(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 April 2006 (27.04.2006)

PCT

(10) International Publication Number
WO 2006/044174 A2

(51) International Patent Classification:
C07D 451/06 (2006.01) *A61K 31/46* (2006.01)
C07D 451/02 (2006.01) *A61P 3/04* (2006.01)
C07D 451/04 (2006.01)

(21) International Application Number:
PCT/US2005/035457

(22) International Filing Date: 4 October 2005 (04.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/618,292 13 October 2004 (13.10.2004) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ARYL SUBSTITUTED 8-AZABICYCLO[3.2.1]OCTANE COMPOUNDS AS LIGANDS OF THE MELANIN CONCENTRATING HORMONE RECEPTOR

(57) Abstract: Aryl substituted 8-azabicyclo[3.2.1]octane compounds and analogues thereof, are provided. Such compounds may be used to modulate MCH binding to MCH receptors *in vivo* or *in vitro*, and are particularly useful in the treatment of a variety of metabolic, feeding, neuropsychiatric, reproductive and sexual disorders in humans, domesticated companion animals and livestock animals. Pharmaceutical compositions and methods for treating such disorders are provided, as are methods for using such ligands for detecting MCH receptors (*e.g.*, receptor localization studies).

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ARYL SUBSTITUTED 8-AZA-BICYCLO[3.2.1]OCTANE COMPOUNDS AS LIGANDS OF THE MELANIN CONCENTRATING HORMONE RECEPTOR

FIELD OF THE INVENTION

Aryl substituted 8-azabicyclo[3.2.1]octane compounds and analogues thereof that are melanin concentrating hormone receptor modulators are provided herein. Methods for using such compounds for treating a variety of metabolic, eating and sexual disorders, and as probes for the detection and localization of MCH receptors are also described.

BACKGROUND OF THE INVENTION

Melanin concentrating hormone, or MCH, is a cyclic 19 amino acid neuropeptide first identified as a regulator of skin coloration in fish and other vertebrates, and subsequently as a regulator of food intake and energy balance in higher vertebrates. In many species, including humans, MCH is produced in the hypothalamus. MCH is also produced at various peripheral sites, including the gastrointestinal tract and testis.

The postulated role of MCH in feeding behavior and body weight regulation is confirmed by the finding that i.c.v. injection of MCH increases caloric consumption in rats over similarly treated control animals. Furthermore, rats having the *ob/ob* genotype exhibit a 50-80% increase in MCH mRNA expression as compared to leaner *ob/+* genotype mice, and prepro-MCH knockout mice, as well as MCH receptor knockout mice, are leaner than normal mice, due to hypophagia and an increased metabolic rate.

MCH activity is mediated via binding to specific receptors. Like other G protein-coupled receptors (*e.g.*, neuropeptide Y (NPY) and beta-adrenergic receptors), MCH receptors are membrane-spanning proteins, generally found on cell surfaces, that consist of a single contiguous amino acid chain comprising an extracellular N-terminal domain, seven membrane-spanning alpha helical domains (connected by three intracellular loop domains alternating with three extracellular loop domains), and an intracellular C-terminal domain. Signal transduction is typically initiated by the binding of extracellular MCH to the receptor. This elicits conformational changes in the extracellular domains. When the receptor is functioning properly, these conformational changes propagate through the transmembrane domains and result in a coordinated change in the intracellular portions of the receptor. This precise alteration in the intracellular domains acts to trigger the associated G-protein complex to modulate intracellular signaling.

Human Melanin Concentrating Hormone Receptor-1 (MCH1R) is a 353 amino acid, 7-transmembrane, alpha-helical, G protein-coupled receptor, initially reported as orphan receptor SLC-

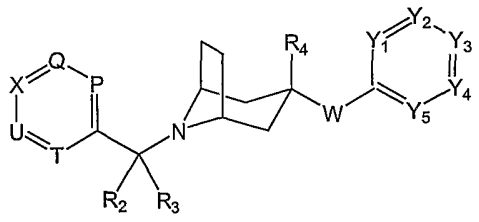
1. Immunohistochemistry studies of rat brain sections indicate that MCH1R is widely expressed in brain. MCH1R expression is found in olfactory tubercle, cerebral cortex, substantia nigra, basal forebrain CA1, CA2, and CA3 fields of the hippocampus, amygdala, and in nuclei of the hypothalamus, thalamus, midbrain and hindbrain. Strong signals are observed in the ventromedial and dorsomedial nuclei of the hypothalamus, two areas of the brain involved in feeding behavior. Upon binding MCH, MCH1R recombinantly expressed in HEK 293 cells mediates a dose dependent release of intracellular calcium. Cells expressing MCH1R also exhibit a pertussis toxin sensitive dose-dependent inhibition of forskolin-elevated cyclic AMP, indicating that the receptor couples to a $G_{i/o}$ G-protein alpha subunit. Certain monkey and human MCH1R sequences, as well as various chimeric MCH1R proteins, have been disclosed in U.S. Patent Application Serial Number 10/309,515 (published as 2003/0114644 on June 19, 2003).

A second MCH receptor (designated MCH2R) has also been identified. MCH2R has an overall amino acid identity of more than 30% with MCH1R, and is detected specifically in the same regions of the brain as MCH1R. Monkey and canine MCH2R sequences, as well as various chimeric MCH2R proteins, have been disclosed in U.S. Patent Application Serial Number 10/291,990 (published as 2003/0148457 on August 7, 2003).

Agents capable of modulating MCH receptor activity are highly desirable for the treatment of a variety of diseases and disorders, including obesity, eating disorders (*e.g.*, bulimia and anorexia), sexual disorders *(e.g.,* anorgasmic or psychogenic impotence) and metabolic disorders, such as diabetes. Small molecule, non-peptide antagonists of MCH receptors would be of particular value for such therapies. The present invention fulfills this need, and provides further related advantages.

SUMMARY OF THE INVENTION

The present invention provides aryl substituted 8-azabicyclo[3.2.1]octane compounds and analogues thereof of Formula I and pharmaceutically acceptable salts thereof.



or a pharmaceutically acceptable salt thereof, wherein:

W is absent or CR_5R_6, wherein R_5 and R_6 are independently hydrogen, halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, or haloC_1-C_2alkyl, or R_5 and R_6 are taken together to form an oxo group;

Y_1, Y_2, Y_3, Y_4 and Y_5 are each nitrogen or CR_1, wherein no more than 3 of Y_1, Y_2, Y_3, Y_4, and Y_5 are nitrogen.

Each R_1 is independently:

(i) hydrogen, halogen, hydroxy, nitro, cyano, amino, -$CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy, hydroxyC_1-C_6alkyl, C_1-C_6alkylthio, C_1-C_8alkylether, aminoC_1-C_6alkyl, mono- or di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, mono- or di-C_1-C_6alkylcarboxamide, C_1-C_6alkylsulfonyl, (C_3-C_7cycloalkyl)C_0-C_6alkyl, or (heterocycloalkyl)C_0-C_6alkyl; or

(ii) any two adjacent R_1 may be joined to form a fused 5- or 6-membered carbocycle or heterocycle, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, C_1-C_4alkyl, C_1-C_4alkoxy, haloC_1-C_4alkyl, and haloC_1-C_4alkoxy.

Wherein when Y_1, Y_2, Y_3, Y_4 and Y_5 are all CR_1 at least one R_1 is not hydrogen;

R_2 and R_3 are independently hydrogen, halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, or haloC_1-C_2alkyl; or R_2 and R_3 are taken together to form an oxo group; or R_3 is taken together with R_9 to form a fused 5- to 10-membered carbocycle or heterocycle.

R_4 is hydrogen, halogen, hydroxy, amino, C_1-C_4alkyl, C_1-C_4alkoxy, mono- or di-C_1-C_4alkylamino, -NHCHO, C_2-C_4alkanoylamino, haloC_1-C_2alkyl, or haloC_1-C_2alkoxy.

P is nitrogen or CR_7.

Q is nitrogen or CR_8.

U is nitrogen or CR_9.

T is nitrogen or CR_{10}.

X is nitrogen or CR_{11}.

Wherein no more than 3 of P, Q, U, T, and X are nitrogen;

R_7 is:

(i) hydrogen, halogen, hydroxy, nitro, cyano, -COOH, or a group of the formula -L-M; or

(ii) taken together with R_8 to form a fused 5- or 6-membered carbocycle or heterocycle.

R_8 is:

(i) hydrogen, halogen, hydroxy, nitro, cyano, -COOH, or a group of the formula -L-M; or

(ii) taken together with R_7 to form a fused 5- or 6-membered carbocycle or heterocycle;

(iii) taken together with R_{11} to form a fused 5- to 10-membered carbocycle or heterocycle, each of which is substituted 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

R_9 is:

(i) hydrogen, halogen, hydroxy, nitro, cyano, -COOH, or a group of the formula -L-M; or

(ii) taken together with R_{10} to form a fused 5- to 10-membered carbocycle or heterocycle.

R_{10} is:

(i) hydrogen, halogen, hydroxy, nitro, cyano, -COOH, or a group of the formula -L-M; or

(ii) taken together with R_3 or R_9 to form a fused carbocycle or heterocycle.

R_{11} is:

(i) bromo, iodo, hydroxy, nitro, or cyano;

(ii) a group of the formula -L-G;

(iii) 5-10 membered cycloalkenyl, aryl, heterocycloalkenyl, or heteroaryl, each of which is substituted with 0 to 5 substituents independently chosen from halogen, amino, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy; or

(iv) taken together with R_8 to form an optionally substituted fused 5- to 10-membered carbocycle or heterocycle.

G is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, aminoC_1-C_6alkyl, or a 5- to 10-membered cycloalkyl or heterocycloalkyl; each of which is substituted with 0 to 3 substituents independently chosen from halogen, amino, and haloC_1-C_2alkoxy, and

G is further substituted with 0 to 1 substituent chosen from

(a) oxo, hydroxy, cyano, -COOH, -(C=O)NH_2, -NH(C=O)H, -SO_2NH_2, and imino,

(b) (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_8alkyl)aminoC_0-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfonamide, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoylamino, mono- and di-C_1-C_6alkylcarboxamide, and C_1-C_6alkyloxime, each of which (b) is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, (C_1-C_4alkoxy)C_0-C_4alkyl, mono- and di-C_1-C_4alkylamino, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy; and

(c) (carbocycle)C_0-C_6alkyl, (heterocycle)C_0-C_6alkyl, (carbocycle)C_0-C_6alkoxy, (heterocycle)C_0-C_6alkoxy, (carbocycle)C_0-C_6alkylamino, and (heterocycle)C_0-C_6alkylamino; each of which (c) is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

Each L is independently a single covalent bond, –N(R_{13})-, -O-, -C(=O)-, –SO_2-, -SO_2NH-, -C(=O)N(R_{13})-, or -N(R_{13})C(=O)-, wherein each R_{13} is independently hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or haloC_1-C_6alkyl.

Each M is independently hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, aminoC_1-C_6alkyl, or a 5- to 10-membered cycloalkyl or heterocycloalkyl.

Within certain aspects, compounds as described herein are MCH receptor modulators and exhibit a K_i of no greater than 1 micromolar, 500 nanomolar, 100 nanomolar, or 10 nanomolar in a MCH receptor binding assay and/or have an EC_{50} or IC_{50} value of no greater than 1 micromolar, 500 nanomolar, 100 nanomolar, or 10 nanomolar in an assay for determining MCH receptor agonist or antagonist activity.

Within certain aspects, compounds or salts as described 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 compound or salts as described herein (*i.e.*, a compound Formula I or a pharmaceutically acceptable salt thereof) in combination with a physiologically acceptable carrier or excipient. Within certain embodiments, a pharmaceutical composition provided herein may further comprise one or more additional active agents (*i.e.*, drugs). Pharmaceutical compositions provided herein may be formulated, for example, as an injectable fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup, or a transdermal patch.

The present invention further provides, within other aspects, methods for treating a disease or disorder associated with MCH receptor activation, comprising administering to a patient in need of such treatment a therapeutically effective amount of a MCH receptor modulator as described above. Such diseases and disorders include, for example, eating disorders (*e.g.*, obesity and bulimia nervosa), sexual disorders, diabetes, heart disease, and stroke. The MCH receptor modulator may be administered orally, or via another means such as intranasally, intravenously, or topically. Within certain embodiments, the patient is a human, companion animal, or livestock animal.

Methods are provided, within other aspects, for determining the presence or absence of MCH receptor in a sample, comprising: contacting a sample with a compound as described above under conditions that permit binding of the compound to MCH receptor; and detecting a level of the compound bound to MCH receptor. Within certain embodiments, the compound is radiolabeled, and the step of detection comprises: separating unbound compound from bound compound; and determining an amount of bound compound in the sample. Detection may be achieved, for example, using autoradiography.

The present invention further provides, within other aspects, methods for modulating binding of ligand to MCH receptor. Certain such methods are performed *in vitro*, and comprise contacting MCH receptor with MCH receptor modulator, as described above under conditions and in an amount sufficient to detectably modulate MCH binding to MCH receptor. Other such methods may be performed *in vivo*, and comprise contacting cells expressing MCH receptor with a compound or modulator as described above in an amount sufficient to detectably modulate MCH binding to cells expressing a cloned MCH receptor *in vitro*.

Methods are further provided for modulating binding of MCH to MCH receptor in a patient, comprising administering to a patient (*i.e.*, a human or non-human animal) a compound or modulator as described above. Patients include, for example, companion animals such as dogs.

Within further aspects, the present invention provides methods for modulating the signal-transducing activity of MCH receptor, comprising contacting an MCH receptor, either *in vivo* or *in vitro*, with an amount of an MCH receptor modulator sufficient to detectably alter MCH receptor activity, under conditions suitable for binding of MCH to MCH receptor. Preferably, the MCH receptor is a MCH1R.

Packaged pharmaceutical preparations, comprising: (a) a pharmaceutical composition as described above in a container; and (b) instructions for using the composition to treat a patient suffering from a disease or disorder associated with MCH receptor activation. Such disorders include, for example eating disorders (*e.g.*, obesity and bulimia nervosa), sexual disorders, diabetes, heart disease, and stroke, are also provided herein.

In yet another aspect, methods of preparing the compounds disclosed herein, including the intermediates, are also provided herein.

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

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention provides aryl substituted 8-azabicyclo[3.2.1]octane compounds and analogues thereof of Formula I. Certain preferred compounds are MCH receptor modulators that may be used *in vitro* or *in vivo*, to inhibit MCH binding to MCH receptors, activate MCH receptors, or to otherwise modulate MCH receptor activity in a variety of contexts, as discussed in further detail below.

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 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. Compound descriptions are intended to encompass compounds with all possible isotopes of atoms occurring in the compounds. Isotopes are those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C. Certain compounds are

described herein using a general formula that includes variables (*e.g.*, R_1, R_2, R_3). 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. In general, the variables (*e.g.* R_1, R_2, R_3) may have any definition described herein that results in a stable compound.

The terms "aryl substituted 8-azabicyclo[3.2.1]octane compounds and analogues thereof" as used herein, encompass all compounds that satisfy Formula I, including any enantiomers, racemates, and stereoisomers, as well as all pharmaceutically acceptable salts of such compounds.

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 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 pharmaceutical salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzene sulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pamoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium, and ammonium. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein, including those listed by *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985). 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, isopropanol, or acetonitrile, is preferred. Pharmaceutically acceptable salts of the aryl substituted 8-azabicyclo[3.2.1]octane compounds and analogues thereof disclosed herein are a preferred compound form.

It will be apparent that each compound of Formula I may, but need not, be formulated as a hydrate, solvate or non-covalent complex. In addition, the various crystal forms and polymorphs are within the scope of the present invention. Also provided herein are prodrugs of the compounds of Formula I. 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 of Formula I. 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 hydroxyl, 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 chain or branched chain saturated aliphatic hydrocarbon. An alkyl group may be bonded to an atom within a molecule of interest via any chemically suitable portion. Alkyl groups include groups having from 1 to 8 carbon atoms (C_1-C_8alkyl), from 1 to 6 carbon atoms (C_1-C_6alkyl), and from 1 to 4 carbon atoms (C_1-C_4alkyl), 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. "C_0-$C_n$alkyl" refers to a single covalent bond (C_0) or an alkyl group having from 1 to n carbon atoms. For example "C_0-C_6alkyl" refers to a single covalent bond or a C_1-C_6alkyl group.

Similarly, "alkenyl" refers to straight or branched chain alkene groups, in which at least one unsaturated carbon-carbon double bond is present. Alkenyl groups include C_2-C_8alkenyl, C_2-C_6alkenyl, and C_2-C_4alkenyl 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 C_2-C_8alkynyl, C_2-C_6alkynyl, and C_2-C_4alkynyl groups, which have from 2 to 8, 2 to 6, or 2 to 4 carbon atoms, respectively. Alkenyl and alkynyl groups may be straight or branched chain.

By "alkoxy," as used herein, is meant an alkyl group as described above attached via an oxygen bridge. Alkoxy groups include C_1-C_8alkoxy, C_1-C_6alkoxy, and C_1-C_4alkoxy groups, which have from 1 to 8, 1 to 6, or 1 to 4 carbon atoms, respectively. Alkoxy groups include, for example, 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-methylpentoxy. Similarly, "alkylthio" refers to an alkyl group as described above attached via a sulfur bridge and "alkylsufonyl" refers to an alkyl groups as described above attached via an -(SO_2)- bridge.

An "(alkoxy)alkyl" group is an alkoxy group as described above attached via an oxygen bridge to an alkyl group, as described above, attached via a single covalent bond of the alkyl carbon.

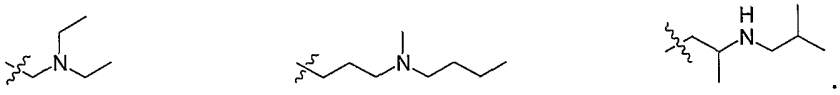
As used herein the term "alkoxycarbonyl" indicates an alkoxy group, as defined above, having the indicated number of carbon atoms, attached through a keto (-(C=O)-) bridge. The alkoxy moiety of the alkoxycarbonyl group has the indicated number of carbon atoms; the carbon of the keto bridge is not included in this number. C_3alkoxycarbonyl group indicates for example, groups of the formula $CH_3(CH_2)_2$-O-(C=O)- or $(CH_3)_2(CH)$-O-(C=O)-.

"Alkanoyl" indicates an alkyl group as defined above, attached through a keto (-(C=O)-) bridge. Alkanoyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C_2alkanoyl group is an acetyl group having the formula $CH_3(C=O)$-.

"Alkanoylamino" indicates and alkanoyl group as defined above attached through an amino linker, e.g. a group of the formula $CH_3(C=O)NH$-.

"Alkylamino" refers to a secondary or tertiary amine having the general structure –NH(alkyl) or –N(alkyl)(alkyl), wherein each alkyl may be the same or different. Such groups include, for example, mono- and di-(C_1-C_8alkyl)amino groups, in which each alkyl is straight or branched and may be the same or different and contains the indicated number of carbon atoms, for example from 1 to 8 carbon atoms, from 1 to 6 carbon atoms, or from 1 to 4 carbon atoms, from as well as mono- and di-(C_1-C_6alkyl)amino groups and mono- and di-(C_1-C_4alkyl)amino groups.

