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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 February 2006 (09.02.2006)

PCT

(10) International Publication Number
WO 2006/015279 A1

(51) International Patent Classification[7]: C07C 217/54, 237/20, C07D 211/36, 401/12, 405/04, A61K 31/4523, A61P 3/04, 3/10, 15/00

(21) International Application Number:
PCT/US2005/027125

(22) International Filing Date: 27 July 2005 (27.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/591,753 28 July 2004 (28.07.2004) US

(71) Applicant *(for all designated States except US)*: **NEUROGEN CORPORATION** [US/US]; 35 North East Industrial Road, Branford, CT 06405 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DOLLER, Dario** [US/US]; 20 Killen Road, Wallingford, CT 06492 (US). **HUTCHISON, Alan, J.** [US/US]; 27 Allison Drive, Madison, CT 06443 (US). **CHENARD, Bertrand, L.** [US/US]; 7 Whaling Drive, Waterford, CT 06385 (US). **DeSIMONE, Robert, W.** [US/US]; 37 Gina Drive, Durham, CT 06422 (US).

(74) Agent: **PELLETIER, Roberta, L.**; Cantor Colburn LLP, 55 Griffin Road South, Bloomfield, CT 06002 (US).

(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, 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).

**Published:**

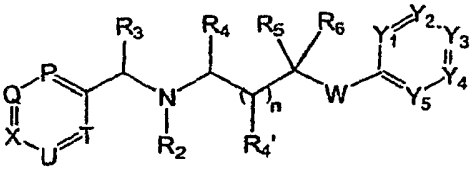
— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*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.*

WO 2006/015279 A1

(54) Title: HETEROCYCLIC DIAMINE COMPOUNDS AS LIGANDS OF THE MELANIN CONCENTRATING HORMONE RECEPTOR USEFUL FOR THE TREATMENT OF OBESITY, DIABETES, EATING AND SEXUAL DISORDERS



(I)

(57) Abstract: Heterocyclic diamine compounds of formula (I) are provided. Such compounds may be used to modulate MCH receptor activity in vivo or in vitro, and are particularly useful in the treatment of a variety of metabolic, feeding 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). Formula: (I).

)PERATION TR

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference NEU-0012-PCT | **FOR FURTHER ACTION** | see Form PCT/ISA/220 as well as, where applicable, item 5 below. |
|---|---|---|
| International application No. PCT/US2005/027125 | International filing date *(day/month/year)* 27/07/2005 | (Earliest) Priority Date *(day/month/year)* 28/07/2004 |
| Applicant NEUROGEN CORPORATION | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] ***Unity of invention is lacking*** *(see Box III).*

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established by this Authority to read as follows:

   HETEROCYCLIC DIAMINE COMPOUNDS AS LIGANDS OF THE MELANIN CONCENTRATING HORMONE RECEPTOR USEFUL FOR THE TREATMENT OF OBESITY, DIABETES, EATING AND SEXUAL DISORDERS

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

# HETEROCYCLIC DIAMINE COMPOUNDS AS LIGANDS OF THE MELANIN CONCENTRATING HORMONE RECEPTOR USEFUL FOR THE TREATMENT OF OBESITY, DIABETES, KATING AND SEXUAL DISORDERS

## CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Patent Application No. 60/591,753, filed July 28, 2004, which is hereby incorporated by reference in its entirety.

## FIELD OF THE INVENTION

This invention relates generally to heterocyclic diamine compounds. The invention further relates to the use of such compounds for treating a variety of metabolic, eating and sexual disorders, and as probes for the detection and localization of melanin concentrating hormone receptors.

## 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 and beta-adrenergic receptors), MCH receptors are membrane-spanning proteins that are generally found on cell surfaces, and 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, which 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.

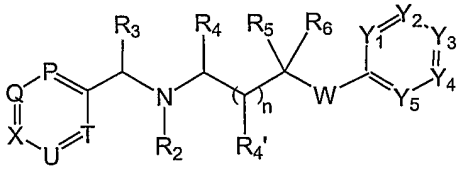
Human Melanin Concentrating Hormone Receptor-1 (MCH1R) is a 353 amino acid, 7-transmembrane, alpha-helical, G protein-coupled receptor, initially reported as orphan receptor SLC-1. Immunohistochemistry studies of rat brain sections indicate that MCH1R is widely expressed in brain. MCH1R expression is 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 (which 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 heterocyclic diamine compounds of Formula I:




Formula I

as well as pharmaceutically acceptable salts of such compounds. Within Formula I:

W is NR, NR(C=O) or oxygen, wherein R is hydrogen or $C_1$-$C_2$alkyl that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino and oxo.

The variable n is 0 or 1.

$Y_1$, $Y_2$, $Y_3$, $Y_4$ and $Y_5$ are independently nitrogen or optionally substituted carbon (*e.g.*, $CR_1$). In certain embodiments, $Y_1$ and $Y_5$ are independently CH or nitrogen; and $Y_2$, $Y_3$ and $Y_4$ are independently nitrogen or $CR_1$, such that: (i) no more than 3 of $Y_1$, $Y_2$, $Y_3$, $Y_4$ and $Y_5$ are nitrogen; and (ii) at least one of $Y_1$, $Y_2$, $Y_3$, $Y_4$ and $Y_5$ is not CH.

Each $R_1$ is independently: (i) hydrogen, halogen, hydroxy, nitro, cyano, amino, aminocarbonyl, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, $C_1$-$C_6$alkoxy, halo$C_1$-$C_6$alkyl, halo$C_1$-$C_6$alkoxy, hydroxy$C_1$-$C_6$alkyl, $C_1$-$C_6$alkylthio, $C_2$-$C_8$alkyl ether, amino$C_1$-$C_6$alkyl, mono- or di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, mono- or di-($C_1$-$C_6$alkyl)aminocarbonyl, ($C_3$-$C_7$cycloalkyl)$C_0$-$C_6$alkyl or (4- to 7-membered heterocycloalkyl)$C_0$-$C_6$alkyl; or (ii) taken together with an adjacent $R_1$ to form a fused 5- or 6-membered carbocycle or heterocycle, each of which is optionally substituted, and preferably each of which is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_4$alkyl and halo$C_1$-$C_4$alkoxy; such that $R_1$ of $Y_1$ and $R_1$ of $Y_5$ are not both $C_2$-$C_4$alkyl.

$R_2$ is (i) hydrogen or $C_1$-$C_4$alkyl; or (ii) taken together with $R_3$ to form a 5- to 7-membered heterocycloalkyl that is optionally substituted, and is preferably substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy.

$R_3$ is (i) $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, $C_2$-$C_4$alkenyl or halo$C_1$-$C_2$alkyl; (ii) taken together with $R_2$ to form an optionally substituted 5- to 7-membered heterocycloalkyl; (iii) taken together with $R_4$ to form a 5- to 7-membered heterocycloalkyl that is optionally substituted, and is preferably substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy; or (iv) taken together with $R_{10}$ to form a fused 5- to 10-membered carbocycle or heterocycle.

