 4- to 7-membered heterocycloalkyl.

22. A compound or salt thereof according to claim 21, wherein R₇ represents 1 or 2 substituents independently chosen from halogen, cyano, C₃₋₄ alkyl, C₃₋₄ alkoxy, C₃₋₄ hydroxyalkyl, C₃₋₄ alkanoyl, (C₃₋₄ cycloalkyl)C₋₂ alky and (4- to 7-membered heterocycloalkyl)C₀₋₂ alky.

23. A compound or salt thereof according to any one of claims 20-22, wherein the compound further satisfies the formula:

24. A compound or salt thereof according to any one of claims 20-22, wherein the compound satisfies the formula:

25. A compound or salt according to any one of claims 1-24, wherein the compound has a Kᵢ value of 1 micromolar or less, as determined using a histamine-induced H₃ receptor GTP binding assay.

26. A compound or salt according to claim 25, wherein the compound has a Kᵢ value of 100 nanomolar or less, as determined using a histamine-induced H₃ receptor GTP binding assay.

27. A compound or salt according to claim 1, wherein the compound is any one of compounds 1-75.
28. A pharmaceutical composition, comprising at least one compound or salt according to any one of claims 1-27 in combination with a physiologically acceptable carrier or excipient.

29. A pharmaceutical composition according to claim 28, wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

30. A method for treating a condition responsive to H3 receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of a compound or salt according to any one of claims 1-27, and thereby alleviating the condition in the patient.

31. A method according to claim 30, wherein the compound exhibits H3 receptor antagonist activity.

32. A method according to claim 30 or claim 31, wherein the condition is attention deficit disorder, attention deficit hyperactivity disorder, dementia, schizophrenia, a cognitive disorder, epilepsy, migraine, excessive daytime sleepiness, shift work sleep disorder, jet lag, narcolepsy, sleep apnea, allergic rhinitis, vertigo, motion sickness, a memory disorder, or Parkinson's disease.

33. A method according to claim 30 or claim 31, wherein the condition is obesity, an eating disorder or diabetes.

34. A method according to any one of claims 30-33, wherein the patient is a human.

35. A compound or salt according to any one of claims 1-27, wherein the compound or salt is radiolabeled.

36. A method for determining the presence or absence of H3 receptor in a sample, comprising the steps of:
   (a) contacting a sample with a compound or salt according to any one of claims 1-27, under conditions that permit binding of the compound to H3 receptor; and
   (b) detecting a level of the compound bound to H3 receptor, and therefrom determining the presence or absence of H3 receptor in the sample.

37. A method according to claim 36, wherein the compound is radiolabeled, and wherein the step of detection comprises the steps of:
   (i) separating unbound compound from bound compound; and
   (ii) detecting the presence or absence of bound compound in the sample.

38. A packaged pharmaceutical preparation, comprising:
   (a) a pharmaceutical composition according to claim 28 in a container; and
instructions for using the composition to treat a condition responsive to H3 receptor modulation in a patient.

39. A packaged pharmaceutical preparation according to claim 38, wherein the condition is attention deficit disorder, attention deficit hyperactivity disorder, dementia, schizophrenia, a cognitive disorder, epilepsy, migraine, excessive daytime sleepiness, shift work sleep disorder, jet lag, narcolepsy, sleep apnea, allergic rhinitis, vertigo, motion sickness, a memory disorder, or Parkinson's disease.

40. A packaged pharmaceutical preparation according to claim 38, wherein the condition is obesity, an eating disorder or diabetes.

41. The use of a compound or salt according to any one of claims 1-27 for the manufacture of a medicament for the treatment of a condition responsive to H3 receptor modulation.

42. A use according to claim 41, wherein the condition is attention deficit disorder, attention deficit hyperactivity disorder, dementia, schizophrenia, a cognitive disorder, epilepsy, migraine, excessive daytime sleepiness, shift work sleep disorder, jet lag, narcolepsy, sleep apnea, allergic rhinitis, vertigo, motion sickness, a memory disorder, or Parkinson's disease.

43. A use according to claim 41, wherein the condition is obesity, an eating disorder or diabetes.