"Alkylaminoalkyl" refers to an alkylamino group linked via an alkyl group (*i.e.*, a group having the general structure -alkyl–NH–alkyl or -alkyl–N(alkyl)(alkyl)) in which each alkyl is selected independently. Such groups include, for example, mono- and di-(C_1-C_6alkyl)aminoC_1-C_6alkyl and mono- and di-(C_1-C_4alkyl)aminoC_1-C_4alkyl, in which each alkyl may be the same or different, and is straight or branched. "Mono- or di-(C_1-C_6alkyl)aminoC_0-C_6alkyl" refers to a mono- or di-(C_1-C_6alkyl)amino group linked via a single covalent bond or a C_1-C_6alkyl group. The following are representative alkylaminoalkyl groups:



As used herein the term "mono- and/ or di-alkylcarboxamide" refers to groups of formula ($alkyl_1$)-NH-(C=O)- and ($alkyl_1$)($alkyl_2$)-N-(C=O)- in which the $alkyl_1$ and $alkyl_2$ groups are independently chosen alkyl groups as defined above having the indicated number of carbon atoms. "Carboxamide" is a group of the formula –(C=O)NH_2.

"Alkyl ether" indicates an alkyl group as described herein attached via an oxygen linker to another alkyl group.

"Alkyloxime" is an alkyl group as described above attached via a –(C=NOH)- linker.

The term "oxo," as used herein, refers to a keto (C=O) group. An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of $-CH_2-$ to $-C(=O)-$. When an aromatic moiety is substituted with an oxo group, the aromatic ring is replaced with the corresponding partially unsaturated ring. For example, a pyridyl group substituted with oxo is a pyridone.

As used herein the term "mono- and/ or di-alkylsulfonamide" refers to groups of formula $(alkyl_1)$-NH-(SO_2)- and $(alkyl_1)(alkyl_2)$-N-(SO_2)- in which the $alkyl_1$ and $alkyl_2$ groups are independently chosen alkyl groups as defined above having the indicated number of carbon atoms.

As used herein the term "alkylsulfonyl" refers to a substituent of the formula (alkyl)-SO_2- in which the alkyl group has the indicated number of carbon atoms, and the point of attachment is on the sulfur atom.

"Aminoalkyl" is an alkyl group as defined above substituted with at least one amino substituent. When indicated an aminoalkyl group may be further substituted with additional amino or non-amino substituent.

As used herein, the term "aryl" indicates aromatic groups containing only carbon in the aromatic ring or rings. Such aromatic groups may be further substituted with carbon or non-carbon atoms or groups. Typical aryl groups contain 1 or 2 separate, fused, or pendant rings and from 6 to about 12 ring atoms, without heteroatoms as ring members. Where indicated aryl groups may be substituted. Such substitution may include fusion to a 5 to 7-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently chosen from N, O, and S, to form, for example, a 3,4-methylenedioxy-phenyl group. Aryl groups include, for example, phenyl, naphthyl, including 1-naphthyl and 2-naphthyl, and bi-phenyl.

In the term "(aryl)alkyl", aryl and alkyl are as defined above, and the point of attachment is on the alkyl group. For example (phenyl)C_0-C_2alkyl indicates a phenyl group indicates a phenyl group that is directly attached via a single covalent bond ((phenyl)C_0alkyl) or attached through an alkyl group having from 1 to about 2 carbon atoms. Similarly an aryl group may be attached through other linker groups, for example included herein are arylC_1-C_6alkanoylamino and (aryl)alkoxy groups, in which aryl carries the definition set forth above, and is attached via the indicated linker group.

A "carbocycle" has from 1 to 3 fused, pendant, or spiro rings, containing only carbon ring members. Typically, a heterocyclic ring comprises contains from 3 to 8 ring members (rings having from 4 or 5 to 7 ring members are recited in certain embodiments) and carbocycles comprising fused, pendant, or spiro rings typically contain from 9 to 14 ring members. Carbocycles may be optionally substituted with a variety of substituents, as indicated. Unless otherwise specified, a carbocycle may be a cycloalkyl group (*i.e.*, each ring is saturated), a partially saturated group, or an aryl group (*i.e.*, at least one ring within the group is aromatic). A carbocyclic group may generally be linked via any ring or substituent atom, provided that a stable compound results. Certain carbocyclic groups are 4-

to 7-membered or 5- to 7-membered groups that are optionally substituted. Representative aromatic carbocycles are phenyl, naphthyl and biphenyl. In certain embodiments preferred carbocycles are carbocycles having a single ring, such as phenyl and 3- to 7- membered cycloalkyl groups.

A carbocycle may be directly attached or attached via an indicated linker group. For example (carbocycle)alkyl, (carbocycle)alkoxy, and (carbocycle)alkylamino substituents are present in some embodiments described herein. In each case "carbocycle" carries the definition set forth above and is covalently bound to the indicated linker group, which carries the definition set forth above.

A "cycloalkyl" group is a carbocycle as described above, which is fully saturated. In certain embodiments preferred cycloalkyl groups are 3- to 7-membered cycloalkyl groups having a single saturated ring, e.g. cyclopropyl, cyclopentyl, and cyclohexyl. A "cycloalkylC_0-$C_n$alkyl" is a cycloalkyl group linked via a single covalent bond or a C_1-$C_n$alkyl group, e.g. a C_1-C_4alkyl group. Similarly a "cycloalkenyl" group is a 3- to 7- membered carbocycle having at least one carbon-carbon double bond, but which is not fully aromatic, e.g. a cycloalkenyl group.

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

A "haloalkyl" is a branched or straight-chain alkyl group, substituted with 1 or more halogen atoms (*e.g.*, "haloC_1-C_6alkyl" groups have from 1 to 6 carbon atoms; "haloC_1-C_4alkyl" groups have from 1 to 4 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di-, or trifluoromethyl; mono-, di-, or trichloromethyl; mono-, di-, tri-, tetra-, or pentafluoroethyl; mono-, di-, tri-, tetra- or pentachloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl.

"Haloalkoxy" indicates a haloalkyl group as defined above attached through an oxygen bridge. "haloC_1-C_6alkoxy" groups have from 1 to 6 carbon atoms.

As used herein "hydroxyalkyl" is an alkyl group as defined herein, having the indicated number of carbon atoms, and substituted with at least one hydroxyl substituent (-OH). When indicated, hydroxyalkyl groups, like other groups described herein, may be additionally substituted.

A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -$CONH_2$ is attached through the carbon atom.

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

A "heterocycle" has from 1 to 3 fused, pendant, or spiro rings, at least one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom, with the remaining ring atoms being carbon). 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 3 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 SO_2. 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), a partially saturated group, or a heteroaryl group (*i.e.*, at least one ring within the group is aromatic). A heterocyclic group may generally be linked via any ring or substituent atom, provided that a stable compound results. N-linked heterocyclic groups are linked via a component nitrogen atom. Certain heterocyclic groups are 4- to 7-membered or 5- to 7-membered groups that are optionally substituted. 4-to 7-membered heterocycloalkyl groups include, for example, piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, morpholino, thiomorpholino, and 1,1-dioxo-thiomorpholin-4-yl. Such groups may be substituted as indicated. Representative aromatic heterocycles are azocinyl, pyridyl, pyrimidyl, imidazolyl, and tetrazolyl.

In certain embodiments preferred heterocycles are 5- to 7-membered heterocycle having a single saturated, partially unsaturated or aromatic heterocyclic ring with 5 to 7 ring members, 1 or 2 ring members independently chosen from N, O, and S, with remaining ring members being carbon.

A heterocycle may be directly attached or attached via an indicated linker group. For example (heterocycle)alkyl, (heterocycle)alkoxy, and (heterocycle)alkylamino substituents are present in some embodiments described herein. In each case, "heterocycle" carries the definition set forth above and is covalently bound to the indicated linker group, which carries the definition set forth above.

As used herein, "heteroaryl" indicates a stable 5- to 7-membered monocyclic aromatic ring which contains from 1 to 3, or preferably from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon or a stable bicyclic or tricyclic system containing at least one 5- to 7-membered aromatic ring which contains from 1 to 3, or preferably from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon. When the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heteroaryl group is not more than 2. It is particularly preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, oxazolyl, pyranyl, pyrazinyl, pyrazolopyrimidinyl, pyrazolyl, pyridizinyl, pyridyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienylpyrazolyl, thiophenyl, triazolyl, benzo[*d*]oxazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxadiazolyl, dihydrobenzodioxynyl, furanyl, imidazolyl, indolyl, and isoxazolyl.

A "heterocyclolalkyl" group is a heterocycle as described above, which is fully saturated. In certain embodiments preferred heterocycloalkyl groups have a single saturated ring with 5 to 7 ring members, 1 or 2 ring members independently chosen from N, O, and S, with remaining ring members being carbon. A "heterocycloalkylC_0-$C_n$alkyl" is a heterocycloalkyl group linked via a single covalent

bond or C_1-$C_n$alkyl group, *e.g.*, a C_1-C_4alkyl group. Similarly a "heterocycloalkenyl" group is a 5- to 7-membered heterocycle having a single ring that contains at least one carbon-carbon, carbon-nitrogen, or nitrogen-nitrogen double bond, but which is not fully aromatic, with 1 or 2 ring members independently chosen from N, O, and S, with remaining ring members being carbon.

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. Substituents or aromatic groups are generally covalently bonded to a ring carbon atom. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent, 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 are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Such optional substituents include, for example, hydroxy, halogen, cyano, nitro, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_1-C_8alkoxy, C_2-C_8alkyl ether, C_3-C_8alkanone, C_1-C_8alkylthio, amino, mono- or di-(C_1-C_8alkyl)amino, C_1-C_8haloalkyl, C_1-C_8haloalkoxy, C_1-C_8alkanoyl, C_2-C_8alkanoyloxy, C_1-C_8alkoxycarbonyl, -COOH, -$CONH_2$, mono- or di-(C_1-C_8alkyl)aminocarbonyl, -SO_2NH_2, and/or mono or di(C_1-C_8alkyl)sulfonamide, as well as carbocyclic and heterocyclic groups. Optional substitution is also indicated by the phrase "substituted with 0 to X substituents," where X is the maximum number of possible 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 substitutents).

The term "MCH receptor" refers to any naturally-occurring mammalian (especially human, monkey, or canine) MCH type 1 or type 2 receptor, as well as chimeric receptors in which one or more domains of a naturally-occurring MCH1R or MCH2R are replaced with a corresponding domain of a different G protein-coupled receptor, such that the ability of the chimeric receptor to bind MCH and mediate a dose-dependent release of intracellular calcium is not diminished. MCH receptors for use within the various assays and other methods described herein include, for example, recombinantly expressed human MCH receptor (*e.g.,* Genbank Accession No. Z86090; SEQ ID NO:29 of U.S. Patent Application Publication Number 2003/0148457), monkey MCH receptor (*e.g.,* SEQ ID NO:2, 34 or 36 of U.S. Patent Application Publication Number 2003/0114644) or canine MCH receptor (*e.g.,* SEQ ID NO:39 of U.S. Patent Application Publication Number 2003/0114644). Chimeric MCH

receptors that may be used as described herein include, for example, those disclosed in U.S. Patent Application Publication Numbers 2003/0114644 and 2003/0148457.

A "MCH receptor modulator," also referred to herein as a "modulator," is a compound that alters (increases or decreases) MCH receptor activation and/or MCH receptor-mediated signal transduction. MCH receptor modulators specifically provided herein are aryl-substituted piperazine derivatives. A modulator may be a MCH receptor agonist or antagonist. In certain embodiments, a modulator may exhibit an EC_{50} or IC_{50} at MCH receptor that is less than 1 micromolar, 500 nM, 200 nM, 100 nM, 50 nM, 25 nM or 10 nM in a standard calcium mobilization assay (as described in Example 13, herein) and/or an agonist-stimulated GTP gamma^{35}S binding assay (as described in Example 11, herein). A modulator may be a MCH receptor agonist or antagonist, although, for certain purposes described herein, a modulator preferably inhibits MCH receptor activation resulting from binding of MCH (*i.e.*, the modulator is an antagonist).

A MCH receptor modulator binds with "high affinity" if the K_i at a MCH receptor is less than 1 micromolar, preferably less than 500 nanomolar, 100 nanomolar, or 10 nanomolar. A modulator binds "specifically" to MCH receptor if it binds to a MCH receptor (total binding minus nonspecific binding) with a K_i that is 10-fold, preferably 100-fold, and more preferably 1000-fold, less than the K_i measured for modulator binding to other G protein-coupled receptors. For example, a modulator may have a K_i of 500 nanomolar or less in an MCH receptor ligand binding assay and a K_i of at least 1 micromolar in a dopamine receptor ligand binding assay, such as the assay described in Example 7 (pages 111-112) of PCT International Publication Number WO 02/094799, which is hereby incorporated by reference. Representative assays for determining K_i at MCH receptor are provided in Examples 9 and 12, herein.

A modulator is considered an "antagonist" if it detectably inhibits MCH binding to MCH receptor and/or MCH-mediated signal transduction (using, for example, the representative assay provided in Example 9 or Example 12). In general, such an antagonist has an IC_{50} value of less than 1 micromolar, preferably less than 100 nanomolar, and more preferably less than 10 nanomolar within the assay provided in Example 9 and/ or the assay provided in Example 12. MCH receptor antagonists include neutral antagonists and inverse agonists.

An "inverse agonist" is a compound that reduces the activity of MCH receptor below its basal activity level in the absence of added ligand. Inverse agonists may also inhibit the activity of MCH at MCH receptor, and/or may also inhibit binding of MCH to MCH receptor. The ability of a compound to inhibit the binding of MCH to MCH receptor may be measured by a binding assay, such as the binding assay given in Examples 9 or 12. The basal activity of MCH receptor, as well as the reduction in MCH receptor activity due to the presence of antagonist, may be determined from a

calcium mobilization assay, such as the assay of Example 13, or an agonist-stimulated GTP gamma^{35}S binding assay, such as the assay described in Example 11.

A "neutral antagonist" of MCH receptor is a compound that inhibits the activity of MCH at MCH receptor, but does not significantly change the basal activity of the receptor (*e.g.*, within an assay as described in Example 11 or Example 13 performed in the absence of ligand, MCH receptor activity is reduced by no more than 10%, more preferably by no more than 5%, and even more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). Neutral antagonists may also inhibit ligand binding to MCH receptor.

As used herein, a "MCH receptor agonist" is a compound that elevates the activity of the receptor above the basal activity level of the receptor (*i.e.*, enhances MCH receptor activation and/or MCH receptor-mediated signal transduction). MCH receptor agonist activity may be identified using the representative assays provided in Examples 11 and 13. In general, such an agonist has an EC_{50} value of less than 1 micromolar, preferably less than 100 nanomolar, and more preferably less than 10 nanomolar within one or both of the assays provided in Examples 11 and 13.

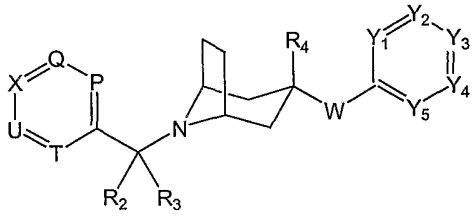
A "therapeutically effective amount" (or dose) is an amount that, upon administration, is sufficient to provide a discernible patient benefit. For example, a therapeutically effective amount may reduce symptom severity or frequency, or to result in detectable weight loss. Alternatively, or in addition, a therapeutically effective amount may improve patient status or outcome and/or prevent or delay disease or symptom onset. 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 the binding of ligand to MCH receptor *in vitro* (using the assay provided in Example 9 or Example 12) and/or MCH-mediated signal transduction (using an assay provided in Example 11 or Example 13).

A "disease or disorder associated with MCH receptor activation," as used herein is any condition that is characterized by inappropriate stimulation of MCH receptor, regardless of the amount of MCH present locally, and/or that is responsive to modulation of MCH receptor activity (*i.e.*, the condition or a symptom thereof is alleviated by such modulation). Such conditions include, for example, metabolic disorders (such as diabetes), heart disease, stroke, eating disorders (such as obesity and bulimia nervosa) and sexual disorders such as anorgasmic and psychogenic impotence, as well as other diseases and disorders recited herein.

A "patient" is any individual treated with a MCH modulator as 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 MCH receptor modulation, or may be free of such symptom(s) (*i.e.*, treatment may be prophylactic).

MELANIN CONCENTRATING HORMONE RECEPTOR MODULATORS

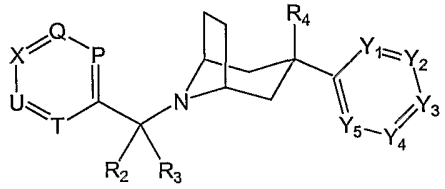
As noted above, the present invention provides and comprises aryl substituted 8-azabicyclo[3.2.1]octane compounds and analogues thereof of Formula I described above, as well as pharmaceutically acceptable salts thereof,



Formula I

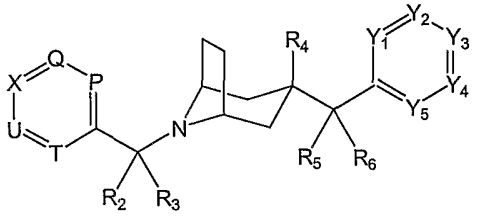
Additionally compounds and salts of Formula I in which one or more of the following conditions are met are provided herein:

i. W is absent; e.g. compounds and salts of Formula II are provided herein:



Formula II.

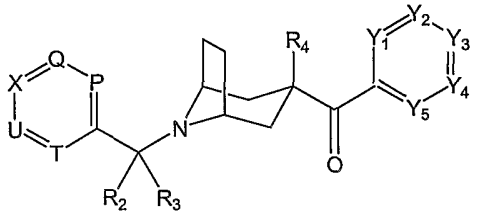
ii. W is CR_5R_6; e.g. compounds and salts of Formula III are provided herein:



Formula III.

iii. R_5 and R_6 are independently hydrogen or methyl.

iv. R_5 and R_6 are taken together to form an oxo group, e.g compounds and salts of Formula IV are provided herein:

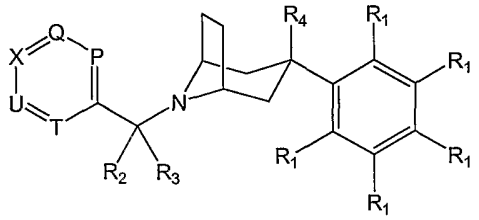


Formula IV.