$R_4$ is (i) hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy; or (ii) taken together with $R_3$ to form an optionally substituted 5- to 7-membered heterocycloalkyl.

$R_4'$ is hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

$R_5$ and $R_6$ are (i) independently hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy; or (ii) taken together to form an oxo group.

P is nitrogen or $CR_7$; Q is nitrogen or $CR_8$; U is nitrogen or $CR_9$; T is nitrogen or $CR_{10}$; and X is nitrogen or $CR_{11}$; such that no more than 3 of P, Q, U, T and X are nitrogen. In certain embodiments, at least two of P, Q, U, T and X are substituted carbon.

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

(iii) taken together with $R_{11}$ to form a fused 5- to 10-membered carbocycle or heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, ($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

$R_9$ 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) hydrogen, halogen, hydroxy, nitro, cyano or –COOH;

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

(iii) taken together with $R_8$ to form a fused, optionally substituted carbocycle or heterocycle.

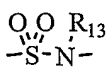
G is $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, or a 5- to 10-membered cycloalkyl, heterocycloalkyl, aryl or heteroaryl; each of which is substituted with from 0 to 5 substituents independently chosen from:

(a) oxo, halogen, amino, hydroxy, cyano, nitro, -COOH, -NH(C=O)H, aminosulfonyl, aminocarbonyl, -(C=N)OH and imino;

(b) $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, ($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkoxy, halo$C_1$-$C_6$alkyl, halo$C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_8$alkyl)amino$C_0$-$C_6$alkyl, $C_1$-$C_6$alkylsulfonyl, $C_1$-$C_6$alkylthio, mono- and di-($C_1$-$C_6$alkyl)aminosulfonyl, $C_1$-$C_6$alkoxycarbonyl, $C_2$-$C_4$alkanoyl, $C_2$-$C_6$alkanoylamino, mono- and di-($C_1$-$C_6$alkyl)aminocarbonyl and $C_1$-$C_6$alkyloxime; each of which is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkoxy, ($C_1$-$C_4$alkoxy)$C_0$-$C_4$alkyl, mono- and di-($C_1$-$C_4$alkyl)amino, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy; and

(c) (carbocycle)$C_0$-$C_6$alkyl, (heterocycle)$C_0$-$C_6$alkyl, (carbocycle)$C_0$-$C_6$alkoxy, (heterocycle)$C_0$-$C_6$alkoxy, (carbocycle)$C_0$-$C_6$alkylamino and (heterocycle)$C_0$-$C_6$alkylamino; each of which is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, ($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

Each L is independently a single covalent bond, N($R_{13}$) (*i.e.*,  ), O, S, C(=O) (*i.e.*,  ), C(=O)O (*i.e.*, ), OC(=O) (*i.e.*, ), SO (*i.e.*,  ), $SO_2$ (*i.e.*,  ), $SO_2N(R_{13})$

(*i.e.*,  ), $C(=O)N(R_{13})$ (*i.e.*, ), $N(R_{13})SO_2$ (*i.e.*, ) or $N(R_{13})C(=O)$ (*i.e.*,  ), wherein each $R_{13}$ is independently hydrogen, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl or halo$C_1$-$C_6$alkyl.

Each M is independently hydrogen, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, halo$C_1$-$C_6$alkyl, hydroxy$C_1$-$C_6$alkyl, $C_2$-$C_6$alkyl ether, amino$C_1$-$C_6$alkyl, $C_5$-$C_{10}$cycloalkyl or 5- to 10-membered heterocycloalkyl, each of which is optionally substituted.

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

The present invention further provides, within other aspects, pharmaceutical compositions comprising at least one heterocyclic diamine compound provided herein 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, an oral liquid, a tablet, a gel, a pill, a capsule, a syrup or a transdermal patch.

Methods are further provided for modulating binding of ligand (*e.g.*, MCH) to cellular MCH receptor, comprising contacting cells expressing MCH receptor with a MCH receptor modulator as described above, in an amount that would be sufficient to detectably modulate MCH binding to MCH receptor *in vitro*. The cells may, but need not, be present in a human nor non-human animal.

In other aspects, methods are provided for modulating binding of ligand (*e.g.*, MCH) to MCH receptor *in vitro*, comprising MCH receptor with a MCH receptor modulator as described above, in an amount sufficient to detectably modulate MCH binding to MCH receptor.

Within further aspects, the present invention provides methods for modulating the signal-transducing activity of MCH receptor in a cell, comprising contacting a cell expressing MCH receptor, either *in vivo* or *in vitro*, with a MCH receptor modulator as described above, under conditions and in an amount that is sufficient to detectably alter the electrophysiology of the cell.

Within certain embodiments of the above methods, the MCH receptor is a MCH1R.

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, obesity, eating disorders (*e.g.,* 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 (*e.g.,* dog or cat) or livestock.

Also provided herein are methods for treating a patient, comprising diagnosing the patient as having a disease or disorder associated with MCH receptor activation, correlating the diagnosis of a disease or disorder associated with MCH receptor activation with the need for administration of a MCH receptor modulator, and administering to the patient an effective amount of a MCH receptor modulator as described above.

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

Packaged pharmaceutical preparations are also provided, comprising: (a) a pharmaceutical composition as described above in a container; and (b) instructions for using the composition to treat a patient suffering from or at risk for developing a disease or disorder associated with MCH receptor activation.

In yet another aspect, methods for 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 heterocyclic diamine compounds 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 in the present invention unless otherwise specified. Where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. 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 may have any definition described herein that results in a stable compound.

The term "heterocyclic diamine compound" refers to any compound that satisfies Formula I, or is a pharmaceutically acceptable salt of such a compound, including compounds in which W is oxygen. Certain heterocyclic diamine compounds further satisfy one or more additional formulas provided herein; the phrase "heterocyclic diamine compound of Formula x" is intended to encompass both compounds of Formula x and the 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 or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific 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.

It will be apparent that each heterocyclic diamine compound 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 heterocyclic diamine compounds provided herein. 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 heterocyclic diamine compound. 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, phosphate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to yield the parent compounds.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include groups having from 1 to 8 carbon atoms ($C_1$-$C_8$alkyl), from 1 to 6 carbon atoms ($C_1$-$C_6$alkyl) and from 1 to 4 carbon atoms ($C_1$-$C_4$alkyl), 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, "$C_0$-$C_6$alkyl" refers to a single covalent bond or a $C_1$-$C_6$alkyl group. In some instances, a substituent of an alkyl group is specifically indicated. For example, "hydroxy$C_1$-$C_6$alkyl" refers to a $C_1$-$C_6$alkyl group that has at least one hydroxy substituent; amino$C_1$-$C_6$alkyl refers to a $C_1$-$C_6$alkyl group that has at least one amino substituent. Such groups may have additional substituents as well, as indicated.