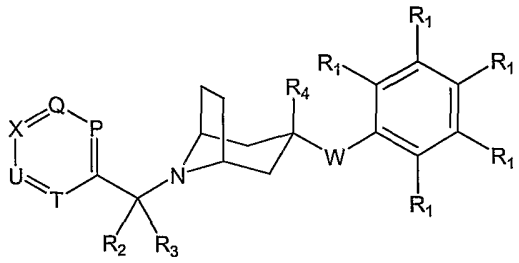
v. One and only one of Y_1, Y_2, Y_3, Y_4 and Y_5 is nitrogen.

vi. One of Y_1, Y_4, and Y_5 is nitrogen.

vii. Y_1, Y_2, Y_3, Y_4, and Y_5 are all CR_1, e.g., compounds and salts of Formula V and Formula VI are provided herein:



Formula V

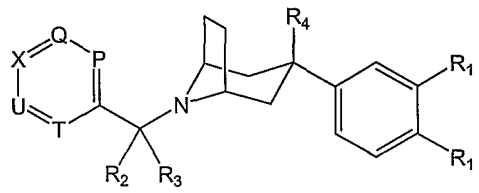


Formula VI

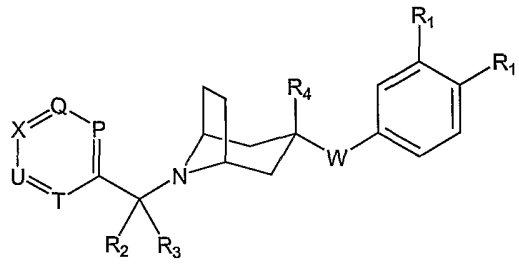
viii. Each R_1 is independently hydrogen, halogen, hydroxy, nitro, cyano, amino, C_1-C_4alkyl, C_2-C_4alkenyl, C_1-C_4alkoxy, haloC_1-C_2alkyl, haloC_1-C_2alkoxy, hydroxyC_1-C_4alkyl, C_1-C_4alkylthio, aminoC_1-C_6alkyl, mono- or di-(C_1-C_4alkyl)amino, or (C_3-C_7cycloalkyl)C_0-C_2alkyl.

ix. Each R_1 is independently hydrogen, halogen, C_1-C_2alkyl, C_2-C_4alkenyl, C_1-C_2alkoxy, haloC_1-C_2alkyl, or haloC_1-C_2alkoxy.

x. Y_1, Y_2, Y_3, Y_4, and Y_5 are all CR_1; and the R_1 of Y_1, Y_4, and Y_5 are all hydrogen, e.g. compounds and salts of Formula VII and Formula VIII are provided herein:



Formula VII



Formula VIII

xi. R_1 of Y_2 is halogen, methyl, methoxy, or trifluoromethyl, and R_1 of Y_3 is hydrogen, halogen, methyl, methoxy, or trifluoromethyl.

xii. R_1 of Y_2 is hydrogen, halogen, methyl, methoxy, or trifluoromethyl, and R_1 of Y_3 is halogen, methyl, methoxy, or trifluoromethyl.

xiii. R_1 of Y_2 is methoxy or trifluoromethyl, and R_1 of Y_3 is chloro.

xiv. R_2 and R_3 are independently hydrogen or methyl.

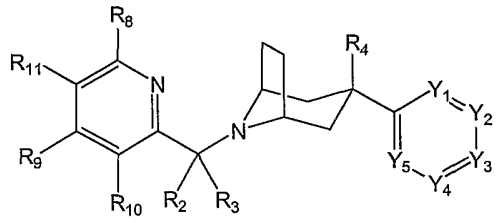
xv. R_2 and R_3 are both hydrogen.

xvi. R_2 is joined with R_3 to form an oxo group.

xvii. R_4 is hydrogen, hydroxy, amino, -NHCHO, or C_2alkanoylamino.

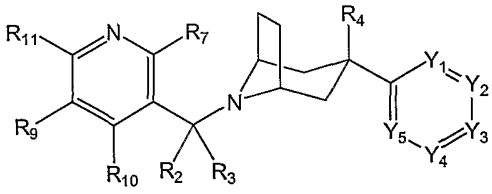
xviii. R_4 hydroxy.

xix. P is nitrogen or CR_7; Q is CR_8; U is CR_9; T is CR_{10}; and X is CR_{11}, e.g. compounds and salts of Formula IX are provided herein



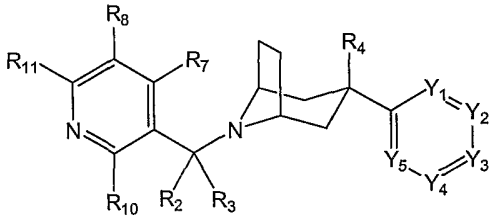
Formula IX.

xx. P is CR_7; Q is nitrogen; U is CR_9; T is CR_{10}; and X is CR_{11}, e.g. compounds and salts of Formula X are provided herein:



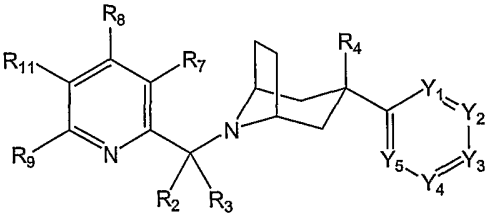
Formula X.

xxi. P is CR_7; Q is CR_8; U is nitrogen; T is CR_{10}; and X is CR_{11}, e.g. compounds and salts of Formula XI are provided herein:



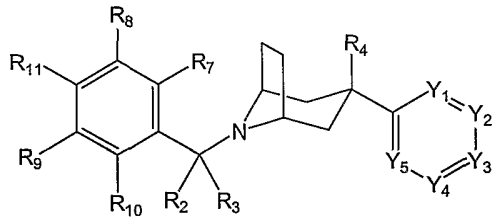
Formula XI

xxii. P is CR_7; Q is CR_8; U is CR_9; T is nitrogen; and X is CR_{11}, e.g. compounds and salts of Formula XII are provided herein:



Formula XII

xxiii. P is CR_7; Q is CR_8; U is CR_9; T is CR_{10}; and X is CR_{11}, e.g. compounds and salts of Formula XIII are provided herein:



Formula XIII.

xxiv. R_7, R_8, R_9, and R_{10} are independently hydrogen, halogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, mono- or di-C_1-C_6alkylamino, haloC_1-C_2alkyl, or haloC_1-C_2alkoxy.

xxv. R_7 and R_8 are independently hydrogen, C_1-C_2alkyl, or C_1-C_2alkoxy; and R_9 and R_{10} are hydrogen.

xxvi. R_7 and R_8 are both methyl.

xxvii. R_{11} is a group of the formula -L-G.

xxviii. G is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, aminoC_1-C_6alkyl, or a 5- to 10-membered cycloalkyl or heterocycloalkyl; each of which is substituted with 0 to 3 substituents independently chosen from halogen, amino, and haloC_1-C_2alkoxy.

G is further substituted with at least one substituent independently chosen from

(a) oxo, hydroxy, cyano, -COOH, -(C=O)NH_2, -NH(C=O)H, -SO_2NH_2, and imino,

(b) (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_8alkyl)aminoC_0-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfonamide, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoylamino, mono- and di-C_1-C_6alkylcarboxamide, and C_1-C_6alkyloxime, each of which (b) is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, (C_1-C_4alkoxy)C_0-C_4alkyl, mono- and di-C_1-C_4alkylamino, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy, and

(c) (carbocycle)C_0-C_6alkyl, (heterocycle)C_0-C_6alkyl, (carbocycle)C_0-C_6alkoxy, (heterocycle)C_0-C_6alkoxy, (carbocycle)C_0-C_6alkylamino, and (heterocycle)C_0-C_6alkylamino, wherein the carbocycle is phenyl, naphthyl, C_3-C_7cycloalkyl, or C_3-C_7cycloalkenyl, and the heterocycle is pyrrolidinyl, tetrahydrofuranyl, dioxolanyl, tetrahydropyranyl, isothiazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, dihydropyrrolyl, pyrazolyl, furanyl, thienyl, pyrazolyl, oxazolyl, thiazolyl, thiadiazolyl, isoxazolyl, imidiazolyl, triazolyl, tetrazolyl, pyridinyl, tetrahydropyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, benzodioxanyl, indolyl, isoindolyl, indazolyl, indanyl, quinolinyl, isoquinolinyl, or benzimidazolyl; each of which (c) are substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

xxix. L is -O-.

xxx. G is C_1-C_6alkyl, each of which is substituted with 0 to 3 substituents independently chosen from halogen, amino, and haloC_1-C_2alkoxy.

G is further substituted with at least one substituent independently chosen from

(a) oxo, hydroxy, cyano, -COOH, -(C=O)NH_2, -NH(C=O)H,

(b) C_1-C_6alkoxy, mono- and di-(C_1-C_6alkyl)amino, C_1-C_6alkylsulfonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfonamide, C_1-C_6alkoxycarbonyl, and C_2-C_6alkanoylamino, each of which (b) is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, (C_1-C_4alkoxy)C_0-C_4alkyl, mono- and di-C_1-C_4alkylamino, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy, and

(c) (carbocycle)C_0-C_6alkyl and (heterocycle)C_0-C_6alkyl, wherein the carbocycle is phenyl, naphthyl, C_3-C_7cycloalkyl, or C_3-C_7cycloalkenyl, and the heterocycle is pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, furanyl, thienyl, oxazolyl, thiazolyl, imidiazolyl, triazolyl, pyridinyl, pyrimidinyl or, pyrazinyl, each of which (c) are substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-(C_1-C_4alkyl)amino, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

xxxi. G is C_1-C_4alkyl.

xxxii. G is C_1-C_6alkyl substituted with at least one substituent independently chosen from (a) oxo, hydroxy, -(C=O)NH_2, and -NH(C=O)H, and (b) C_1-C_4alkoxy, mono- and di-(C_1-C_4alkyl)amino, C_1-C_4alkoxycarbonyl, and C_2-C_4alkanoylamino, each of which (b) is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, C_1-C_2alkoxy, mono- and di-C_1-C_4alkylamino, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

xxxiii. G is C_1-C_6alkyl substituted with at least one substituent independently chosen from (carbocycle)C_0-C_6alkyl and (heterocycle)C_0-C_6alkyl, wherein the carbocycle is phenyl or C_3-C_7cycloalkyl, and the heterocycle is pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, furanyl, thienyl, imidiazolyl, pyridinyl, pyrimidinyl, or pyrazinyl, each of which (carbocycle)C_0-C_6alkyl and (heterocycle)C_0-C_6alkyl is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, C_1-C_2alkoxy, mono- and di-C_1-C_4alkylamino, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

xxxiv. R_{11} is taken together with R_8 to form a fused carbocycle or heterocycle; which is substituted with 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

xxxv. R_{11} is taken together with R_8 to form a fused 5 or 6 membered heterocycloalkyl ring having 1 or 2 oxygen atoms; which is substituted with 0 to 2 substituents independently chosen from halogen, hydroxy, methyl, and methoxy.

xxxvi. R_{11} is taken together with R_8 to form a fused 5 or 6 membered heterocycloalkyl ring having 1 or 2 oxygen atoms; which is substituted with 0 to 2 substituents independently chosen from halogen, hydroxy, methyl, and methoxy and R_7, R_9, and R_{10} are independently hydrogen or methyl.

Representative compounds of Formulas I-XIII include, but are not limited to, those specifically described in Examples 1-7. It will be apparent that the compounds recited therein 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 pharmaceutically acceptable form, such as a hydrate, free base, or acid addition salt.

Certain aryl substituted 8-azabicyclo[3.2.1]octane compounds and analogues thereof provided herein detectably alter (modulate) MCH binding to MCHR1 and/or MCHR2 receptor, as determined using a standard *in vitro* MCH receptor binding assay and/or calcium mobilization assay. References herein and in the claims to a "MCH receptor ligand binding assay" refer to either of the standard *in vitro* receptor binding assay provided in Examples 9 and 12. Within such assays, the receptor is incubated with labeled MCH (or other suitable ligand) and a test compound. A test compound that detectably modulates binding of ligand to MCH receptor will result in a decrease or increase in the amount of label bound to the MCH receptor preparation, relative to the amount of label bound in the absence of the compound. Preferably, such a compound will exhibit a K_i at an MCH receptor that is less than 1 micromolar, more preferably less than 500 nM, 100 nM, 20 nM or 10 nM, within an assay performed as described in Example 9 and/or within an assay performed as described in Example 12. Certain preferred compounds are MCH receptor antagonists, and exhibit IC_{50} values of about 4 micromolar or less, more preferably 1 micromolar or less, still more preferably about 100 nanomolar or less, or 10 nanomolar or less within a standard *in vitro* MCH receptor mediated calcium mobilization assay, as provided in Example 13 and/or an agonist-stimulated GTP gamma^{35}S binding assay, as described in Example 11.

If desired, MCH 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, still more preferably less than 1 mg/kg), toxicity (a preferred MCH receptor modulator is nontoxic when a therapeutically effective amount is administered to a subject), side effects (a preferred MCH 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 MCH receptor modulator exhibits an *in vitro* half-life that is equal to 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 MCH receptor modulators used to treat CNS disorders, while low brain levels of MCH receptor modulators used to treat peripheral disorders are preferred. 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. Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described within Example 15, herein.

As noted above, preferred MCH receptor modulators 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 when administered in minimum therapeutically effective amounts, or when contacted with cells at a concentration that is sufficient to inhibit the binding of MCH receptor ligand to MCH receptor *in vitro* : (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement and (4) does not cause substantial release of liver enzymes.

[0100] As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that satisfies the criteria set forth in Example 14, herein. In other words, cells treated as described in Example 14 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. The concentration of compound used in such assays is generally at least 10-fold, 100-fold or 1000-fold greater than the EC_{50} or IC_{50} for the modulator in the assay of Example 11 or 13.

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 preferred embodiments, such doses do not elevate such serum levels by more than 75% or 50% over matched controls. Alternatively, compound 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 of 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 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 MCH 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, MCH receptor modulators provided herein may be isotopically-labeled or radiolabeled. For example, compounds of Formula I 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, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}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.

PHARMACEUTICAL COMPOSITIONS

Aryl-substituted piperazine derivatives can be administered as the neat chemical, but are preferably administered as a pharmaceutical composition comprising such a compound, together with at least one physiologically acceptable carrier or excipient. Representative carriers include, 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 and proteins. Additional optional components include, adjuvants, diluents, 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).

Pharmaceutical carriers must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal being treated. The carrier can be inert or it can possess pharmaceutical benefits. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Representative pharmaceutically acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; synthetic oils; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; polyols such as propylene glycol, glycerine, sorbitol, mannitol and polyethylene glycol; alginic acid; phosphate buffer solutions; emulsifiers, such as the TWEENS; wetting agents, such as sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

To prepare a pharmaceutical composition, effective concentrations of one or more aryl-substituted piperazine derivatives provided herein are mixed with one or more a suitable

pharmaceutical carriers or excipients. In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactant, such as TWEEN, or dissolution in aqueous sodium bicarbonate. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the chosen carrier.

Pharmaceutical compositions may be formulated for administration by any suitable route, including orally, topically, parenterally, by inhalation or spray, sublingually, transdermally, via buccal administration, rectally, as an ophthalmic solution or by other means, and may be prepared in dosage unit formulations. Dosage formulations suitable for oral use include, for example, tablets, troches, lozenges, liquid solutions, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, tinctures, syrups or elixirs. Compositions intended for oral use may further contain one or more optional agents, such as sweetening agents (*e.g.,* glycerol, propylene glycol, sorbitol or sucrose), flavoring agents, coloring agents and preserving agents, in order to provide pharmaceutically appealing and palatable preparations. Such formulations may also contain a demulcent. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water.

Orally Administered Liquid Formulations

Compounds provided herein can be incorporated into oral liquid preparations such as, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs. Moreover, formulations containing these compounds can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may further contain one or more conventional additives, such as suspending agents (*e.g.,* sorbitol syrup, methyl cellulose, glucose/sugar, syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminum stearate gel and hydrogenated edible fats); emulsifying agents (*e.g.,* lecithin, sorbitan monsoleate or acacia); and/or non-aqueous vehicles such as edible oils (*e.g.,* almond oil, fractionated coconut oil, silyl esters, propylene glycol and ethyl alcohol) and preservatives (*e.g.,* methyl or propyl p-hydroxybenzoate and sorbic acid).

Suspensions

Aqueous suspensions contain the active material(s) in admixture with excipients (*e.g.,* suspending agents, wetting agents and/or preservatives) suitable for the manufacture of aqueous suspensions. Suspending agents include, for example, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, AVICEL RC-591, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia. Dispersing or wetting agents include, for example, lecithin, polysorbate 80, naturally-occurring phosphatides such as lecithin, condensation

products of an alkylene oxide with fatty acids (*e.g.*, polyoxyethylene stearate), condensation products of ethylene oxide with long chain aliphatic alcohols (*e.g.*, heptadecaethyleneoxycetanol), condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (*e.g.*, polyoxyethylene sorbitol substitute), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (*e.g.*, polyethylene sorbitan substitute). Representative preservatives include, for example, ethyl- or n-propyl- p-hydroxybenzoate, sodium benzoate and methyl paraben.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil (*e.g.*, peanut oil, olive oil, sesame oil or coconut oil), a mineral oil (such as liquid paraffin) or a mixture of such oils. The oily suspensions may further contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to improve palatability. If desired, these compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Emulsions

Pharmaceutical compositions provided herein may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, mineral oil, or mixture thereof as described above. Suitable emulsifying agents include naturally-occurring gums (*e.g.*, gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.*, soy bean phosphatide, lecithin and esters or partial esters derived from fatty acids and hexitol), and anhydrides (*e.g.*, sorbitan monoleate and condensation products of the above partial esters with ethylene oxide, such as polyoxyethylene sorbitan monoleate).

Dispersible Powders

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, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

Tablets and Capsules

Tablets typically comprise conventional pharmaceutically compatible inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; and/or lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint and fruit flavors, are useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The

selection of carrier components often depends on secondary considerations such as taste, cost and shelf stability.

Such compositions may also be coated by conventional methods, typically with pH-dependent or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such coatings typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methylcellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

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

Injectable and Parenteral Formulations

Pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. Such a suspension may be formulated according to the known art using dispersing or wetting agents and suspending agents as described above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent (*e.g.,* as a solution in 1,3-butanediol). Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil synthetic (*e.g.,* synthetic mono- or diglycerides) may be employed. In addition, fatty acids such as oleic acid are useful in the preparation of injectable formulations.

Pharmaceutical compositions may be administered parenterally in a sterile medium. Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intrathecal injection or infusion techniques. The active agent(s), depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Adjuvants such as local anesthetics, preservatives and buffering agents can also be dissolved in the vehicle. In many compositions for parenteral administration, at least about 90% by weight of the total composition is carrier. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol and sesame oil.

Suppositories

Pharmaceutical compositions may also be administered rectally, in the form of suppositories. Such compositions can be prepared by mixing the active ingredient(s) with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Topical Formulations

Pharmaceutical compositions may be formulated for local or topical application, such as for topical application to the skin or mucous membranes. Topical compositions may be in any suitable form including, for example, solutions, creams, ointments, gels, lotions, milks, cleansers, moisturizers, sprays, skin patches and the like. Such solutions may, for example, be formulated as 0.01%-10% isotonic solutions, pH about 5-7, with appropriate salts. Pharmaceutical compositions may also be formulated for transdermal administration as a transdermal patch.

Topical compositions containing the active compound can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate and the like. Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows: emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, iso-propyl isostearate, stearic acid, iso-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, iso-propyl myristate, iso-propyl palmitate, iso-propyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate and myristyl myristate; propellants, such as propane, butane, iso-butane, dimethyl ether, carbon dioxide and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, iso-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose and ethylene glycol monostearate.

Pharmaceutical compositions may also be topically administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Other Formulations and Additional Components

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more soluble filler substances such as sucrose, sorbitol and mannitol, and/or binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methylcellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

Compositions for inhalation are typically 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).

In addition to or together with the above modes of administration, a pharmaceutical composition 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.

Pharmaceutical compositions may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules that function in different ways to enhance MCH receptor modulator effect. Particular classes of activity enhancers include skin penetration enhancers and absorption enhancers.

Pharmaceutical Compositions for Combination Therapy

Pharmaceutical compositions provided herein may also contain additional active agents, which can be chosen from a wide variety of molecules and can function in different ways to enhance the therapeutic effects of a MCH receptor modulator, or to provide a separate therapeutic effect that does not substantially interfere with the activity of the MCH receptor modulator. Such optional active agents, when present, are typically employed in the compositions described herein at a level ranging from about 0.01% to about 50% by weight of the composition, preferably 0.1% to 25%, 0.2% to 15, 0.5% to 10% or 0.5% to 5% by weight of the composition. For example, compositions intended for the treatment of obesity and/or eating disorders, such as bulimia nervosa, may further comprise leptin, a leptin receptor agonist, a melanocortin receptor 4 (MC4) agonist, sibutramine, dexfenfluramine, a growth hormone secretagogue, a beta-3 agonist, a 5HT-2 agonist, an orexin antagonist, a neuropeptide Y_1 or Y_5 antagonist, a galanin antagonist, a CCK agonist, a GLP-l agonist, a cannabinoid receptor antagonist (*e.g.*, a CB1 antagonist) and/or a corticotropin-releasing hormone agonist. Other active ingredients that may be included within the compositions provided herein include antidepressants, inhibitors of dipeptidyl peptidase IV (DPP IV) and/or diuretics.

In certain embodiments, an additional active agent is a CB1 antagonist. Representative CB1 antagonists include, for example, certain pyrimidines (*e.g.*, PCT International Application Publication No. WO 04/029,204), pyrazines (*e.g.*, PCT International Application Publication Nos. WO 01/111,038; WO 04/111,034 and WO 04/111,033), azetidine derivatives (*e.g.*, US Patent Nos. 6,518,264; 6,479,479 and 6,355,631; and PCT International Application Publication No. WO 03/053431), pyrazole derivatives (*e.g.*, US Patent Nos. 6,509,367 and 6,476,060; and PCT International Application Publication Nos. WO 03/020217 and WO 01/029007), pyrazolecarboxylic acid and pyrazole carboxamide derivatives (*e.g.*, US patent Nos. 6,645,985; 6,432,984; 6,344,474; 6,028,084; 5,925,768; 5,624,941 and 5,462,960; published US applications US 2004/0039024; US 2003/0199536 and US 2003/0003145; and PCT International Application Publication Nos. WO 03/078413; WO 03/027076; WO 03/026648 and WO 03/026647); aroyl substituted benzofurans (*e.g.*, LY-320135, US Patent No. 5,747,524); substituted imidazoles (*e.g.*, published US application US 2003/0114495 and PCT International Application Publication Nos. WO 03/063781 and WO 03/040107); substituted furo[2,3-b]pyridine derivatives (*e.g.*, PCT International Application Publication No. WO 04/012671); substituted aryl amides (*e.g.*, PCT International Application Publication Nos. WO 03/087037 and WO 03/077847); substituted bicyclic or spirocyclic amides (*e.g.*, PCT International Application Publication Nos. WO 03/086288 and WO 03/082190); and substituted 2,3-diphenyl pyridines (*e.g.*, PCT International Application Publication No. WO 03/082191). Other CB1 antagonists are cannabidiol and its derivatives. Preferred CB1 antagonists include, for example, aryl substituted pyrazole carboxamides such as SR-141716A (N-piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1-H-pyrazole-3-carboxamide, also known as RIMONABANT™ or ACOMPLIA™) as well analogues thereof such as AM251 (N-piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1-H-pyrazole-3-carboxamide) and AM281 (N-(morpholin-4-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1-H-pyrazole-3-carboxamide); various azetidine compounds (*e.g.*, US Patent Nos. 6,518,264; 6,479,479 and 6,355,631) and the imidazoles 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide and 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1*H*-imidazole-4-carbohydrazide.

Packaged Pharmaceutical Preparations

Pharmaceutical compositions may be packaged for treating or preventing a disease or disorder that is associated with MCH receptor activation (*e.g.*, treatment of metabolic disorders such as diabetes, heart disease, metabolic syndrome, stroke, obesity and eating disorders such as bulimia, fluid balance disorders, skin disorders such as pigmentation disorders and vitiligo, neuropsychiatric disorders such as anxiety, depression, reward system disorders and cognitive deficits, alterations in NMDA receptor function, reproductive function disorders or sexual disorders such as anorgasmic or

psychogenic impotence), or for promoting weight loss. Pharmaceutical compositions may also be packaged for modulating bone mass (*i.e.,* inhibiting loss of bone mass and/or stimulating an increase in bone mass). Packaged pharmaceutical preparations comprise a container holding a therapeutically effective amount of MCH receptor modulator as described herein and instructions (*e.g.,* labeling) indicating that the contained composition is to be used for promoting weight loss, modulating bone mass or for treating or preventing a disease or disorder that is associated with MCH receptor activation in the patient. Prescribing information may be provided separately to a patient or health care provider, or may be provided as a label or package insert. Prescribing information may include, for example, efficacy, dosage and administration, contraindication and adverse reaction information pertaining to the pharmaceutical formulation. Certain packaged pharmaceutical preparations further include a second therapeutic agent as discussed above.

Dosages

Aryl-substituted piperazine derivatives are generally present within a pharmaceutical composition in a therapeutically effective amount. Compositions 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), with dosages ranging from 0.1 mg to 50 mg, 30 mg or 10 mg particularly preferred. The amount of active ingredient that may be combined with the carrier to produce a single dosage form will vary depending upon the patient to be treated and the particular mode of administration. Dosage unit forms generally contain from about 1 mg to about 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. Dosage units generally contain from about 10 μg to about 500 mg of each active ingredient. Optimal dosages may be established using routine testing and procedures that are well known in the art.

METHODS OF USE

Within certain aspects, the present invention provides methods for inhibiting the development or progression of a disease or disorder responsive to MCH receptor modulation. In other words, therapeutic methods provided herein may be used to treat a patient already afflicted with such a disease or disorder, or may be used to prevent or delay the onset of such a disease or disorder in a patient who is free of detectable disease or disorder that is associated with MCH receptor activation. As noted above, a disease or disorder is "associated with MCH receptor activation" if it is characterized by inappropriate stimulation of MCH receptor, regardless of the amount of MCH

present locally, and/or is responsive to modulation of MCH receptor activity. Such conditions include, for example, metabolic disorders (such as diabetes), heart disease, metabolic syndrome, stroke, obesity and eating disorders (such as bulimia nervosa), fluid balance disorders, skin disorders such as pigmentation disorders and vitiligo, alterations in NMDA receptor function, and sexual disorders such as anorgasmic or psychogenic impotence. These conditions may be diagnosed and monitored using criteria that have been established in the art. In addition, MCH antagonists provided herein may be used to promote weight loss in patients, and MCH agonists provided herein may be used to promote weight gain in patients. MCH antagonists may also be used to modulate a patient's bone mass (*i.e.,* to inhibit loss of bone mass and/or stimulate an increase in bone mass). Patients may include humans, domesticated companion animals (pets, such as dogs and cats) and livestock animals, with dosages and treatment regimes as described above.Additional conditions that are associated with MCH receptor activation include:

Cognitive impairment and memory disorders, such as Alzheimer's disease, Parkinson's disease, mild cognitive impairment (MCI), age-related cognitive decline (ARCD), stroke, traumatic brain injury, AIDS associated dementia, and dementia associated with depression, anxiety and psychosis (including schizophrenia and hallucinatory disorders);

Anxiety, depression and other mood disorders, including general anxiety disorder (GAD), agoraphobia, panic disorder with and without agoraphobia, social phobia, specific phobia, post traumatic stress disorder, obsessive compulsive disorder (OCD), dysthymia, adjustment disorders with disturbance of mood and anxiety, separation anxiety disorder, anticipatory anxiety acute stress disorder, adjustment disorders and cyclothymia;

Reward system disorders such as addiction (*e.g.,* opioid, nicotine or alcohol);

Pain such as migraine, peripheral inflammatory pain, neuropathic pain and sympathetic nervous system associated pain; and

Peripheral indications such as respiratory disorders (*e.g.,* asthma), urinary disorders (*e.g.,* urinary incontinence), gastrointestinal disorders, reproductive function disorders and cardiovascular disorders (*e.g.,* arteriosclerosis and hypertension).

Frequency of dosage may vary depending on the compound used and the particular disease to be treated or prevented. In general, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of eating disorders and obesity, a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of impotence a single dose that rapidly reaches effective concentrations is desirable. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the patient's age, body weight, general health, sex and diet, the time and route of administration, the rate of excretion, any coadministered drugs and the severity of the particular

disease. In certain embodiments, administration at meal times is preferred. In general, the use of the minimum dosage that is sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art.

In other aspects, methods for treating a patient are provided, comprising diagnosing the patient as having a disease or disorder associated with MCH receptor activation, correlating the diagnosis of the disease or disorder with the need for MCH modulator administration, and administering an a effective amount of an aryl-substituted piperazine derivative provided herein. A method for treating a patient comprising administering an effective amount of an aryl-substituted piperazine derivative of Formula I to a patient having a disease or disorder associated with MCH receptor activation is also provided herein.

Within certain embodiments the disease or disorder associated with MCH receptor activation is obesity, an eating disorder, a sexual disorder, diabetes, heart disease, metabolic syndrome, stroke, anxiety, depression, a skin pigmentation disorder, a reward system disorder, a cognitive disorder, or a fluid balance disorder. Within other embodiments, the MCH receptor modulator is used to modulate bone mass.

Within certain embodiments provided herein the aryl-substituted piperazine derivative of Formula I is administered orally, intranasally, intravenously or topically.

Within certain aspects, MCH receptor modulators provided herein may be used within combination therapy for the treatment of conditions associated with MCH receptor modulation. Within combination therapy, a MCH receptor modulator is administered to a patient along with a second therapeutic agent that is not primarily a MCH receptor modulator, but that is appropriate for treatment of the condition(s) of interest. The MCH receptor modulator and second therapeutic agent(s) may be present in the same pharmaceutical composition, or may be administered separately in either order. Suitable second therapeutic agents include those listed above.

Suitable dosages for MCH receptor modulator(s) within such combination therapy are generally as described herein. Dosages 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 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 of the invention is less than the maximum dose advised by the manufacturer for administration of the second therapeutic agent without combination administration of a MCH receptor modulator. More preferably this dosage is less than ¾, even more preferably less than ½, and highly preferably, less than ¼ of the maximum dose, while most

preferably the dose is less than 10% of the maximum dose advised by the manufacturer for administration of the second therapeutic agent(s) when administered without combination administration of a MCH receptor modulator. It will be apparent that the dosage amount of MCH receptor modulator component of the combination needed to achieve the desired effect may similarly be affected by the dosage amount and potency of the second therapeutic agent component of the combination.

In certain preferred embodiments, the combination administration of a MCH receptor modulator with a second therapeutic agent is accomplished by packaging one or more MCH receptor modulators and one or more second therapeutic agents in the same package, either in separate containers within the package or in the same container as a mixture of one or more MCH receptor modulators and one or more second 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 or package insert indicating that the one or more MCH receptor modulators and one or more second therapeutic agents are to be taken together for the treatment of a condition that is associated with MCH receptor activation, such as obesity.

In certain embodiments, one or more MCH receptor modulators provided herein are used along with one or more CB1 antagonists within a combination therapy. Such combinations are of particular use for weight management, to reduce appetite and/or food intake or to prevent or treat obesity (*e.g.,* promote weight loss). Patients may include humans, domesticated companion animals and livestock animals, with dosages and treatment regimes as described above. The MCH receptor modulator(s) may be administered to the patient at the same time as the CB1 antagonist(s) (*e.g.,* as a single dosage unit), or may be administered separately (before or after CB1 antagonist). Within preferred embodiments, the MCH receptor modulator(s) and CB1 antagonist(s) are ultimately simultaneously present at effective concentrations in a body fluid (*e.g.,* blood) of the patient. An effective concentration of MCH receptor modulator or CB1 antagonist is a concentration that is sufficient to reduce one or more of food consumption, appetite and/or body mass index in the patient when repeatedly coadministered as described herein.

Within separate aspects, the present invention provides a variety of *in vitro* uses for the compounds provided herein. For example, such compounds may be used as probes for the detection and localization of MCH receptors, in samples such as tissue sections, as positive controls in assays for receptor activity, as standards and reagents for determining the ability of a candidate agent to bind to MCH receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such assays can be used to characterize MCH receptors in living subjects. Compounds provided herein are also useful as standards and reagents in determining the ability of a test compound to bind to MCH receptor.

Within methods for determining the presence or absence of MCH receptor in a sample, a sample may be incubated with a compound as provided herein under conditions that permit binding of the compound to MCH receptor. The amount of compound bound to MCH receptor in the sample is then detected. For example, a compound may be labeled using any of a variety of well-known techniques (*e.g.,* radiolabeled with a radionucleide such as tritium, as described herein), and incubated with the sample (which may be, for example, a preparation of cultured cells, a tissue preparation or a fraction thereof). A suitable incubation time may generally be determined by assaying the level of binding that occurs over a period of time. Following incubation, unbound compound is removed, and bound compound detected using any method 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 may be simultaneously contacted with radiolabeled compound and a greater amount of unlabeled compound. Unbound labeled and unlabeled compound is then removed in the same fashion, and bound label is detected. A greater amount of detectable label in the test sample than in the control indicates the presence of MCH receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of MCH receptors 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 culture and cell separation methods. For example, compounds may be linked to the interior surface of a tissue culture plate or other cell culture support, for use in immobilizing MCH receptor-expressing cells for screens, assays and growth in culture. Compounds may also be used to facilitate cell identification and sorting *in vitro*, permitting the selection of cells expressing a MCH receptor. Preferably, the compound(s) for use in such methods are labeled as described herein. Within one preferred embodiment, a compound linked to a fluorescent marker, such as fluorescein, is contacted with the cells, which are then analyzed by fluorescence activated cell sorting (FACS).

Within other aspects, methods are provided for modulating binding of MCH to an MCH receptor *in vitro* or *in vivo*, comprising contacting a MCH receptor with a sufficient amount of a modulator provided herein, under conditions suitable for binding of MCH to the receptor. Preferably, within such methods, MCH binding to receptor is inhibited by the modulator. The MCH receptor may be present in solution, in a cultured or isolated cell preparation or within a patient. Preferably, the MCH receptor is a MCH1R receptor present in the hypothalamus. In general, the amount of compound contacted with the receptor should be sufficient to modulate MCH binding to MCH receptor *in vitro* within, for example, a binding assay as described in Example 9 and/or Example 12. MCH receptor preparations used to determine *in vitro* binding may be obtained from a variety of

sources, such as from HEK 293 cells or Chinese Hamster Ovary (CHO) cells transfected with a MCH receptor expression vector, as described herein.

Also provided herein are methods for modulating the signal-transducing activity of cellular MCH receptors, by contacting MCH receptor, either *in vitro* or *in vivo*, with a sufficient amount of a modulator as described above, under conditions suitable for binding of MCH to the receptor. Preferably, within such methods, signal-transducing activity is inhibited by the modulator. The MCH receptor may be present in solution, in a cultured or isolated cell preparation or within a patient. In general, the amount of modulator contacted with the receptor should be sufficient to modulate MCH receptor signal transducing activity *in vitro* within, for example, a calcium mobilization assay as described in Example 13 and/or an agonist-stimulated GTP gamma^{35}S binding assay as described in Example 11. An effect on signal-transducing activity may be assessed as an alteration in the electrophysiology of the cells, using standard techniques, such as intracellular patch clamp recording or patch clamp recording. If the receptor is present in an animal, an alteration in the electrophysiology of the cell may be detected as a change in the animal's feeding behavior.

GENERAL SYNTHETIC METHODS

The following Schemes illustrate representative synthetic methods for compounds of Formula I, wherein the variables are as defined above.

In certain embodiments, a MCH receptor modulator 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 in certain instances 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 or ^{2}H), fluorine (*e.g.,* ^{18}F or ^{19}F), 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.

PREPARATION OF MCH RECEPTOR MODULATORS

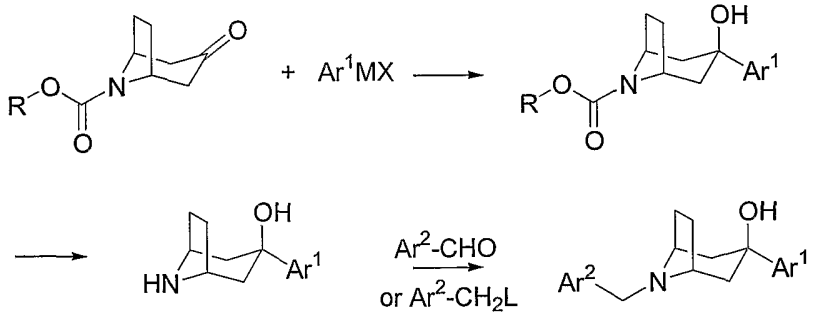
The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification.

Compounds provided herein may generally be prepared using standard synthetic methods. Starting materials are generally readily available from commercial sources, such as Sigma-Aldrich Corp. (St. Louis, MO). For example, a synthetic route similar to that shown in the Schemes A may be used. It will be apparent that the final product and any intermediate(s) shown in the following schemes may be extracted, dried, filtered and/or concentrated, and may be further purified (*e.g.*, by chromatography). Each variable (*e.g.*, "R") in the following Schemes, refers to any group consistent with the description of the compounds provided herein. An individual skilled in the art may find modifications of one or several of the synthetic steps described herein without diverting significantly from the overall synthetic scheme. Further experimental details for synthesis of representative compounds via these Schemes are provided in Examples 1-6, herein.