"Alkylene" refers to a divalent alkyl group, as defined above. $C_0$-$C_4$alkylene is a single covalent bond or an alkylene group having from 1 to 4 carbon atoms.

"Alkenyl" refers to straight or branched chain alkene groups, which comprise at least one unsaturated carbon-carbon double bond. Alkenyl groups include $C_2$-$C_8$alkenyl, $C_2$-$C_6$alkenyl and $C_2$-$C_4$alkenyl 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 $C_2$-$C_8$alkynyl, $C_2$-$C_6$alkynyl and $C_2$-$C_4$alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

A "cycloalkyl" is a group that comprises one or more saturated and/or partially saturated rings in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of the foregoing, such as cyclohexenyl. Certain cycloalkyl groups are $C_3$-$C_7$cycloalkyl, in which the ring contains from 3 to 7 ring members. Cycloalkyl groups that comprise at least one carbon-carbon double bond are specifically designated "cycloalkenyl" (*e.g.*, 5-10 membered cycloalkenyl). A "cycloalkyl$C_0$-$C_n$alkyl" is a cycloalkyl group linked via a single covalent bond or a $C_1$-$C_n$alkylene group (*e.g.*, $C_3$-$C_7$cycloalkyl)$C_0$-$C_6$alkyl). "$C_5$-$C_{10}$cycloalkenyl" indicates a partially saturated cycloalkyl group having from 5 to 10 ring members.

By "alkoxy," as used herein, is meant an alkyl group as described above attached via an oxygen bridge. Alkoxy groups include $C_1$-$C_6$alkoxy and $C_1$-$C_4$alkoxy groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy and 3-methylpentoxy are representative alkoxy groups. Similarly, "alkylthio" refers to an alkyl group as described above attached via a sulfur bridge.

"Alkylsulfonyl" refers to groups of the formula –($SO_2$)–alkyl, in which the sulfur atom is the point of attachment. Alkylsulfonyl groups include $C_1$-$C_6$alkylsulfonyl and $C_1$-$C_4$alkylsulfonyl groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively. Methylsulfonyl is one representative alkylsulfonyl group.

The term "oxo," as used herein, refers to a keto group (C=O). An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of –$CH_2$– to –C(=O)–. An oxo group that is a substituent of an aromatic carbon atom results in a conversion of –CH– to –C(=O)– and a loss of aromaticity.

Similarly, "oxime" refers to a group of the formula C=NOH. An oxime group that is a substituent of a nonaromatic carbon atom results in a conversion of –$CH_2$– to –C(=NOH)–. "Alkyloxime" is an alkyl group as described above attached via a –(C=NOH)- linker.

The term "alkanoyl" refers to an acyl group (*e.g.*, –(C=O)–alkyl). 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 $C_2$alkanoyl group is an acetyl group having the formula -(C=O)$CH_3$. Alkanoyl groups include, for example, $C_2$-$C_8$alkanoyl, $C_2$-$C_6$alkanoyl and $C_2$-$C_4$alkanoyl groups, which have from 2 to 8, from 2 to 6 or from 2 to 4 carbon atoms, respectively. "$C_1$alkanoyl" refers to –(C=O)H, which (along with $C_2$-$C_8$alkanoyl) is encompassed by the term "$C_1$-$C_8$alkanoyl."

"Alkyl ether" or "(alkoxy)alkyl" refers to a linear or branched ether substituent (*i.e.*, an alkyl group that is substituted with an alkoxy group). Such groups include $C_2$-$C_6$alkyl ether and $C_2$-$C_4$alkyl ether. By way of example, a $C_2$alkyl ether group has the structure –$CH_2$–O–$CH_3$.

"($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkoxy" refers to an alkyl ether group (containing from 1 to 6 carbons on either side of the oxygen) linked via an oxygen.

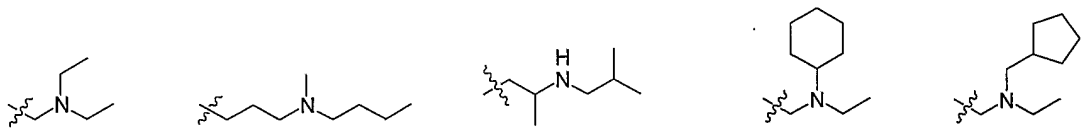
The term "alkoxycarbonyl" refers to an alkoxy group attached through a keto (-(C=O)-) bridge (*i.e.*, a group having the general structure –C(=O)–O–alkyl). Alkoxycarbonyl groups include $C_1$-$C_8$, $C_1$-$C_6$ and $C_1$-$C_4$alkoxycarbonyl groups, which have from 1 to 8, 6 or 4 carbon atoms, respectively, in the alkoxy portion of the group (*i.e.*, the carbon of the keto bridge is not included in the indicated number of carbon atoms). "$C_1$alkoxycarbonyl" refers to –C(=O)–O–$CH_3$; $C_3$alkoxycarbonyl indicates –C(=O)–O–$(CH_2)_2CH_3$ or –C(=O)–O–$(CH)(CH_3)_2$.

"Alkanoylamino," as used herein, refers to an alkanoyl group attached through an amino linker (*i.e.*, a group having the general structure –N(R)–C(=O)–alkyl), in which R is hydrogen or $C_1$-$C_6$alkyl. Alkanoylamino groups include $C_2$-$C_8$, $C_2$-$C_6$ and $C_2$-$C_4$alkanoylamino groups, which have from 2 to 8, 6 or 4 carbon atoms, respectively.

"Alkylamino" refers to a secondary or tertiary amine having the general structure –NH–alkyl or –N(alkyl)(alkyl), wherein each "alkyl" is independently selected. Such groups include, for example, mono- and di-($C_1$-$C_8$alkyl)amino groups, as well as mono- and di-($C_1$-$C_6$alkyl)amino groups and mono- and di-($C_1$-$C_4$alkyl)amino groups.

"Alkylamino" refers to a secondary or tertiary amine having the general structure –NH–alkyl or –N(alkyl)(alkyl), wherein each "alkyl" is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Such groups include, for example, mono- and di-($C_1$-$C_8$alkyl)amino groups, as well as mono- and di-($C_1$-$C_6$alkyl)amino groups and mono- and di-($C_1$-$C_4$alkyl)amino groups.