In the following Schemes and synthetic Examples 1-6, the following abbreviations are used:

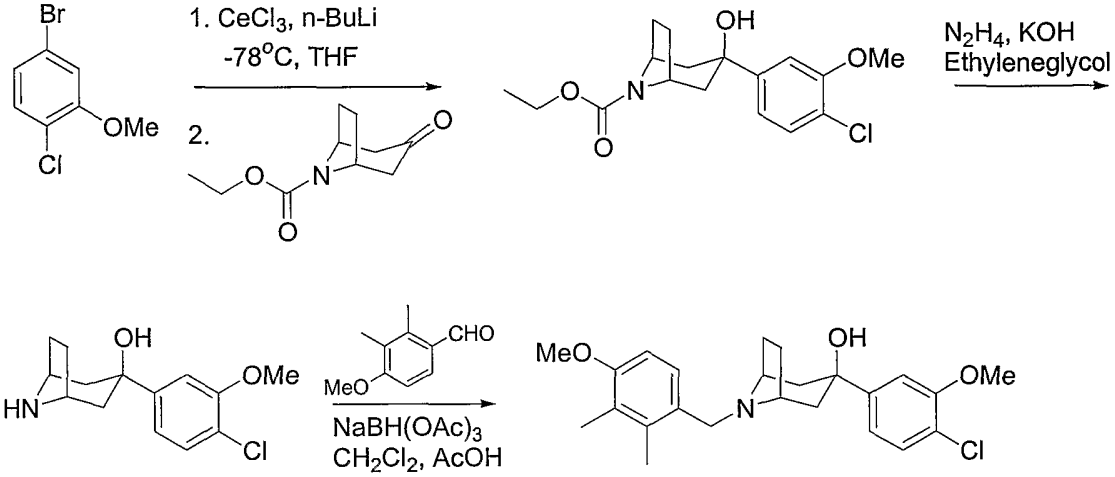
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
LC	Liquid chromatography
MeOH	Methyl alcohol
MS	Mass spectrometry
MsCl	Mesyl chloride
n-BuLi	n-Butyllithium
NMR	Nuclear magnetic resonance
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography

SCHEME A.



Briefly, a commercially available *N*-protected tropinone derivative such as but not limited to *N*-carbethoxy-4-tropinone, tropinone, BOC-nortropinone is reacted with an arylorganometallic reagent such as but not limited to arylmagnesium halides (Grignard reagents), aryllithium, arylsodium, arylzinc halides, aryl copper halides, or arylcerium halides in an inert reaction solvent such as but not limited to ethyl ether, tetrahydrofuran, diisopropyl ether, methyl-tert-butyl ether, benzene, toluene and the like at a reaction temperature between -78 °C and 120 °C, more preferably between 0°C and 60°C to furnish the N-protected 3-aryl-3-hydroxy-8-azabicyclo[3.2.1]octane. The addition of the organometallic reagent takes place highly preferably from the less-hindered side (see for example Langbein, A. *et al.* 8-Arylalkyl-3-phenyl-3-nortropanols, their acid addition salts and their pharmaceutical compositions. US 4,393,069, 7/12/83). The protecting group on the nitrogen atom can then be removed using a number of methods familiar to those skilled in the art (see for example Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis*, John Wiley and Sons, Inc., New York, 1999). Finally, reductive amination reaction with an appropriately substituted benzaldehyde or acetophenone under acidic catalysis (for example but not limited to acetic acid, propionic acid, HCl and the like) with an excess of $NaBH_4$, $NaCH_3CN$, $NaBH(OAc)_3$ and the like under a nitrogen atmosphere yields the desired product after purification by appropriate chromatographic techniques. Alternatively, the last step can be carried out by reacting the 3-aryl-8-azabicyclo[3.2.1]octan-3-ol with an appropriately substituted benzylic chloride, bromide, iodide, tosylate, mesylate, benzenesulfonate and the like in a solvent such as EtOH, DMF, DMSO, acetonitrile, propionitrile, acetone and the like in the presence of a base such as but not limited to K_2CO_3, Na_2CO_3, $NaHCO_3$, Cs_2CO_3 and the like at temperatures between room temperature and 140 °C.

EXAMPLE 1. SYNTHESIS OF 8-(4-METHOXY-2,3-DIMETHYLBENZYL)-3-(4-CHLORO-3-METHOXYPHENYL)-8-AZA-BICYCLO[3.2.1]OCTAN-3-OL



Step 1. Ethyl 3-(4-chloro-3-methoxyphenyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate

Anhydrous $CeCl_3$ (33.4 g, 136.4 mmol) is placed in an oven-dried flask, heated under high vacuum system for 5 min. The flask is then cooled to -78°C under nitrogen, THF (200 mL) and 5-bromo-2-chloro-anisole (20 g, 90.9 mmol) are added, followed by n-BuLi (109.1 mmol, 68.2 mL of 1.6 M in hexane). The mixture is stirred at -78°C for 1h. Ethyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (19.7 g in 100 mL of THF, 99.9 mmol) is then added dropwise, the mixture is stirred at -78°C for 1h, then room temperature for 2h. The reaction is quenched with half saturated NH_4Cl, and the organic layer is separated. The aqueous phase is extracted with ethyl acetate. Organic layers are combined, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue is purified by silica gel chromatography (hexane/ethyl acetate = 3/1) to afford 11.1 g of white solid. LC/MS *m/z*: 340 (M+1).

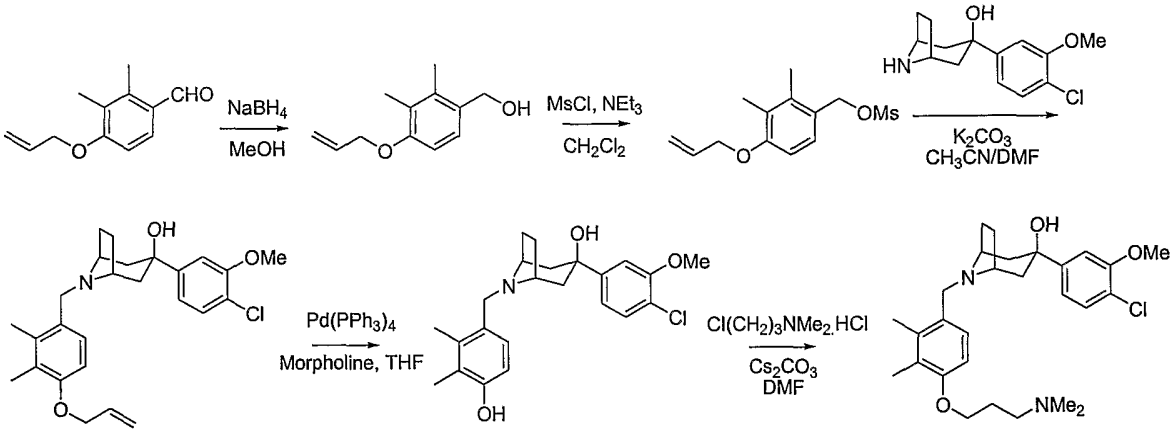
Step 2. 3-(4-chloro-3-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol

The ethyl 3-(4-chloro-3-methoxyphenyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate obtained in step 1 (11.1 g) is treated with KOH (48 g, 0.86 mol), and hydrazine monohydrate (8 mL) in $HOCH_2CH_2OH$ (240 mL) at reflux for 4h. The reaction mixture is then cooled to room temperature, poured into 200 mL of water and extracted with $CHCl_3$ (3x). The extract is washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to yield 3-(4-chloro-3-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol (5.35 g, 22.3%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.29 (d, 1H), 7.11 (s, 1H), 6.98 (d, 1H), 3.91 (s, 3H), 3.66 (s, 2H), 2.24-2.36 (m, 4H), 1.78-1.85 (m, 6H); LC-MS *m/z*: 268 (M+1).

Step 3. 8-(4-methoxy-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol.

To a solution of 4-methoxy-2,3-dimethylbenzaldehyde (0.06 g, 0.36 mmol) and 3-(4-chloro-3-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol (0.10 g, 0.37 mmol) in anhydrous dichloroethane (5 mL) are added AcOH (0.025 mL, 0.44 mmol) and $NaBH(OAc)_3$ (0.24 g, 0.53 mmol). The reaction mixture is stirred overnight at 70 °C and then cooled to room temperature and diluted with CH_2Cl_2. The organic layers are washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue is submitted to flash chromatography eluting with 10 % MeOH-CH_2Cl_2 containing 1% NH_4OH to afford 8-(4-methoxy-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol as a clear oil (53 mg, 33 % yield). ^1H NMR (300 MHz, CD_3OD): δ 7.27 (d, J = 6.3Hz, 1H), 7.05-7.15 (m, 2H), 6.9-7.0 (m, 1H), 6.62-6.7 (m,1H), 3.9 (s, 2H), 3.80 (s, 6H), 3.44-3.58 (m, 2H), 3.22-3.32 (m, 2H), 2.12-2.41 (multiplet containing two singlets at 2.18, 2.38, 8H), 2.0-2.1 (m, 2H), 1.7-1.82 (m, 2H); LC-MS *m/z*: 416 (M+1).

EXAMPLE 2. SYNTHESIS OF 8-(4-(3-(DIMETHYLAMINO)PROPOXY)-2,3-DIMETHYLBENZYL)-3-(4-CHLORO-3-METHOXYPHENYL)-8-AZA-BICYCLO[3.2.1]OCTAN-3-OL



Step 1. *[4-(Allyloxy)-2,3-dimethylphenyl]methanol*

To a solution of 4-(allyloxy)-2,3-dimethylbenzaldehyde (1.0 g, 5.2 mmol) in anhydrous MeOH (Should this be EtOH or MeOH – doesn't match scheme) (20 mL) at 0°C is added $NaBH_4$ (0.3 g, 7.8 mmol) in small portions. The reaction mixture is stirred at room temperature for 5 min, then quenched with water. Ethanol is removed under reduced pressure and the aqueous solution is extracted with ethyl acetate. The organic layer is washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by filtration through a silica gel plug (hexane/ethyl acetate: 4/1) to afford [4-(allyloxy)-2,3-dimethylphenyl]methanol (1.0 g, 99.1%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.10 (d, 1H), 6.69 (d, 1H), 6.07 (m, 1H), 5.44 (m, 1H), 5.28 (m, 1H), 4.64 (s, 2H), 4.53 (m, 2H), 2.30 (s, 3H), 2.22 (s, 3H); LC-MS *m/z*: 175 (M^+-OH).

Step 2. *4-(Allyloxy)-2,3-dimethylbenzyl methanesulfonate*

To a solution of the alcohol obtained in step 1 (0.47 g, 2.42 mmol) in anhydrous CH_2Cl_2 (10mL) at 0°C is added TEA (0.68 mL, 4.84 mmol), followed by CH_3SO_2Cl (0.28 mL, 3.62 mmol). The mixture is stirred at room temperature for 2h. The solvent is removed under reduced pressure. The residue is dried on high vacuum pump overnight, and used in the next step without further purification.

Step 3. *8-[4-(Allyloxy)-2,3-dimethylbenzyl]-3-(4-chloro-3-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol*

To a solution of 3-(4-chloro-3-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol (0.59 g, 2.2 mmol) in anhydrous DMF (10 mL) under nitrogen is added K_2CO_3 (0.61 g, 4.4 mmol), followed by 4-(allyloxy)-2,3-dimethylbenzyl methanesulfonate in 10 mL of anhydrous CH_3CN. The mixture is heated at 80°C for 24 h, then cooled to room temperature, quenched with water, and extracted with ethyl acetate. The organic layer is washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue is purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH : 90/9/1) to afford 8-[4-(allyloxy)-2,3-dimethylbenzyl]-3-(4-chloro-3-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol (0.41 g, 42.3%) as a white semi-solid: LC-MS *m/z*: 442.

Step 4. *3-(4-Chloro-3-methoxyphenyl)-8-(4-hydroxy-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol*

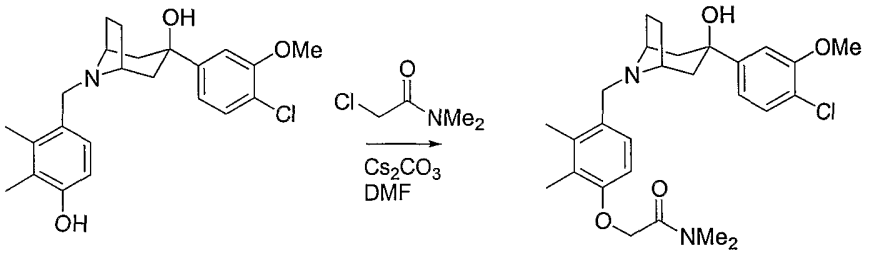
The mixture of 8-[4-(allyloxy)-2,3-dimethylbenzyl]-3-(4-chloro-3-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol (0.37 g, 0.84 mmol) obtained in step 3, morpholine (80.5 μL, 0.92mmol) and $Pd(PPh_3)_4$ (58.2 mg, 0.05 mmol) in 10 mL of CH_2Cl_2 is stirred at room temperature under nitrogen overnight. The reaction mixture is then diluted with 10 mL of CH_2Cl_2, washed with half-saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue is purified by preparative TLC (CH_2Cl_2/MeOH/NH_4OH : 90/9/1) to afford 3-(4-chloro-3-methoxyphenyl)-8-(4-hydroxy-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol (0.20 g, 60%) as a yellow solid: ^1H NMR ($CDCl_3$) δ 7.27 (d, 1H), 7.12 (d, 1H), 6.93-6.99 (m, 2H), 6.58 (d, 1H), 3.89 (s, 3H), 3.49 (s, 2H), 3.30 (bs, 2H), 2.34 (s, 3H), 1.74-2.29 (m, 13 H); LC-MS *m/z*: 402 (M+1).

Step 5. *8-(4-(3-(Dimethylamino)propoxy)-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol*

To a solution of 3-(4-chloro-3-methoxyphenyl)-8-(4-hydroxy-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol obtained in step 4 (20 mg, 0.05 mmol) in anhydrous DMF (1 mL) is added Cs_2CO_3 (24.2 mg, 0.075 mmol), followed by $Me_2NCH_2CH_2CH_2Cl{\cdot}HCl$ (0.06 mmol) and catalytic amounts of NaI. The mixture is heated at 60°C overnight. The reaction is then cooled to room temperature, diluted with ethyl acetate, washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by preparative TLC

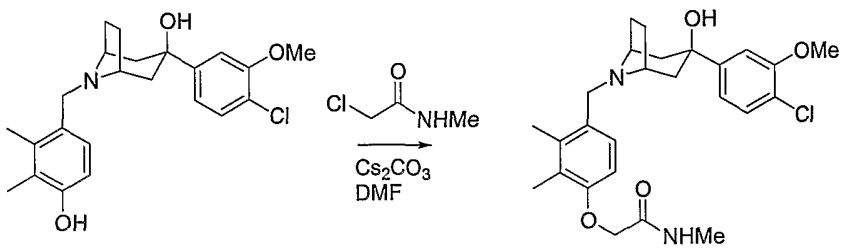
(CH_2Cl_2/MeOH/NH_4OH : 95/5/1) to furnish 8-(4-(3-(dimethylamino)propoxy)-2,3-dimethyl-benzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol as a yellow oil (15.4 mg, 63.2%). ^1H NMR ($CDCl_3$) δ 7.20 (d, 1H), 6.92-7.10 (m, 3H), 6.60 (d, 1H), 3.94 (t, 2H), 3.85 (s, 3H), 3.49 (bs, 2H), 3.25 (bs, 1H), 2.46 (t, 2H), 1.70-2.30 (m, 24 H); LC-MS *m/z*: 487 (M+1).

EXAMPLE 3. SYNTHESIS OF 2-(4-{[3-(4-CHLORO-3-METHOXYPHENYL)-3-HYDROXY-8-AZABICYCLO[3.2.1]OCT-8-YL]METHYL}-2,3-DIMETHYLPHENOXY)-*N*,*N*-DIMETHYLACETAMIDE



To a solution of 3-(4-chloro-3-methoxyphenyl)-8-(4-hydroxy-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol obtained in step 4, Example 2, (20 mg, 0.05 mmol) in anhydrous DMF (1 mL) is added Cs_2CO_3 (24.2 mg, 0.075 mmol), followed by 2-chloro-*N*,*N*-dimethylacetamide (0.06 mmol) and catalytic amounts of NaI. The mixture is heated at 60°C overnight. The reaction is then cooled to room temperature, diluted with ethyl acetate, washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by preparative TLC (CH_2Cl_2/MeOH/NH_4OH: 95/5/1) to furnish 2-(4-{[3-(4-chloro-3-methoxyphenyl)-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]methyl}-2,3-dimethylphenoxy)-*N*,*N*-dimethylacetamide as a yellow oil (19.7 mg, 81%): ^1H NMR ($CDCl_3$) δ 7.21 (d, 1H), 6.99-7.00 (m, 2H), 6.88 (d, 1H), 6.59 (d, 1H), 4.60 (s, 2H), 3.83 (s, 3H), 3.42 (s, 2H), 3.18 (s, 1H), 3.03 (s, 3H), 2.91 (s, 3H), 2.28 (s, 3H), 1.68-2.34 (m, 13H); LC-MS *m/z*: 487.

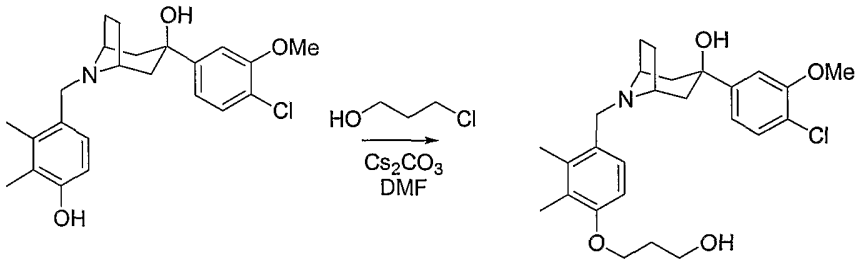
EXAMPLE 4. SYNTHESIS OF 2-(4-{[3-(4-CHLORO-3-METHOXYPHENYL)-3-HYDROXY-8-AZABICYCLO[3.2.1]OCT-8-YL]METHYL}-2,3-DIMETHYLPHENOXY)-*N*-METHYLACETAMIDE



To a solution of 3-(4-chloro-3-methoxyphenyl)-8-(4-hydroxy-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol obtained in step 4 (20 mg, 0.05 mmol) in anhydrous DMF (1 mL) is

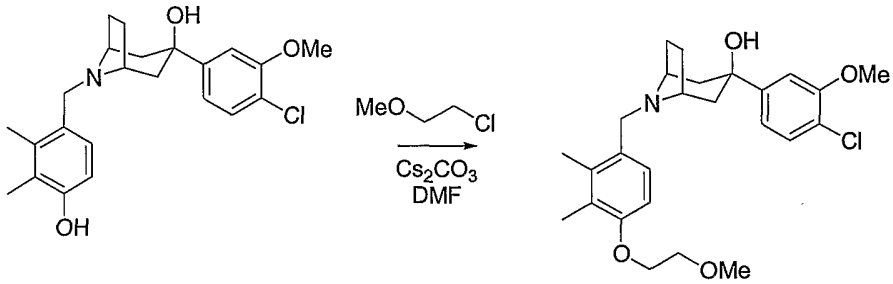
added Cs_2CO_3 (24.2 mg, 0.075 mmol), followed by 2-chloro-*N*-methylacetamide (0.06 mmol) and catalytic amounts of NaI. The mixture is heated at 60°C overnight. The reaction is then cooled to room temperature, diluted with ethyl acetate, washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by preparative TLC (CH_2Cl_2/MeOH/NH_4OH: 95/5/1) to furnish 2-(4-{[3-(4-chloro-3-methoxyphenyl)-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]methyl}-2,3-dimethylphenoxy)-*N*-methylacetamide as a yellow oil (14.5 mg, 61%): ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H), 7.10 (m, 2H), 6.93 (d, 1H), 6.60 (d, 1H), 4.48 (s, 2H), 3.91 (s, 3H), 3.51 (s, 2H), 3.26 (bs, 2H), 2.93 (d, 3H), 1.76-2.41 (m, 16H); LC-MS *m/z*: 473.

EXAMPLE 5. SYNTHESIS OF 3-(4-CHLORO-3-METHOXYPHENYL)-8-[4-(3-HYDROXYPROPOXY)-2,3-DIMETHYLBENZYL]-8-AZABICYCLO[3.2.1]OCTAN-3-OL



Using the same reaction conditions as in Example 4, but replacing 2-chloro-*N*-methylacetamide with equivalent amounts of $HOCH_2CH_2CH_2Cl$, the title compound is obtained (5.5 mg, 23.9%): LC-MS *m/z*: 460.

EXAMPLE 6. SYNTHESIS OF 3-(4-CHLORO-3-METHOXYPHENYL)-8-[4-(2-METHOXYETHOXY)-2,3-DIMETHYLBENZYL]-8-AZABICYCLO[3.2.1]OCTAN-3-OL

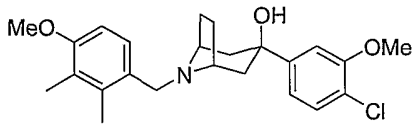
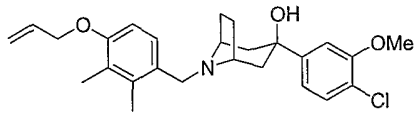
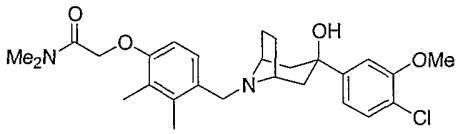
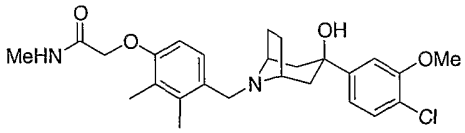
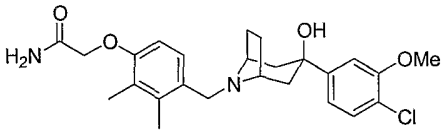
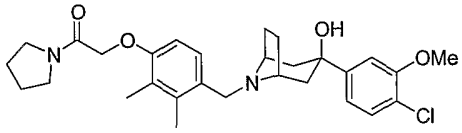
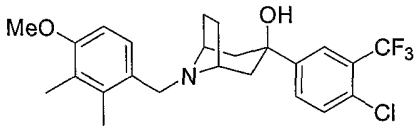
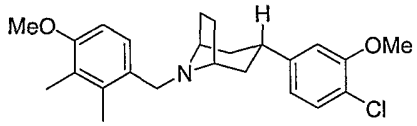
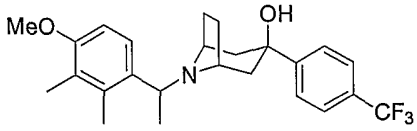
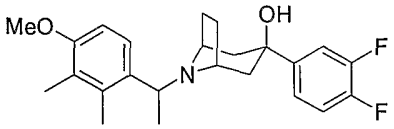


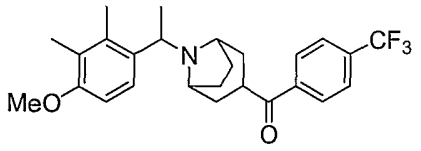
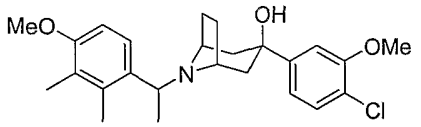
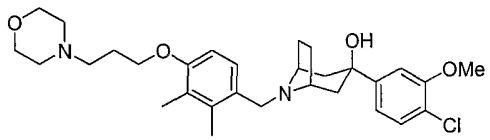
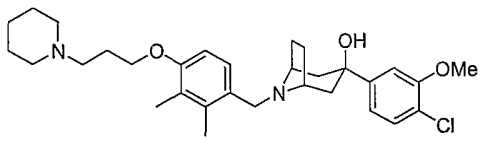
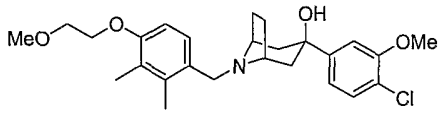
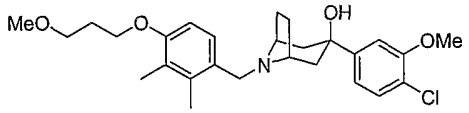
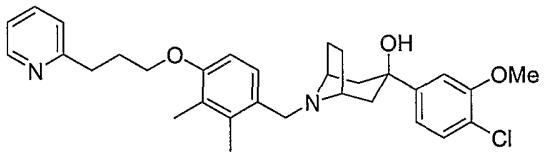
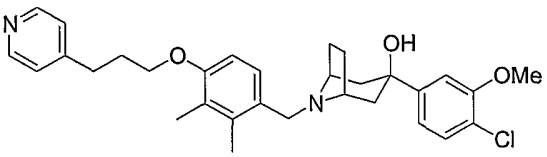
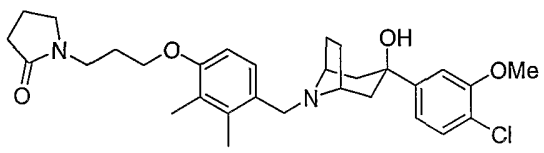
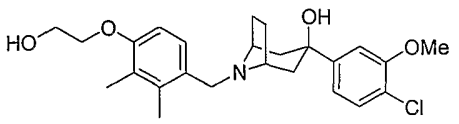
Using the same reaction conditions as in Example 4, but substituting 2-chloro-*N*-methylacetamide with equivalent amounts of $HOCH_2CH_2CH_2Cl$, the title compound is obtained (12.1 mg, 52.3%): LC-MS m/z: 460.

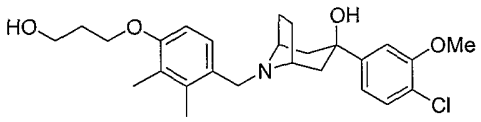
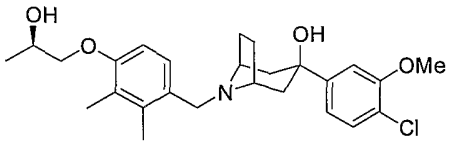
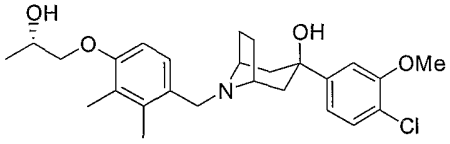
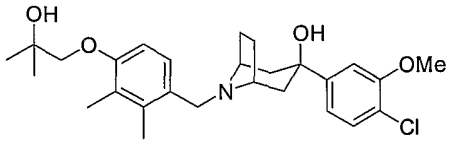
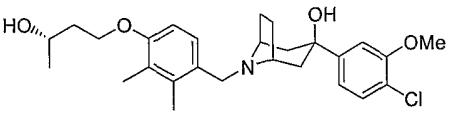
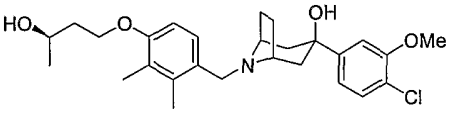
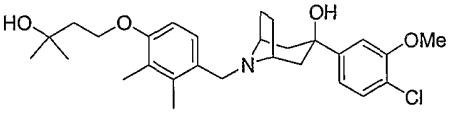
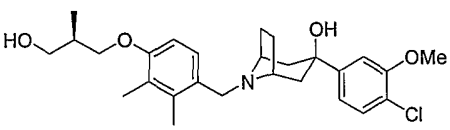
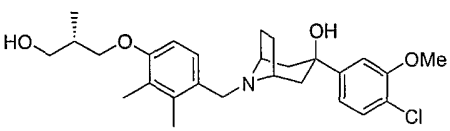
EXAMPLE 7. ADDITIONAL HETEROCYCLIC ARYL SUBSTITUTED 8-AZABICYCLO[3.2.1]OCTANE COMPOUNDS

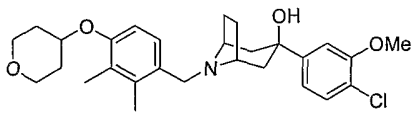
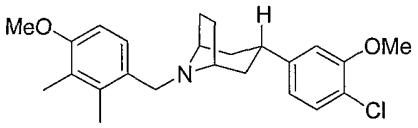
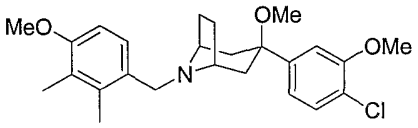
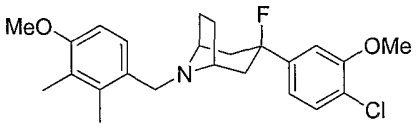
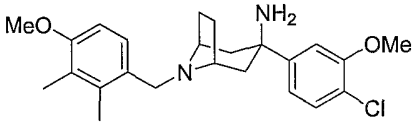
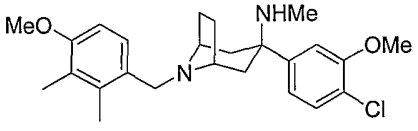
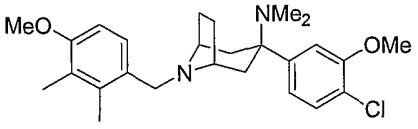
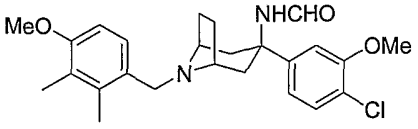
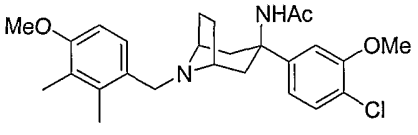
The following compounds are synthesized according to the methods given in Examples 1-6. Compounds 1, 2, 3, 4, 15 and 21, in TABLE I, exhibit a K_i less than 1 micromolar in the MCH1 receptor binding assay of Example 13.

TABLE I

Cmp. #	Structure	Name
1.		8-(4-methoxy-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol
2.		8-[4-(allyloxy)-2,3-dimethylbenzyl]-3-(4-chloro-3-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-ol
3.		2-(4-{[3-(4-chloro-3-methoxyphenyl)-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]methyl}-2,3-dimethylphenoxy)-*N*,*N*-dimethylacetamide
4.		2-(4-{[3-(4-chloro-3-methoxyphenyl)-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]methyl}-2,3-dimethylphenoxy)-*N*-methylacetamide
5.		2-(4-{[3-(4-chloro-3-methoxyphenyl)-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl]methyl}-2,3-dimethylphenoxy)acetamide
6.		3-(4-chloro-3-methoxyphenyl)-8-[2,3-dimethyl-4-(2-oxo-2-pyrrolidin-1-ylethoxy)benzyl]-8-azabicyclo[3.2.1]octan-3-ol
7.		8-(4-methoxy-2,3-dimethylbenzyl)-3-(4-chloro-3-trifluoromethylphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol
8.		8-(4-methoxy-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octane
9.		8-(1-(4-methoxy-2,3-dimethylphenyl)ethyl)-3-(4-(trifluoromethyl)phenyl)-8-aza-bicyclo[3.2.1]octan-3-ol
10.		3-(3,4-difluorophenyl)-8-(1-(4-methoxy-2,3-dimethylphenyl)ethyl)-8-aza-bicyclo[3.2.1]octan-3-ol

Cmp. #	Structure	Name
11.		(8-(1-(4-methoxy-2,3-dimethylphenyl)ethyl)-8-aza-bicyclo[3.2.1]octan-3-yl)(4-(trifluoromethyl)phenyl)methanone
12.		3-(4-chloro-3-methoxyphenyl)-8-(1-(4-methoxy-2,3-dimethylphenyl)ethyl)-8-aza-bicyclo[3.2.1]octan-3-ol
13.		8-(2,3-dimethyl-4-(3-morpholinopropoxy)benzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol
14.		8-(2,3-dimethyl-4-(3-(piperidin-1-yl)propoxy)benzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol
15.		8-(4-(2-methoxyethoxy)-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol
16.		8-(4-(3-methoxypropoxy)-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol
17.		8-(2,3-dimethyl-4-(3-(pyridin-2-yl)propoxy)benzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol
18.		3-(4-chloro-3-methoxyphenyl)-8-[2,3-dimethyl-4-(3-pyridin-4-ylpropoxy)benzyl]-8-azabicyclo[3.2.1]octan-3-ol
19.		1-(3-(4-((3-(4-chloro-3-methoxyphenyl)-3-hydroxy-8-aza-bicyclo[3.2.1]octan-8-yl)methyl)-2,3-dimethylphenoxy)-propyl)pyrrolidin-2-one
20.		3-(4-chloro-3-methoxyphenyl)-8-[4-(2-hydroxyethoxy)-2,3-dimethylbenzyl]-8-

Cmp. #	Structure	Name
		azabicyclo[3.2.1]octan-3-ol
21.		3-(4-chloro-3-methoxyphenyl)-8-[4-(3-hydroxypropoxy)-2,3-dimethylbenzyl]-8-azabicyclo[3.2.1]octan-3-ol
22.		3-(4-chloro-3-methoxyphenyl)-8-(4-{[(2*R*)-2-hydroxypropyl]oxy}-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol
23.		3-(4-chloro-3-methoxyphenyl)-8-(4-{[(2*S*)-2-hydroxypropyl]oxy}-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol
24.		3-(4-chloro-3-methoxyphenyl)-8-[4-(2-hydroxy-2-methylpropoxy)-2,3-dimethylbenzyl]-8-azabicyclo[3.2.1]octan-3-ol
25.		3-(4-chloro-3-methoxyphenyl)-8-(4-{[(3*S*)-3-hydroxybutyl]oxy}-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol
26.		3-(4-chloro-3-methoxyphenyl)-8-(4-{[(3*R*)-3-hydroxybutyl]oxy}-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol
27.		3-(4-chloro-3-methoxyphenyl)-8-[4-(3-hydroxy-3-methylbutoxy)-2,3-dimethylbenzyl]-8-azabicyclo[3.2.1]octan-3-ol
28.		3-(4-chloro-3-methoxyphenyl)-8-(4-{[(2*R*)-3-hydroxy-2-methylpropyl]oxy}-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol
29.		3-(4-chloro-3-methoxyphenyl)-8-(4-{[(2*S*)-3-hydroxy-2-methylpropyl]oxy}-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-ol

Cmp. #	Structure	Name
30.		3-(4-chloro-3-methoxyphenyl)-8-[2,3-dimethyl-4-(tetrahydro-2*H*-pyran-4-yloxy)benzyl]-8-azabicyclo[3.2.1]octan-3-ol
31.		3-(4-chloro-3-methoxyphenyl)-8-(4-methoxy-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octane
32.		3-(4-chloro-3-methoxyphenyl)-3-methoxy-8-(4-methoxy-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octane
33.		3-(4-chloro-3-methoxyphenyl)-3-fluoro-8-(4-methoxy-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octane
34.		3-(4-chloro-3-methoxyphenyl)-8-(4-methoxy-2,3-dimethylbenzyl)-8-azabicyclo[3.2.1]octan-3-amine
35.		3-(4-chloro-3-methoxyphenyl)-8-(4-methoxy-2,3-dimethylbenzyl)-*N*-methyl-8-azabicyclo[3.2.1]-octan-3-amine
36.		3-(4-chloro-3-methoxyphenyl)-8-(4-methoxy-2,3-dimethylbenzyl)-*N*,*N*-dimethyl-8-azabicyclo[3.2.1]-octan-3-amine
37.		*N*-[3-(4-chloro-3-methoxyphenyl)-8-(4-methoxy-2,3-dimethyl-benzyl)-8-azabicyclo[3.2.1]oct-3-yl]formamide
38.		*N*-[3-(4-chloro-3-methoxyphenyl)-8-(4-methoxy-2,3-dimethyl-benzyl)-8-azabicyclo[3.2.1]oct-3-yl]acetamide

EXAMPLE 8. PURIFIED RAT STRIATUM CELL MEMBRANES.

The MCH1R receptor source is a rat striatum homogenate. The rats are naïve Sprague Dawley or Wistar rats which are not food deprived overnight, and weigh roughly 250±25 grams. The striatum is rapidly/carefully dissected away from the cortex, mid-brain and hippocampus. The striatum is weighed, and homogenized in Prep buffer (50 mM Tris, pH 7.4, 10 mM $MgCl_2$, 2 mM EGTA: 23 mL per gram of striatum, typically 150 mg of tissue plus 3.5 mL of prep buffer), homogenizing for 30 seconds using a BRINKMAN POLYTRON at setting 5. The crude striatal homogenate is washed 2 times with Prep buffer and sampled for protein analysis between washes. Once the protein concentration has been determined, the final protein pellet is suspended in binding buffer at a protein density of 275 µg/200 µL binding buffer. The protein concentration of the resulting membrane preparation (hereinafter "rat striatal membranes") is conveniently measured using a Bradford protein assay (Bio-Rad Laboratories, Hercules, CA).

EXAMPLE 9. RADIOLIGAND BINDING ASSAYS

This Example illustrates a standard assay of Melanin Concentrating Hormone receptor binding that may be used to determine the binding affinity of compounds for the MCH receptor. ^{125}I-labeled S36057 (New England Nuclear Corp., Boston, MA), a stable analogue of MCH, is used as the radioligand.

Purified rat striatal membranes, prepared by the method given in Example 8 above, are resuspended by Dounce homogenization (tight pestle) in binding buffer (50 mM Tris pH. 7.4, 1.0 mM Mg Cl_2, 5 mM KCl, 1 mM $CaCl_2$, 120 mM NaCl, 1 mM bacitracin, 0.02 mg/mL Aprotinin & 0.1% BSA).