"Alkylaminoalkyl" refers to an alkylamino group linked via an alkylene group (*i.e.*, a group having the general structure –alkylene–NH–alkyl or –alkylene–N(alkyl)(alkyl)) in which each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Alkylaminoalkyl groups include, for example, mono- and di-($C_1$-$C_8$alkyl)amino$C_1$-$C_8$alkyl, mono- and di-($C_1$-$C_6$alkyl)amino$C_1$-$C_6$alkyl and mono- and di-($C_1$-$C_6$alkyl)amino$C_1$-$C_4$alkyl. "Mono- or di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl" refers to a mono- or di-($C_1$-$C_6$alkyl)amino group linked via a single covalent bond or a $C_1$-$C_6$alkylene group. The following are representative alkylaminoalkyl groups:



It will be apparent that the definition of "alkyl" as used in the terms "alkylamino" and "alkylaminoalkyl" differs from the definition of "alkyl" used for all other alkyl-containing groups, in the inclusion of cycloalkyl and (cycloalkyl)alkyl groups (*e.g.*, ($C_3$-$C_7$cycloalkyl)$C_0$-$C_6$alkyl).

The term "aminocarbonyl" refers to an amide group (*i.e.*, -(C=O)$NH_2$). "Mono- or di-($C_1$-$C_8$alkyl)aminocarbonyl" is an aminocarbonyl group in which one or both of the hydrogen atoms is

replaced with $C_1$-$C_8$alkyl. If both hydrogen atoms are so replaced, the alkyl groups may be the same or different.

"Aminosulfonyl" refers to groups of the formula $-(SO_2)-NH_2$, in which the sulfur atom is the point of attachment. The term "mono- or di-($C_1$-$C_n$alkyl)aminosulfonyl" refers to groups that satisfy the formula $-(SO_2)-NR_2$, in which the sulfur atom is the point of attachment, and in which one R is $C_1$-$C_n$alkyl and the other R is hydrogen or an independently chosen $C_1$-$C_n$alkyl.

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

A "haloalkyl" is an alkyl group that is substituted with 1 or more independently chosen halogens (*e.g.*, "halo$C_1$-$C_8$alkyl" groups have from 1 to 8 carbon atoms; "halo$C_1$-$C_6$alkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl. The term "haloalkoxy" refers to a haloalkyl group as defined above attached via an oxygen bridge. "halo$C_1$-$C_6$alkoxy" groups have 1 to 6 carbon atoms.

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

A "carbocycle" or "carbocyclic group" comprises at least one ring formed entirely by carbon-carbon bonds (referred to herein as a carbocyclic ring), and does not contain a heterocycle. Unless otherwise specified, each ring within a carbocycle may be independently saturated, partially saturated or aromatic, and is optionally substituted as indicated. A carbocycle generally has from 1 to 3 fused, pendant or spiro rings; carbocycles within certain embodiments have one ring or two fused rings. Typically, each ring contains from 3 to 8 ring members (*i.e.*, $C_3$-$C_8$); $C_4$-$C_7$ or $C_5$-$C_7$ rings are recited in certain embodiments. Carbocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain carbocycles are $C_4$-$C_{10}$ (*i.e.*, contain from 4 to 10 ring members and 1 or two rings). Certain representative carbocycles are cycloalkyl as described above. Other carbocycles are aryl (*i.e.*, contain at least one aromatic carbocyclic ring, with or without one or more additional aromatic and/or cycloalkyl rings). Such aryl carbocycles include, for example, phenyl, naphthyl (*e.g.*, 1-naphthyl and 2-naphthyl), biphenyl, fluorenyl, indanyl and 1,2,3,4-tetrahydro-naphthyl. In certain embodiments, preferred carbocycles are carbocycles having a single ring, such as phenyl and 3- to 7-membered cycloalkyl groups.

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 and/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. Aryl groups include those in which an aromatic ring is fused to a 5 to 7-membered saturated or partially saturated cyclic group that

optionally contains 1 or 2 heteroatoms independently chosen from N, O and S (*e.g.*, a 3,4-methylenedioxy-phenyl group.

Certain carbocycles and aryl groups are attached via an indicated linker group (*e.g.*, (carbocycle)alkyl, (carbocycle)alkoxy and (carbocycle)alkylamino groups). In each case the carbocycle is a substituent of the indicated linker group, each of which carries the definition set forth above. "(Carbocycle)$C_0$-$C_6$alkylamino" refers to a carbocycle linked via an amino (-NH-) linker or via a mono- or di-($C_1$-$C_6$alkyl)amino group in which the point of attachment of the carbocycle may be at any carbon atom in a mono- or di-($C_1$-$C_6$alkyl)amino group or at the nitrogen atom in a mono-($C_1$-$C_6$alkyl)amino group.

The term "arylalkyl" refers to an aryl group linked via an alkylene bridge. For example, phenyl$C_0$-$C_2$alkyl indicates a phenyl group that is attached via a single covalent bond (phenyl$C_0$alkyl) or attached through an alkylene group having 1 or 2 carbon atoms. Similarly, an aryl group may be attached through other linker groups; such groups include, for example, aryl$C_1$-$C_6$alkanoylamino and arylalkoxy groups, in which the aryl is attached via the indicated linker group.

A "heterocycle" or "heterocyclic group" 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 independently chosen from O, S and N, with the remaining ring atoms being carbon). Additional rings, if present, may be heterocyclic or carbocyclic. Typically, a heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 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 or partially saturated) or a heteroaryl group (*i.e.*, at least one heterocyclic ring within the group is aromatic), such as a 5- to 10-membered heteroaryl (which may be monocyclic or bicyclic) or a 6-membered heteroaryl (*e.g.*, pyridyl or pyrimidyl). N-linked heterocyclic groups are linked via a component nitrogen atom. 4-to 7-membered heterocycloalkyl groups include, for example, piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, morpholino, thiomorpholino and 1,1-dioxo-thiomorpholin-4-yl. Representative aromatic heterocycles include azocinyl, pyridyl, pyrimidyl, imidazolyl and tetrazolyl. In certain embodiments, preferred heterocycles are 5- to 7-membered heterocycles 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.

Certain heterocycles are attached via an indicated linker group (*e.g.*, (heterocycle)alkyl, (heterocycle)alkoxy and (heterocycle)alkylamino groups). In each case the heterocycle is covalently bound to the indicated linker group, each of which carries the definition set forth above.

As used herein, "heteroaryl" indicates a monocyclic, bicyclic or tricyclic ring system that comprises at least one 5- or 6-membered heterocyclic aromatic ring that contains from 1 to 4 (preferably from 1 to 3 or from 1 to 2) heteroatoms independently chosen from N, O and S, with remaining ring atoms being carbon. If the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. It is generally preferred that the total number of S and O atoms in the heteroaryl group is not more than 2; in certain embodiments, 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 or partially saturated. In certain embodiments preferred heterocycloalkyl groups are 5- to 7-membered heterocycloalkyl groups having a single saturated ring with 5 to 7 ring members, 1 or 2 ring members independently chosen from N, O and S, and remaining ring members being carbon. A "heterocycloalkyl$C_0$-$C_n$alkyl" is a heterocycloalkyl group linked via a single covalent bond or $C_1$-$C_n$alkylene group, such as a $C_1$-$C_4$alkylene group. A "5- to 10-membered heterocycloalkenyl" is a partially saturated heterocycloalkyl group having from 5 to 10 ring members.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a ring substituent may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. Substituents of 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). Optional substitution is also indicated by the phrase "substituted with from 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 substituents).

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 heterocyclic diamine compounds. 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 10, herein) and/or an agonist-stimulated GTP gamma$^{35}$S binding assay (as described in Example 8, 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 6 and 9, 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 8 or Example 10); in general, such an antagonist has a $IC_{50}$ value of less than 1 micromolar, preferably less than 100 nanomolar, and more preferably less than 10 nanomolar within the assay provided in Example 8 and/or the assay provided in Example 10. 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 assays given in Examples 6 and 9. 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 10, or an agonist-stimulated GTP gamma$^{35}$S binding assay, such as the assay described in Example 8.

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 8 or Example 10 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 8 and 10. 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 8 and 10.

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, and/or may 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 an assay provided in Example 6 or Example 9) and/or MCH-mediated signal transduction (using an assay provided in Example 8 or Example 10).

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.

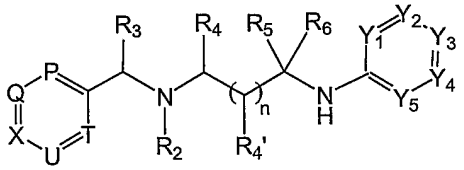
A "patient" is any individual treated with a heterocyclic diamine compound as provided herein. Patients include humans, as well as other animals such as companion animals (*e.g.*, dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to MCH receptor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

HETEROCYCLIC DIAMINE COMPOUNDS

As noted above, the present invention provides heterocyclic diamine compounds of Formula I. Certain such compounds are MCH receptor modulators, which may be specific for a particular MCH receptor (*e.g.*, type 1 or type 2) or may inhibit or enhance ligand binding to multiple MCH receptors. MCH receptor modulators may be used to modulate MCH receptor activity *in vivo*, especially in the treatment of metabolic, feeding and sexual disorders in humans, domesticated companion animals and livestock animals. Modulators may also be used within a variety of *in vitro* assays, such as assays for receptor activity, as probes for detection and localization of MCH receptors and as standards in assays of MCH binding and MCH-mediated signal transduction. The MCH receptor modulators provided herein are generally multi-aryl (*i.e.*, have a plurality of unfused or fused aryl groups), non-peptide and amino acid free, and detectably modulate MCH receptor activity at submicromolar concentrations, preferably at subnanomolar concentrations.

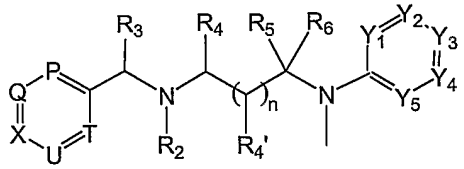
Certain heterocyclic diamine compounds satisfy one or more of the following conditions:

(a) W is NH (*i.e.*, compounds of Formula II):



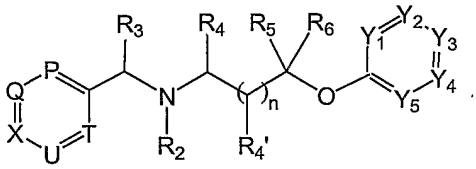
Formula II

(b) W is NR and R is methyl (*i.e.*, compounds of Formula III):



Formula III

(c) W is oxygen (*i.e.*, compounds of Formula IV):



Formula IV

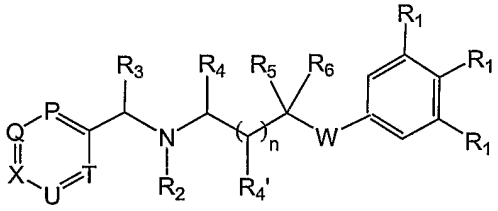
(d) n is 0.

(e) n is 1.

(f) One and only one of $Y_1$, $Y_2$, $Y_3$, $Y_4$ and $Y_5$ is nitrogen.

(g) Exactly one of $Y_1$, $Y_4$ and $Y_5$ is nitrogen.

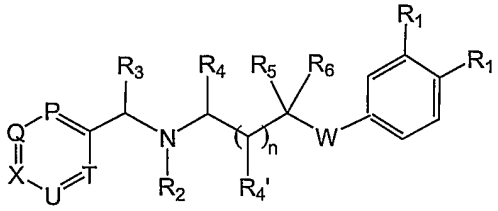
(h) $Y_1$ and $Y_5$ are each CH, and $Y_2$, $Y_3$ and $Y_4$ are all $CR_1$ (*i.e.*, compounds of Formula V):



Formula V

*The $R_1$ Variable*

Within certain heterocyclic diamine compounds of Formula I, and the subformulas thereof, each $R_1$ is independently hydrogen, halogen, hydroxy, nitro, cyano, amino, $C_1$-$C_4$alkyl, $C_2$-$C_4$alkenyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl, halo$C_1$-$C_2$alkoxy, hydroxy$C_1$-$C_4$alkyl, $C_1$-$C_4$alkylthio, amino$C_1$-$C_6$alkyl, mono- or di-($C_1$-$C_4$alkyl)amino or ($C_3$-$C_7$cycloalkyl)$C_0$-$C_2$alkyl. Within further such heterocyclic diamine compounds, each $R_1$ is independently hydrogen, halogen, $C_1$-$C_2$alkyl, $C_2$-$C_4$alkenyl, $C_1$-$C_2$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy. Within still further such heterocyclic diamine compounds, $Y_1$, $Y_4$ and $Y_5$ are each CH, and $Y_2$ and $Y_3$ are independently chosen from $CR_1$ (*i.e.*, compounds of Formula VI):



Formula VI

Within certain heterocyclic diamine compounds of Formula VI, $R_1$ of $Y_2$ is halogen, methyl, methoxy or trifluoromethyl, and $R_1$ of $Y_3$ is hydrogen, halogen, methyl, methoxy or trifluoromethyl. Within other heterocyclic diamine compounds of Formula VI, $R_1$ of $Y_2$ is hydrogen, halogen, methyl, methoxy or trifluoromethyl, and $R_1$ of $Y_3$ is halogen, methyl, methoxy or trifluoromethyl.

*The $R_2$ Variable*

Further provided herein are heterocyclic diamine compounds of Formula I, and the subformulas thereof, wherein the $R_2$ variable satisfies one or more of the following conditions:

(a) $R_2$ is hydrogen or methyl.

(b) $R_2$ is hydrogen.

(c) $R_2$ is taken together with $R_3$ to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy.