The optimal rat striatal homogenate input has been determined, via a protein linearity experiment, to be 275 µg / data point / 250 µL. At 30pM [^{125}I]-S36057, this amount of protein binds 10-15% of the input radioligand. At a [^{125}I]-S36057 input of 30 pM (roughly 1/2 to 1/3 Kd) the specific binding signal is routinely 50%. Non specific binding is defined with 1µM MCH. Displacement binding studies, designed to determine the IC_{50}/K_i of exogenously added compounds, are run at 30 pM [^{125}I]-S36057. These displacement studies are routinely run to verify activity in the rat striatum homogenate MCH1R preparation. Upon mixing of all assay components (100 µL tissue, 100µl assay buffer, 25 µL radiolabel, and 2.5 µL compound if required, 25 µL assay buffer or nonspecific if required), the reaction is mixed and incubated at RT for 2 h in a 96-well deepwell dish. The binding reaction is terminated by rapid filtration over a 1% PEI treated filter on a 96-well Tomtec harvester, followed by washing with 50 mM Tris, pH 7.4, 120 mM NaCl. For saturation binding analysis, rat striatal membranes (275 µg) are added to polypropylene tubes containing 25 pM – 0.5 nM [^{125}I]S36057. Nonspecific binding is determined in the presence of 10 µM MCH (Tocris Cookson

Inc., Ellisville, MO, USA) and accounts for less than 10 % of total binding. For evaluation of guanine nucleotide effects on receptor affinity, GTPγS is added to duplicate tubes at the final concentration of 50 μM.

For competition analysis, membranes (275 μg) are added to polypropylene tubes containing 0.03 nM [^{125}I]S36057. Non-radiolabeled displacers are added to separate assays at concentrations ranging from 10^{-10} M to 10^{-5} M to yield a final volume of 0.250 mL. Nonspecific binding is determined in the presence of 10 μM MCH and accounts for less than 30% of total binding. Following a 2 h incubation at room temperature, the reaction is terminated by rapid vacuum filtration. Samples are filtered over presoaked (0.3% non-fat dry milk for 2 h prior to use) GF/C WHATMAN filters and rinsed 2 times with 5 mL cold 50 mM Tris pH 7.4. Remaining bound radioactivity is quantified by gamma counting. K_i and Hill coefficient ("nH") are determined by fitting the Hill equation to the measured values with the aid of SIGMAPLOT software.

EXAMPLE 10. PURIFIED RECOMBINANT CHO CELL MEMBRANES EXPRESSING MONKEY MCH1R

Cynomolgus macaque hypothalamus MCH1 cDNA is prepared and cloned into PCDNA3.1 (INVITROGEN Corp., Carlsbad, CA) as described in PCT International Application publication number WO 03/059289, which published on July 24, 2003. The resulting MCH1 expression vector is stably transfected into Chinese hamster ovary (CHO) cells (American Type Culture Collection, Manassas, VA) via calcium precipitation. The disclosure of WO 03/059289 at page 51-52 directed to the preparation and storage of membrane pellets prepared from CHO cells stably transfected with the MCH1 vector is hereby incorporated by reference.

CHO mMCH1R cell pellets 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 BRINKMAN POLYTRON homogenizer (setting 5 for 30 seconds). The homogenate is centrifuged (536 x g/ 10 min/ 4°C) to pellet the nuclei. The supernatant containing isolated 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 needed. The protein concentration of the resulting membrane preparation (hereinafter "P2 membranes") is conveniently measured using a Bradford protein assay (Bio-Rad Laboratories, Hercules, CA).

EXAMPLE 11. AGONIST-INDUCED GTP BINDING

Agonist-stimulated GTP gamma^{35}S binding ("GTP binding") activity can be used to identify agonist and antagonist compounds and to differentiate neutral antagonist compounds from those that

possess inverse agonist activity. This activity can also be used to detect partial agonism mediated by antagonist compounds. A compound being analyzed in this assay is referred to herein as a "test compound."

Agonist-stimulated GTP binding on purified P2 membranes (prepared as described in Example 10) is assessed using MCH as agonist in order to ascertain the level of signal, and EC_{50} value of MCH as measured by GTP binding.

P2 membranes from the CHO cells 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, 0.1% BSA, 0.1 mM bacitracin, 100 KIU/mL aprotinin, 5 μM GDP, 10 μg/mL saponin) and added to reaction tubes at a concentration of 50 μg protein/reaction tube. After adding increasing doses of the agonist MCH at concentrations ranging from 10^{-12} M to 10^{-6} M, reactions are initiated by the addition of 100 pM GTP gamma^{35}S. In competition experiments, non-radiolabeled test compounds (*e.g.*, compounds provided herein) are added to separate assays at concentrations ranging from 10^{-10} M to 10^{-5} M along with 10 nM MCH to yield a final volume of 0.25 mL.

Neutral antagonists are those test compounds that reduce the MCH stimulated GTP binding activity towards, but not below, baseline (the level of GTP bound by membranes in this assay in the absence of added MCH or other agonist and in the further absence of any test compound).

An antagonist test compound that elevates GTP binding activity above baseline in the absence of added MCH in this GTP binding assay is characterized as having partial agonist activity. Preferred antagonist compounds described 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.

Following a 60-min incubation at room temperature, the reactions are terminated by vacuum filtration over 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, 120 mM NaCl). The amount of G-alpha-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 mM GTP gamma^{35}S and typically represents less than 10% of total binding. Data is expressed as percent above basal (baseline). The results of these GTP binding experiments are analyzed using SIGMAPLOT software and IC_{50} determined. The IC_{50} is then used to generate K_i as described by Cheng and Prusoff (1973) *Biochem Pharmacol. 22(23)*:3099-108.

Preferred compounds are MCH1 receptor antagonists that do not possess significant (*e.g.*, greater than 5%) agonist activity in any of the MCH mediated functional assays discussed herein. Specifically, this undesired agonist activity can be evaluated, for example, in the GTP binding assay described above, by measuring small molecule mediated GTP binding in the absence of the agonist,

MCH. The preferred extent of MCH1R agonist activity exhibited by compounds of the invention is less than 10%, more preferably less than 5% and most preferably less than 2% of the response elicited by the agonist, MCH.

EXAMPLE 12. MELANIN CONCENTRATING HORMONE RECEPTOR BINDING ASSAY

This Example illustrates a standard assay of melanin concentrating hormone receptor binding that may be used to determine the binding affinity of compounds for the MCH receptor.

Cynomolgus macaque hypothalamus MCH1 cDNA is prepared and cloned into PCDNA3.1 (INVITROGEN Corp., Carlsbad, CA), and HEK293 cells (American Type Culture Collection, Manassas, VA) are stably transfected with the MCH1 expression vector as described in PCT International Application publication number WO 03/059289, which published on July 24, 2003. The disclosure of WO 03/059289 at page 52 directed to the preparation and storage of the transfected HEK293 cells is hereby incorporated by reference.

At the time of assay, pellets are thawed by addition of wash buffer (25 mM Hepes with 1.0 mM $CaCl_2$, 5.0 mM $MgCl_2$, 120 mM NaCl, pH 7.4) and homogenized for 30 seconds using a BRINKMAN POLYTRON, setting 5. Cells are centrifuged for 10 minutes at 48,000 x g. The supernatant is discarded and the pellet is resuspended in fresh wash buffer, and homogenized again. An aliquot of this membrane homogenate is used to determine protein concentration via the Bradford method (BIO-RAD Protein Assay Kit, #500-0001, BIO-RAD, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 50-75 mg of total membrane protein. The homogenate is centrifuged as before and resuspended to a protein concentration of 333 μg/mL in binding buffer (Wash buffer + 0.1% BSA and 1.0 μM final phosphoramidon) for an assay volume of 50 μg membrane protein/150 μL binding buffer. Phosphoramidon was from SIGMA BIOCHEMICALS, St. Louis, MO (cat# R-7385).

Competition binding assays are performed at room temperature in Falcon 96 well round bottom polypropylene plates. Each assay well contains 150 μL of MCH receptor-containing membranes prepared as described above, 50 μL ^{125}I-Tyr MCH, 50 μL binding buffer, and 2 μL test compound in DMSO. ^{125}I-Tyr MCH (specific activity = 2200 Ci/mmol) is purchased from NEN, Boston, MA (Cat # NEX 373) and is diluted in binding buffer to provide a final assay concentration of 30 pM.

Non-specific binding is defined as the binding measured in the presence of 1 μM unlabeled MCH. MCH is purchased from BACHEM U.S.A., King of Prussia, PA (cat # H-1482). Assay wells used to determine MCH binding contain 150 μL of MCH receptor containing membranes, 50 μL ^{125}I-Tyr MCH, 25 μL binding buffer and 25 μL binding buffer.

Assay plates are incubated for 1 hour at room temperature. Membranes are harvested onto WALLAC™ glass fiber filters (PERKIN-ELMER, Gaithersburg, MD) which were pre-soaked with 1.0% PEI (polyethyleneimine) for 2 hours prior to use. Filters are allowed to dry overnight, and then counted in a WALLAC 1205 BETA PLATE counter after addition of WALLAC BETA SCINT™ scintillation fluid.

For saturation binding, the concentration of ^{125}I-Tyr MCH is varied from 7 to 1,000 pM. Typically, 11 concentration points are collected per saturation binding curve. Equilibrium binding parameters are determined by fitting the allosteric Hill equation to the measured values using SIGMAPLOT software (SPSS Inc., Chicago, IL). For preferred compounds, K_i values are below 1 micromolar, preferably below 500 nanomolar, more preferably below 100 nanomolar.

EXAMPLE 13. CALCIUM MOBILIZATION ASSAY

This Example illustrates a representative functional assay for monitoring the response of cells expressing melanin concentrating hormone receptors to melanin concentrating hormone. This assay can also be used to determine if test compounds act as agonists or antagonists of melanin concentrating hormone receptors.

Chinese Hamster Ovary (CHO) cells (American Type Culture Collection; Manassas, VA) are stably transfected with the MCH expression vector via calcium phosphate precipitation, and are grown to a density of 15,000 cells/well in FALCON™ black-walled, clear-bottomed 96-well plates (#3904, BECTON-DICKINSON, Franklin Lakes, NJ) in Ham's F12 culture medium (MEDIATECH, Herndon, VA) supplemented with 10% fetal bovine serum, 25 mM HEPES and 500 μg/mL (active) G418. Prior to running the assay, the culture medium is emptied from the 96 well plates. Fluo-3 calcium sensitive dye (Molecular Probes, Eugene, OR) is added to each well (dye solution: 1 mg FLUO-3 AM, 440 μL DMSO and 440 μL 20% pluronic acid in DMSO, diluted 1:4, 50 μL diluted solution per well). Plates are covered with aluminum foil and incubated at 37°C for 1-2 hours. After the incubation, the dye is emptied from the plates, cells are washed once in 100 μL KRH buffer (0.05 mM KCl, 0.115 M NaCl, 9.6 mM NaH_2PO_4, 0.01 mM $MgSO_4$, 25 mM HEPES, pH 7.4) to remove excess dye; after washing, 80 μL KRH buffer is added to each well.

Fluorescence response is monitored upon the addition of either human MCH receptor or test compound by a FLIPR™ plate reader (Molecular Devices, Sunnyvale, CA) by excitation at 480 nm and emission at 530 nm.

In order to measure the ability of a test compound to antagonize the response of cells expressing MCH receptors to MCH, the EC_{50} of MCH is first determined. An additional 20 μL of KRH buffer and 1 μL DMSO are added to each well of cells, prepared as described above. 100 μL

human MCH in KRH buffer is automatically transferred by the FLIPR instrument to each well. An 8-point concentration response curve, with final MCH concentrations of 1 nM to 3 μM, is used to determine MCH EC_{50}.

Test compounds are dissolved in DMSO, diluted in 20 μL KRH buffer, and added to cells prepared as described above. The 96 well plates containing prepared cells and test compounds are incubated in the dark, at room temperature for 0.5–6 hours. It is important that the incubation not continue beyond 6 hours. Just prior to determining the fluorescence response, 100 μL human MCH diluted in KRH buffer to 2 x EC_{50} is automatically added by the FLIPR instrument to each well of the 96 well plate for a final sample volume of 200 μL and a final MCH concentration of EC_{50}. The final concentration of test compounds in the assay wells is between 1 nM and 5 μM. Typically, cells exposed to one EC_{50} of MCH exhibit a fluorescence response of about 10,000 Relative Fluorescence Units. Cells incubated with antagonists of the MCH receptor exhibit a response that is significantly less than that of the control cells to the $p \leq 0.05$ level, as measured using a parametric test of statistical significance. Typically, antagonists of the MCH receptor decrease the fluorescence response by about 20%, preferably by about 50%, and most preferably by at least 80% as compared to matched controls.

The ability of a compound to act as an agonist of the MCH receptor is determined by measuring the fluorescence response of cells expressing MCH receptors, using the methods described above, in the absence of MCH. Compounds that cause cells to exhibit fluorescence above background are MCH receptor agonists.

EXAMPLE 14. MDCK CYTOTOXICITY ASSAY

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine kidney (MDCK) cell cytotoxicity assay.

1 μL of test compound is added to each well of a clear bottom 96-well plate (PACKARD, Meriden, CT) to give final concentration of compound in the assay of 10 μM, 100 μM or 200 μM. Solvent without test compound is added to control wells.

MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are maintained in sterile conditions following the instructions in the ATCC production information sheet. Confluent MDCK cells are trypsinized, harvested, and diluted to a concentration of 0.1 x 10^6 cells/mL with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 μL of diluted cells is added to each well, except for five standard curve control wells that contain 100 μL of warm medium without cells. The plate is then incubated at 37°C under 95% O_2, 5% CO_2 for 2 hours with constant shaking. After incubation, 50 μL of mammalian cell lysis solution (from the PACKARD (Meriden, CT) ATP-LITE-M Luminescent ATP detection kit) is added per

well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes.

Compounds causing toxicity will decrease ATP production, relative to untreated cells. The ATP-LITE-M Luminescent ATP detection kit is generally used according to the manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution is reconstituted in 5.5 mL of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 μL of serially diluted PACKARD standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM, and 12.5 nM. PACKARD substrate solution (50 μL) is added to all wells, which are then covered, and the plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes. A white PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil and placing in the dark for 10 minutes. Luminescence is then measured at 22°C using a luminescence counter (*e.g.,* PACKARD TOPCOUNT Microplate Scintillation and Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated from the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells. Cells treated with 10 μM of a preferred test compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μM concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated cells.

EXAMPLE 15. MICROSOMAL *IN VITRO* HALF-LIFE

This Example illustrates the evaluation of compound half-life values ($t_{1/2}$ values) using a representative liver microsomal half-life assay.

Pooled human liver microsomes are obtained from XenoTech LLC (Kansas City, KS). Such liver microsomes may also be obtained from In Vitro Technologies (Baltimore, MD) or Tissue Transformation Technologies (Edison, NJ). Six test reactions are prepared, each containing 25 μL microsomes, 5 μL of a 100 μM solution of test compound, and 399 μL 0.1 M phosphate buffer (19 mL 0.1 M NaH_2PO_4, 81 mL 0.1 M Na_2HPO_4, adjusted to pH 7.4 with H_3PO_4). A seventh reaction is prepared as a positive control containing 25 μL microsomes, 399 μL 0.1 M phosphate buffer, and 5 μL of a 100 μM solution of a compound with known metabolic properties (*e.g.,* DIAZEPAM or CLOZAPINE). Reactions are preincubated at 39°C for 10 minutes.

Cofactor mixture is prepared by diluting 16.2 mg NADP and 45.4 mg glucose-6-phosphate in 4 mL 100 mM $MgCl_2$. Glucose-6-phosphate dehydrogenase solution is prepared by diluting 214.3 μL

glucose-6-phosphate dehydrogenase suspension (Roche Molecular Biochemicals; Indianapolis, IN) into 1285.7 μL distilled water. 71 μL of starting reaction mixture (3 mL cofactor mixture; 1.2 mL glucose-6-phosphate dehydrogenase solution) is added to 5 of the 6 test reactions and to the positive control. 71 μL 100 mM $MgCl_2$ is added to the sixth test reaction, which is used as a negative control. At each time point (0, 1, 3, 5, and 10 minutes), 75 μL of each reaction mix is pipetted into a well of a 96-well deep-well plate containing 75 μL ice-cold acetonitrile. Samples are vortexed and centrifuged 10 minutes at 3500 rpm (Sorval T 6000D centrifuge, H1000B rotor). 75 μL of supernatant from each reaction is transferred to a well of a 96-well plate containing 150 μL of a 0.5 μM solution of a compound with a known LCMS profile (internal standard) per well. LCMS analysis of each sample is carried out and the amount of unmetabolized test compound is measured as AUC, compound concentration vs. time is plotted, and the $t_{1/2}$ value of the test compound is extrapolated.

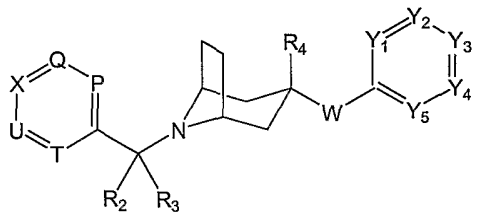
Preferred compounds provided herein exhibit *in vitro* $t_{1/2}$ values of greater than 10 minutes and less than 4 hours, preferably between 30 minutes and 1 hour, in human liver microsomes.