(d) $R_2$ is taken together with $R_3$ to form piperidinyl that is substituted with from 0 to 2 methyl substituents.

*The $R_3$ Variable*

Also provided herein are heterocyclic diamine compounds of Formula I, and the subformulas thereof, wherein the $R_3$ variable satisfies one or more of the following conditions:

(a) $R_3$ is hydrogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, $C_2$-$C_4$alkenyl or halo$C_1$-$C_2$alkyl.

(b) $R_3$ is $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, $C_2$-$C_4$alkenyl or halo$C_1$-$C_2$alkyl.

(c) $R_3$ is hydrogen.

(d) $R_3$ is taken together with $R_4$ to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy.

(e) $R_3$ is taken together with $R_4$ to form piperidinyl that is substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy.

*The $R_4$ and $R_4'$ Variables*

Also provided herein are heterocyclic diamine compounds of Formula I, and the subformulas thereof, wherein the $R_4$ and $R_4'$ variables satisfy one or more of the following conditions:

(a) $R_4$ is hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

(b) $R_4$ is hydrogen or methyl.

(c) $R_4'$ is hydrogen or methyl.

*The $R_5$ and $R_6$ Variables*

Also provided herein are heterocyclic diamine compounds of Formula I, and the subformulas thereof, wherein the $R_5$ and $R_6$ variables satisfy one or more of the following conditions:

(a) $R_5$ and $R_6$ are independently hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

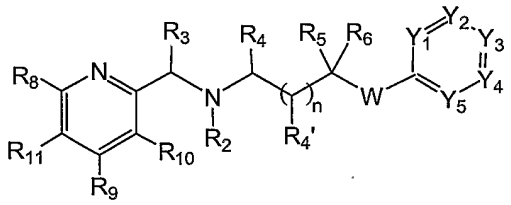
(b) $R_5$ and $R_6$ are independently hydrogen or methyl.

(c) $R_5$ and $R_6$ are taken together to form an oxo group.

*P, Q, U, T and X*

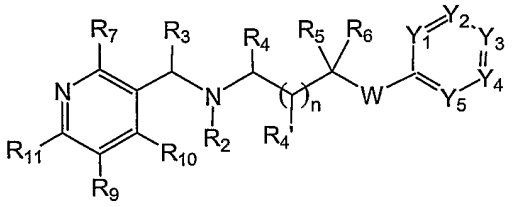
Also provided herein are heterocyclic diamine compounds of Formula I, and the subformulas thereof, that satisfy one of the following conditions:

(a) P is nitrogen; Q is $CR_8$; U is $CR_9$; T is $CR_{10}$; and X is $CR_{11}$ (*i.e.*, compounds of Formula VII):



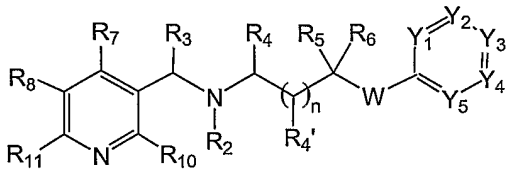
Formula VII

(b) P is $CR_7$; Q is nitrogen; U is $CR_9$; T is $CR_{10}$; and X is $CR_{11}$ (*i.e.*, compounds of Formula VIII):



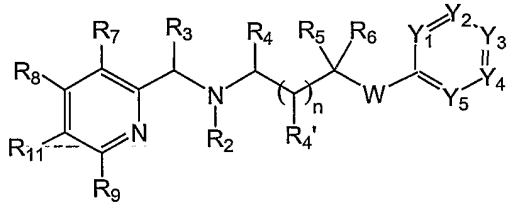
Formula VIII

(c) P is $CR_7$; Q is $CR_8$; U is nitrogen; T is $CR_{10}$; and X is $CR_{11}$ (*i.e.*, compounds of Formula IX):



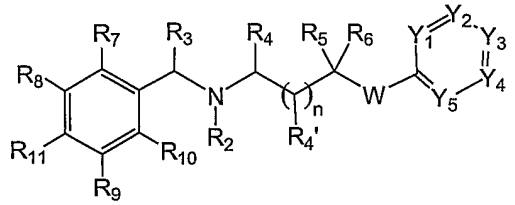
Formula IX

(d) P is $CR_7$; Q is $CR_8$; U is $CR_9$; T is nitrogen; and X is $CR_{11}$, (*i.e.*, compounds of Formula X):



Formula X

(e) P is $CR_7$; Q is $CR_8$; U is $CR_9$; T is $CR_{10}$; and X is $CR_{11}$, (*i.e.*, compounds of Formula XI):



Formula XI

*The $R_7$, $R_8$, $R_9$, $R_{10}$ and $R_{11}$ Variables*

Also provided herein are heterocyclic diamine compounds of Formula I, and the subformulas thereof, wherein the $R_7$, $R_8$, $R_9$, $R_{10}$ and $R_{11}$ variables satisfy one or more of the following conditions:

(a) $R_7$, $R_8$, $R_9$, $R_{10}$ and $R_{11}$ are independently hydrogen, halogen, hydroxy, $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, mono- or di-($C_1$-$C_6$alkyl)amino, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

(b) $R_7$ is hydrogen, $C_1$-$C_2$alkyl or $C_1$-$C_2$alkoxy; and $R_9$ and $R_{10}$ are hydrogen.

(c) $R_7$ is hydrogen or methyl; and $R_8$ and $R_{11}$ are independently hydroxy, halogen, methyl or methoxy.

(d) $R_{11}$ is taken together with $R_8$ to form a fused carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, ($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy. Within certain such compounds, $R_7$, $R_9$ and $R_{10}$ are all hydrogen.

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

(f) $R_7$, $R_8$, $R_9$ and $R_{10}$ are each independently hydrogen, halogen, hydroxy, nitro, cyano, -COOH or a group of the formula -L-M; where each L is independently a single covalent bond, $N(R_{13})$ or O, wherein each $R_{13}$ is independently hydrogen or $C_1$-$C_6$alkyl; and each M is independently hydrogen, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, halo$C_1$-$C_2$alkyl or amino$C_1$-$C_6$alkyl.

(g) $R_7$, $R_8$, $R_9$ and $R_{10}$ are each independently hydrogen, halogen, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_1$-$C_6$alkoxy, mono- or di-($C_1$-$C_6$alkyl)amino, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

(h) $R_7$, $R_8$ and $R_9$ are each independently hydrogen, halogen, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_1$-$C_6$alkoxy, mono- or di-($C_1$-$C_6$alkyl)amino, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy; and $R_{10}$ is hydrogen.

(i) $R_7$ and $R_8$ are independently hydrogen, methyl or methoxy; and $R_9$ and $R_{10}$ are each hydrogen.

(j) $R_7$ and $R_8$ are both methyl, and $R_9$ and $R_{10}$ are each hydrogen.