From the foregoing it will be appreciated that, although specific embodiments have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

W is absent or CR_5R_6, wherein R_5 and R_6 are independently hydrogen, halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, or haloC_1-C_2alkyl, or R_5 and R_6 are taken together to form an oxo group;

Y_1, Y_2, Y_3, Y_4 and Y_5 are each nitrogen or CR_1, wherein no more than 3 of Y_1, Y_2, Y_3, Y_4, and Y_5 are nitrogen;

Each R_1 is independently:

(i) hydrogen, halogen, hydroxy, nitro, cyano, amino, -$CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, haloC_1-C_6alkoxy, hydroxyC_1-C_6alkyl, C_1-C_6alkylthio, C_1-C_8alkylether, aminoC_1-C_6alkyl, mono- or di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, mono- or di-C_1-C_6alkylcarboxamide, C_1-C_6alkylsulfonyl, (C_3-C_7cycloalkyl)C_0-C_6alkyl, or (heterocycloalkyl)C_0-C_6alkyl; or

(ii) any two adjacent R_1 may be joined to form a fused 5- or 6-membered carbocycle or heterocycle, each of which is substituted with 0 to 3 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, C_1-C_4alkyl, C_1-C_4alkoxy, haloC_1-C_4alkyl, and haloC_1-C_4alkoxy;

wherein when Y_1, Y_2, Y_3, Y_4 and Y_5 are all CR_1 at least one R_1 is not hydrogen;

R_2 and R_3 are independently hydrogen, halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, or haloC_1-C_2alkyl; or

R_2 and R_3 are taken together to form an oxo group; or

R_3 is taken together with R_9 to form a fused 5- to 10-membered carbocycle or heterocycle;

R_4 is hydrogen, halogen, hydroxy, amino, C_1-C_4alkyl, C_1-C_4alkoxy, mono- or di-C_1-C_4alkylamino, -NHCHO, C_2-C_4alkanoylamino, haloC_1-C_2alkyl, or haloC_1-C_2alkoxy;

P is nitrogen or CR_7;

Q is nitrogen or CR_8;

U is nitrogen or CR_9;

T is nitrogen or CR_{10};

X is nitrogen or CR_{11};

wherein no more than 3 of P, Q, U, T, and X are nitrogen;

R_7 is: (i) hydrogen, halogen, hydroxy, nitro, cyano, -COOH, or a group of the formula -L-M; or
(ii) taken together with R_8 to form a fused 5- or 6-membered carbocycle or heterocycle;

R_8 is: (i) hydrogen, halogen, hydroxy, nitro, cyano, -COOH, or a group of the formula -L-M; or
(ii) taken together with R_7 to form a fused 5- or 6-membered carbocycle or heterocycle;
(iii) taken together with R_{11} to form a fused 5- to 10-membered carbocycle or heterocycle, each of which is substituted 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy;

R_9 is: (i) hydrogen, halogen, hydroxy, nitro, cyano, -COOH, or a group of the formula -L-M; or
(ii) taken together with R_{10} to form a fused 5- to 10-membered carbocycle or heterocycle;

R_{10} is: (i) hydrogen, halogen, hydroxy, nitro, cyano, -COOH, or a group of the formula -L-M; or
(ii) taken together with R_3 or R_9 to form a fused carbocycle or heterocycle;

R_{11} is: (i) bromo, iodo, hydroxy, nitro, or cyano;
(ii) a group of the formula -L-G;
(iii) 5-10 membered cycloalkenyl, aryl, heterocycloalkenyl, or heteroaryl, each of which is substituted with 0 to 5 substituents independently chosen from halogen, amino, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy; or
(iv) taken together with R_8 to form an optionally substituted fused 5- to 10-membered carbocycle or heterocycle;

G is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, aminoC_1-C_6alkyl, or a 5- to 10-membered cycloalkyl or heterocycloalkyl; each of which is substituted with 0 to 3 substituents independently chosen from halogen, amino, and haloC_1-C_2alkoxy, and

G is further substituted with 0 to 1 substituent chosen from
(a) oxo, hydroxy, cyano, -COOH, -(C=O)NH_2, -NH(C=O)H, -SO_2NH_2, and imino,
(b) (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_8alkyl)aminoC_0-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfonamide, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoylamino, mono- and di-C_1-C_6alkylcarboxamide, and C_1-C_6alkyloxime,
each of which (b) is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, (C_1-C_4alkoxy)C_0-C_4alkyl, mono- and di-C_1-C_4alkylamino, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy; and

(c) (carbocycle)C_0-C_6alkyl, (heterocycle)C_0-C_6alkyl, (carbocycle)C_0-C_6alkoxy, (heterocycle)C_0-C_6alkoxy, (carbocycle)C_0-C_6alkylamino, and (heterocycle)C_0-C_6alkylamino;

each of which (c) is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy;

each L is independently a single covalent bond, $-N(R_{13})-$, -O-, -C(=O)-, $-SO_2-$, $-SO_2NH-$, $-C(=O)N(R_{13})-$, or $-N(R_{13})C(=O)-$, wherein each R_{13} is independently hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or haloC_1-C_6alkyl; and

each M is independently hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, aminoC_1-C_6alkyl, or a 5- to 10-membered cycloalkyl or heterocycloalkyl.

2. A compound or salt of Claim 1, wherein W is absent.

3. A compound or salt of Claim 1, wherein W is CR_5R_6.

4. A compound or salt of Claim 3, wherein R_5 and R_6 are independently hydrogen or methyl.

5. A compound or salt of Claim 3, wherein R_5 and R_6 are taken together to form an oxo group.

6. A compound or salt of any one of Claims 1 to 5, wherein one and only one of Y_1, Y_2, Y_3, Y_4 and Y_5 is nitrogen.

7. A compound or salt of Claim 6, wherein one of Y_1, Y_4, and Y_5 is nitrogen.

8. A compound or salt of any one of Claims 1 to 5, wherein Y_1, Y_2, Y_3, Y_4, and Y_5 are all CR_1.

9. A compound or salt of any one of Claims 1 to 8, wherein

Each R_1 is independently hydrogen, halogen, hydroxy, nitro, cyano, amino, C_1-C_4alkyl, C_2-C_4alkenyl, C_1-C_4alkoxy, haloC_1-C_2alkyl, haloC_1-C_2alkoxy, hydroxyC_1-C_4alkyl, C_1-C_4alkylthio, aminoC_1-C_6alkyl, mono- or di-(C_1-C_4alkyl)amino, or (C_3-C_7cycloalkyl)C_0-C_2alkyl.

10. A compound or salt of Claim 9, wherein

Each R_1 is independently hydrogen, halogen, C_1-C_2alkyl, C_2-C_4alkenyl, C_1-C_2alkoxy, haloC_1-C_2alkyl, or haloC_1-C_2alkoxy.

11. A compound or salt of Claim 10, wherein

Y_1, Y_2, Y_3, Y_4, and Y_5 are all CR_1; and the R_1 of Y_1, Y_4, and Y_5 are all hydrogen.

12. A compound or salt of Claim 11, wherein

R_1 of Y_2 is halogen, methyl, methoxy, or trifluoromethyl, and

R_1 of Y_3 is hydrogen, halogen, methyl, methoxy, or trifluoromethyl.

13. A compound or salt of Claim 11, wherein

R_1 of Y_2 is hydrogen, halogen, methyl, methoxy, or trifluoromethyl, and

R_1 of Y_3 is halogen, methyl, methoxy, or trifluoromethyl.

14. A compound or salt of Claim 11, wherein

R_1 of Y_2 is methoxy or trifluoromethyl, and R_1 of Y_3 is chloro.

15. A compound or salt of any one of Claims 1 to 14, wherein

R_2 and R_3 are independently hydrogen or methyl.

16. A compound or salt of Claim 15, wherein R_2 and R_3 are both hydrogen.

17. A compound or salt of any one of Claims 1 to 14, wherein

R_2 is joined with R_3 to form an oxo group.

18. A compound or salt of any one of Claims 1 to 17, wherein R_4 is hydrogen, hydroxy, amino, -NHCHO, or C_2alkanoylamino.

19. A compound or salt of Claim 18, wherein R_4 hydroxy.

20. A compound or salt of any one of Claims 1 to 19, wherein

P is nitrogen or CR_7; Q is CR_8; U is CR_9; T is CR_{10}; and X is CR_{11}.

21. A compound or salt of any one of Claims 1 to 19, wherein P is CR_7; Q is nitrogen; U is CR_9; T is CR_{10}; and X is CR_{11}.

22. A compound or salt of any one of Claims 1 to 19, wherein P is CR_7; Q is CR_8; U is nitrogen; T is CR_{10}; and X is CR_{11}.

23. A compound or salt of any one of Claims 1 to 19, wherein P is CR_7; Q is CR_8; U is CR_9; T is nitrogen; and X is CR_{11}.

24. A compound or salt of any one of Claims 1 to 19, wherein P is CR_7; Q is CR_8; U is CR_9; T is CR_{10}; and X is CR_{11}.

25. A compound or salt of any one of Claims 1 to 24, wherein

R_7, R_8, R_9, and R_{10} are independently hydrogen, halogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, mono- or di-C_1-C_6alkylamino, haloC_1-C_2alkyl, or haloC_1-C_2alkoxy.

26. A compound or salt of Claim 25, wherein R_7 and R_8 are independently hydrogen, C_1-C_2alkyl, or C_1-C_2alkoxy; and R_9 and R_{10} are hydrogen.

27. A compound or salt of Claim 26, wherein R_7 and R_8 are both methyl.

28. A compound or salt of any one of Claims 1 to 27, wherein R_{11} is a group of the formula -L-G.

29. A compound or salt of Claim 28, wherein

G is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, aminoC_1-C_6alkyl, or a 5- to 10-membered cycloalkyl or heterocycloalkyl; each of which is substituted with 0 to 3 substituents independently chosen from halogen, amino, and haloC_1-C_2alkoxy, and

G is further substituted with at least one substituent independently chosen from

(a) oxo, hydroxy, cyano, -COOH, -(C=O)NH_2, -NH(C=O)H, -SO_2NH_2, and imino,

(b) (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_8alkyl)aminoC_0-C_6alkyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfonamide, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoylamino, mono- and di-C_1-C_6alkylcarboxamide, and C_1-C_6alkyloxime,
each of which (b) is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, (C_1-C_4alkoxy)C_0-C_4alkyl, mono- and di-C_1-C_4alkylamino, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy, and

(c) (carbocycle)C_0-C_6alkyl, (heterocycle)C_0-C_6alkyl, (carbocycle)C_0-C_6alkoxy, (heterocycle)C_0-C_6alkoxy, (carbocycle)C_0-C_6alkylamino, and (heterocycle)C_0-C_6alkylamino, wherein the carbocycle is phenyl, naphthyl, C_3-C_7cycloalkyl, or C_3-C_7cycloalkenyl, and the heterocycle is pyrrolidinyl, tetrahydrofuranyl, dioxolanyl, tetrahydropyranyl, isothiazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, dihydropyrrolyl, pyrazolyl, furanyl, thienyl, pyrazolyl, oxazolyl, thiazolyl, thiadiazolyl, isoxazolyl, imidiazolyl, triazolyl, tetrazolyl, pyridinyl, tetrahydropyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, benzodioxanyl, indolyl, isoindolyl, indazolyl, indanyl, quinolinyl, isoquinolinyl, or benzimidazolyl;
each of which (c) are substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

30. A compound or salt of Claim 29, wherein L is -O-.

31. A compound or salt of Claim 30, wherein

G is C_1-C_6alkyl, each of which is substituted with 0 to 3 substituents independently chosen from halogen, amino, and haloC_1-C_2alkoxy, and

G is further substituted with at least one substituent independently chosen from

(a) oxo, hydroxy, cyano, -COOH, -(C=O)NH_2, -NH(C=O)H,

(b) C_1-C_6alkoxy, mono- and di-(C_1-C_6alkyl)amino, C_1-C_6alkylsulfonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfonamide, C_1-C_6alkoxycarbonyl, and C_2-C_6alkanoylamino, each of which (b) is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, (C_1-C_4alkoxy)C_0-C_4alkyl, mono- and di-C_1-C_4alkylamino, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy, and

(c) (carbocycle)C_0-C_6alkyl and (heterocycle)C_0-C_6alkyl, wherein the carbocycle is phenyl, naphthyl, C_3-C_7cycloalkyl, or C_3-C_7cycloalkenyl, and the heterocycle is pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, furanyl, thienyl, oxazolyl, thiazolyl, imidiazolyl, triazolyl, pyridinyl, pyrimidinyl or, pyrazinyl, each of which (c) are substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-(C_1-C_4alkyl)amino, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

32. A compound or salt of Claim 31, wherein G is C_1-C_4alkyl.

33. A compound or salt of Claim 31, wherein

G is C_1-C_6alkyl substituted with at least one substituent independently chosen from

(a) oxo, hydroxy, -(C=O)NH_2, and -NH(C=O)H, and

(b) C_1-C_4alkoxy, mono- and di-(C_1-C_4alkyl)amino, C_1-C_4alkoxycarbonyl, and C_2-C_4alkanoylamino, each of which (b) is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, C_1-C_2alkoxy, mono- and di-C_1-C_4alkylamino, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

34. A compound or salt of Claim 31, wherein

G is C_1-C_6alkyl substituted with at least one substituent independently chosen from (carbocycle)C_0-C_6alkyl and (heterocycle)C_0-C_6alkyl, wherein the carbocycle is phenyl or C_3-C_7cycloalkyl, and the heterocycle is pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, furanyl, thienyl, imidiazolyl, pyridinyl, pyrimidinyl, or pyrazinyl, each of which (carbocycle)C_0-C_6alkyl and (heterocycle)C_0-C_6alkyl is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, C_1-C_2alkoxy, mono- and di-C_1-C_4alkylamino, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

35. A compound or salt of any one of Claims 1 to 20 or 22 to 24, wherein

R_{11} is taken together with R_8 to form a fused carbocycle or heterocycle; which is substituted with 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, C_1-C_6alkyl, (C_1-C_6alkoxy)C_0-C_6alkoxy, mono- and di-(C_1-C_6alkyl)aminoC_0-C_6alkyl, C_2-C_4alkanoyl, C_3-C_7cycloalkyl, C_1-C_4alkoxycarbonyl, haloC_1-C_2alkyl, and haloC_1-C_2alkoxy.

36. A compound or salt of Claim 35, wherein

R_{11} is taken together with R_8 to form a fused 5 or 6 membered heterocycloalkyl ring having 1 or 2 oxygen atoms; which is substituted with 0 to 2 substituents independently chosen from halogen, hydroxy, methyl, and methoxy.

37. A compound or salt of Claim 36, wherein R_7, R_9, and R_{10} are independently hydrogen or methyl.

38. A compound or salt thereof of Claim 1, wherein the compound is
8-(4-methoxy-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1] octan-3-ol;
8-(4-methoxy-2,3-dimethylbenzyl)-3-(4-chloro-3-trifluoromethylphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol;
8-(4-methoxy-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octane;
8-(1-(4-methoxy-2,3-dimethylphenyl)ethyl)-3-(4-(trifluoromethyl)phenyl)-8-aza-bicyclo[3.2.1]octan-3-ol;
3-(3,4-difluorophenyl)-8-(1-(4-methoxy-2,3-dimethylphenyl)ethyl)-8-aza-bicyclo[3.2.1] octan-3-ol;
(8-(1-(4-methoxy-2,3-dimethylphenyl)ethyl)-8-aza-bicyclo[3.2.1]octan-3-yl)(4-(trifluoromethyl)phenyl)methanone;
3-(4-chloro-3-methoxyphenyl)-8-(1-(4-methoxy-2,3-dimethylphenyl)ethyl)-8-aza-bicyclo[3.2.1]octan-3-ol;
8-(2,3-dimethyl-4-(3-morpholinopropoxy)benzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol;
8-(2,3-dimethyl-4-(3-(piperidin-1-yl)propoxy)benzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol;
8-(4-(2-methoxyethoxy)-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol;
8-(4-(3-methoxypropoxy)-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol;
8-(4-(3-(dimethylamino)propoxy)-2,3-dimethylbenzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol;
8-(2,3-dimethyl-4-(3-(pyridin-2-yl)propoxy)benzyl)-3-(4-chloro-3-methoxyphenyl)-8-aza-bicyclo[3.2.1]octan-3-ol; or
1-(3-(4-((3-(4-chloro-3-methoxyphenyl)-3-hydroxy-8-aza-bicyclo[3.2.1]octan-8-yl)methyl)-2,3-dimethylphenoxy)propyl)pyrrolidin-2-one.

39. A compound or salt of any one of Claims 1 to 38, wherein the compound exhibits a K_i of 1 micromolar or less in an MCH receptor ligand binding assay or an IC_{50} of 1 micromolar or less in a MCH receptor-mediated calcium mobilization assay.

40. A compound or salt of Claim 39, wherein the compound exhibits a K_i of 500 nanomolar or less in an MCH receptor ligand binding assay.

41. A compound or salt of Claim 39, wherein the compound exhibits a K_i of 100 nanomolar or less in an MCH receptor ligand binding assay.

42. A compound or salt of Claim 39, wherein the compound exhibits a K_i of 10 nanomolar or less in an MCH receptor ligand binding assay.

43. A pharmaceutical composition, comprising a compound or salt of any one of Claims 1 to 42, in combination with at least one physiologically acceptable carrier or excipient.

44. The pharmaceutical composition of Claim 43, wherein the composition is formulated as an injectable fluid, an aerosol, a cream, an oral liquid, a tablet, a gel, a pill, a capsule, a syrup, or a transdermal patch.

45. A packaged pharmaceutical preparation, comprising: a pharmaceutical composition of Claim 43 or 44 in a container; and instructions for using the composition to treat a patient suffering from a disorder associated with MCH receptor activation or to modulate bone mass in a patient.

46. The packaged pharmaceutical preparation of Claim 45, wherein the disorder is an eating disorder, a sexual disorder, obesity, diabetes, heart disease, metabolic syndrome, stroke, anxiety, depression, a skin pigmentation disorder, a reward system disorder, a cognitive disorder, or a fluid balance disorder.

47. A method for modulating binding of MCH to cellular MCH receptor, the method comprising contacting cells expressing MCH receptor with a compound or salt of any one of Claims 1 to 42, in an amount sufficient to detectably modulate MCH binding to MCH receptor *in vitro*, and thereby modulating MCH binding to MCH receptor in the cells.

48. The method of Claim 47, wherein the cells are present in an animal.

49. The method of Claim 48, wherein animal is a human and the cells are brain cells.

50. The method of Claim 47, wherein the modulation is inhibition.

51. A method for modulating binding of MCH to a MCH receptor *in vitro*, the method comprising contacting MCH receptor with a compound or salt of any one of Claims 1 to 42, under conditions and in an amount sufficient to detectably modulate MCH binding to the MCH receptor.

52. A method for altering the signal-transducing activity of a MCH receptor in a cell, the method comprising contacting a cell expressing MCH receptor with a compound or salt, of any one of Claims 1 to 42, under conditions and in an amount sufficient to detectably alter the electrophysiology of the cell, and thereby altering the signal-transducing activity of MCH receptor in the cell.

53. The method of Claim 52, wherein the cell is present in an animal.

54. The method of Claim 52, wherein animal is a human and the cell is a brain cell.

55. The method of Claim 52 wherein the signal-transducing activity of the MCH receptor in a cell is inhibited.

56. The method of Claim 52, wherein the alteration in the electrophysiology of the cell is detected as a change in the animal's feeding behavior.

57. A method for treating a disease or disorder associated with MCH receptor activation, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of any one of Claims 1 to 42.

58. The method of Claim 57, wherein the disease or disorder is an eating disorder, sexual disorder, diabetes, heart disease, metabolic syndrome, stroke, anxiety, depression, a skin pigmentation disorder, a reward system disorder, a cognitive disorder, or a fluid balance disorder.

58. A method for modulating bone mass in a patient, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of any one of Claims 1 to 42.

60. The method of any one of Claims 57-59, wherein the compound or salt is administered orally.

61. The method of any one of Claims 57-59, wherein the compound or salt is administered intranasally, intravenously, or topically.

62. The method of any one of Claims 57-59, wherein the patient is a human.

63. The method of any one of Claims 57-59, wherein the patient is a dog or a cat.

64. A method for treating obesity, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of any one of Claims 1 to 42.

65. The method of Claim 64, wherein the compound or salt is administered orally.

66. The method of Claim 64 or 65, wherein the patient is a human.

67. The method of Claim 64 or 65, wherein the patient is a dog or a cat.

68. A compound or salt, of any one of Claims 1 to 42, wherein the compound or salt is radiolabeled.

69. A method for determining the presence or absence of MCH receptor in a sample, comprising: contacting a sample with a compound or salt of any one of Claims 1 to 42 under conditions that permit binding of the compound or salt to MCH receptor; and detecting a level of compound or salt bound to MCH receptor, and therefrom determining the presence or absence of MCH receptor in the sample.

70. The method according to Claim 69, wherein the compound is radiolabeled, and wherein detecting a level of compound or salt comprises: separating unbound compound from bound compound; and determining an amount of bound compound in the sample.

71. The method of Claim 69, wherein the sample is a tissue section.