*The $R_{11}$ Variables and L and G*

Within certain heterocyclic diamine compounds provided herein, $R_{11}$ is a group of the formula –L-G. In certain embodiments, the variables L and G satisfy one or more of the following conditions:

(a) G is $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl or $C_2$-$C_6$alkynyl; each of which is substituted with from 0 to 5 substituents independently chosen from:

(i) oxo, halogen, hydroxy, amino, cyano, nitro, aminocarbonyl, aminosulfonyl, -COOH, -NH(C=O)H, -(C=N)OH and imino;

(ii) $C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_8$alkyl)amino$C_0$-$C_6$alkyl, $C_1$-$C_6$alkylsulfonyl, $C_1$-$C_6$alkylthio, mono- or di-($C_1$-$C_6$alkyl)aminosulfonyl, $C_1$-$C_6$alkoxycarbonyl, $C_2$-$C_6$alkanoylamino, mono- and di-($C_1$-$C_6$alkyl)aminocarbonyl and $C_1$-$C_6$alkyloxime, each of which is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo,

($C_1$-$C_4$alkoxy)$C_0$-$C_4$alkyl, mono- and di-($C_1$-$C_4$alkyl)amino, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy; and

(iii) (carbocycle)$C_0$-$C_6$alkyl, (heterocycle)$C_0$-$C_6$alkyl, (carbocycle)$C_0$-$C_6$alkoxy, (heterocycle)$C_0$-$C_6$alkoxy, (carbocycle)$C_0$-$C_6$alkylamino and (heterocycle)$C_0$-$C_6$alkylamino, wherein the carbocycle is phenyl, naphthyl or $C_3$-$C_7$cycloalkyl, 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 is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

(b) L is O.

(c) G is $C_1$-$C_6$alkyl or amino$C_1$-$C_6$alkyl, each of which is substituted with from 0 to 5 substituents independently chosen from:

(i) oxo, hydroxy, amino, halogen, cyano, aminocarbonyl, -COOH and -NH(C=O)H;

(ii) $C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino, $C_1$-$C_6$alkylsulfonyl, $C_1$-$C_6$alkylthio, mono- or di-($C_1$-$C_6$alkyl)aminosulfonyl, $C_1$-$C_6$alkoxycarbonyl and $C_2$-$C_6$alkanoylamino, each of which is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_4$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy; and

(iii) phenyl, naphthyl, $C_3$-$C_7$cycloalkyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, furanyl, thienyl, oxazolyl, thiazolyl, imidiazolyl, triazolyl, pyridinyl, pyrimidinyl and pyrazinyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

(d) G is $C_1$-$C_6$alkyl substituted with at least one substituent independently chosen from

(i) oxo, hydroxy, aminocarbonyl and -NH(C=O)H; and

(ii) $C_1$-$C_4$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, $C_1$-$C_4$alkoxycarbonyl and $C_2$-$C_4$alkanoylamino, each of which is substituted with from 0 to 3 substituents independently

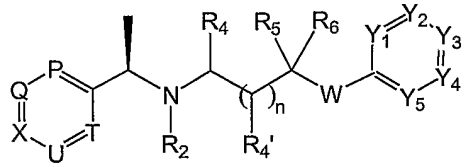
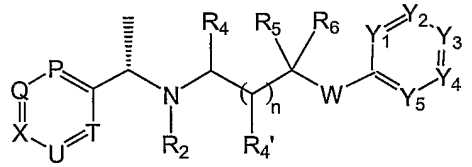
chosen from halogen, hydroxy, oxo, $C_1$-$C_2$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

(e) G is $C_1$-$C_6$alkyl substituted with at least one substituent independently chosen from:

(i) oxo, hydroxy, cyano, aminocarbonyl, -COOH and -NH(C=O)H; and

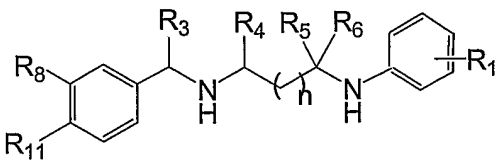
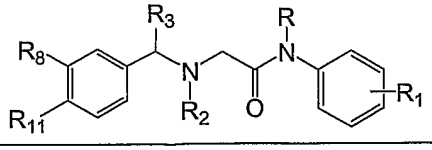
(ii) phenyl, $C_3$-$C_7$cycloalkyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, furanyl, thienyl, imidiazolyl, pyridinyl, pyrimidinyl or pyrazinyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, $C_1$-$C_2$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

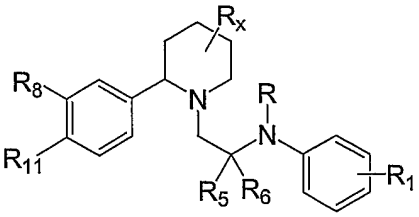
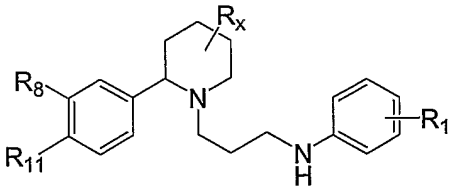
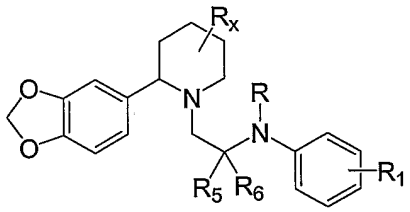
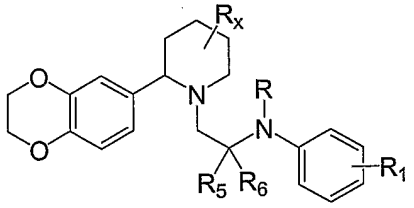
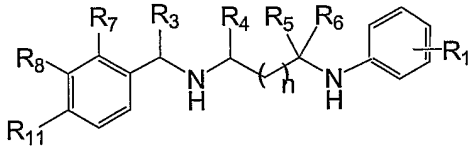
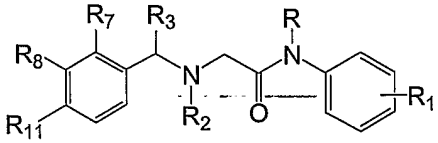
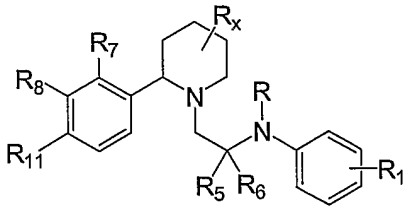
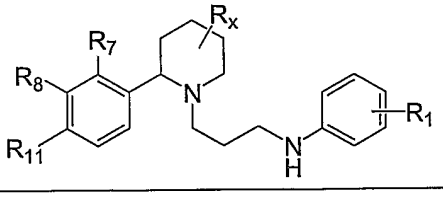
Further provided herein are heterocyclic diamine compounds of Formulas XII and XIII:

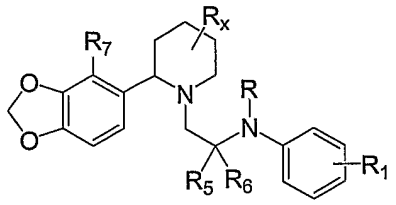
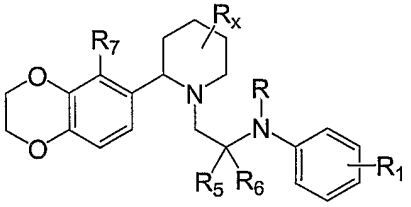
| | |
|---|---|
|  | Formula XII |
|  | Formula XIII |

wherein P, Q, X, U, T, $R_2$, $R_4$, $R_4'$, $R_5$, $R_6$, n, W, $Y_1$, $Y_2$, $Y_3$, $Y_4$ and $Y_5$ carry any of the definitions set forth herein.

Also provided herein are heterocyclic diamine compounds of Formulas XIV – Formula XXV. Within Formula XIV to XX, $R_1$ represents from 0 to 3 substituents (located *meta* or *para* to the point of attachment) independently chosen from $R_1$, above, $R_x$ represents from 0 to 2 substituents independently chosen from halogen, methyl and methoxy, and the remaining variables carry any of the values set forth above.

| | |
|---|---|
|  | Formula XIV |
|  | Formula XV |

| | |
|---|---|
|  | Formula XVI |
|  | Formula XVII |
|  | Formula XVIII |
|  | Formula XIX |
|  | Formula XX |
|  | Formula XXI |
|  | Formula XXII |
|  | Formula XXIII |

| | |
|---|---|
|  | Formula XXIV |
|  | Formula XXV |

Representative heterocyclic diamine compounds of Formulas I-XXV include, but are not limited to, those specifically described in Examples 1-4. 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 may be present as a free base, a pharmaceutically acceptable salt (such as an acid addition salt) or other form, such as a hydrate.

In certain embodiments, heterocyclic diamine compounds provided herein detectably alter (modulate) MCH binding to MCH1R and/or MCH2R, as determined using a standard *in vitro* MCH receptor ligand binding assay and/or functional assay. References herein to a "MCH receptor ligand binding assay" refer to either of the assays provided in Examples 6 and 9. 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 exhibits 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 6 and/or Example 9. Certain 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 10 and/or an agonist-stimulated GTP gamma$^{35}$S binding assay, as described in Example 8.

If desired, heterocyclic diamine compounds 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 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 compound is nontoxic when a therapeutically effective amount is administered to a subject), side effects (a preferred compound 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 compound 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 compounds used to treat CNS disorders, while low brain levels of compounds 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 in Example 12.

As noted above, preferred heterocyclic diamine compounds provided herein are nontoxic. In general, the term "nontoxic" 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 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.

As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that satisfies the criteria set forth in Example 11. In other words, cells treated as described in Example 11 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 8 or 10.

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, a 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 compounds 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, heterocyclic diamine compounds 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, such as increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

PHARMACEUTICAL COMPOSITIONS

Heterocyclic diamine compounds 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 heterocyclic diamine compounds 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-1 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, stroke, obesity and eating disorders such as bulimia, skin disorders such as vitiligo, or sexual disorders such as anorgasmic or psychogenic impotence), or for promoting weight loss. 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 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*

Heterocyclic diamine compounds 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, stroke, eating disorders (such as obesity and bulimia nervosa), disorders of the skin such as vitiligo, 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. 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, aneating disorder, a sexual disorder, diabetes, heart disease or stroke.

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 33 and/or Example 36. 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 37 and/or an agonist-stimulated GTP gamma$^{35}$S binding assay as described in Example 35. 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.

PREPARATION OF HETEROCYCLIC DIAMINE COMPOUNDS

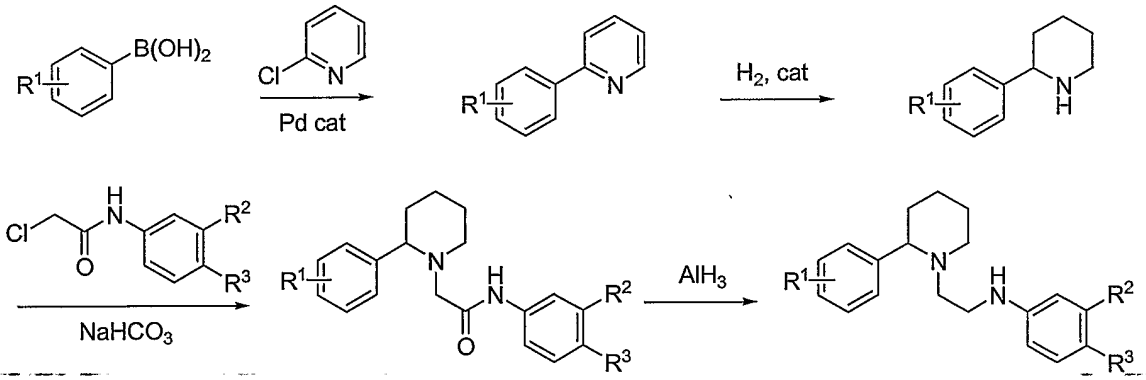
Compounds provided herein may generally be prepared using standard synthetic methods. Starting materials are generally readily available from commercial sources, such as Sigma-Aldrich Corp. (St. Louis, MO). For example, a synthetic route similar to that shown in any one of the following Schemes may be 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 1-4, herein.

In the following Schemes and elsewhere herein, the following abbreviations are used:

| | |
|---|---|
| AcOH | acetic acid |
| $BF_3$ | boron trifluoride |
| BOP | benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | dicyclohexylcarbodiimide |
| DIPE | diisopropyl ether |
| DIPEA | diisopropylethylamine |
| DMF | dimethylformamide |
| $NEt_3$ | triethylamine |
| EtOAc | ethyl acetate |
| $Et_2O$ | diethyl ether |
| EtOH | ethanol |
| LAH | lithium aluminum hydride |

| | |
|---|---|
| LDA | lithium diisopropylamide |
| MeOH | methanol |
| MTBE | methyl *t*-butyl ether |
| OAc | acetate |
| $Pd_2(dba)_3$ | tris(dibenzylideneacetone)dipalladium (0) |
| $PtO_2$ | Platinum dioxide |
| $Pd(PPh_3)_4$ | Tetrakistriphenylphosphine palladium(0) |
| PTLC | preparative thin layer chromatography |
| pyBrop | bromo-tris-pyrrolidine-phosphonium-hexafluorophosphate |
| TBDMS | *tert*-butyl-dimethyl-silyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| h | hour(s) |
| min | minute(s) |

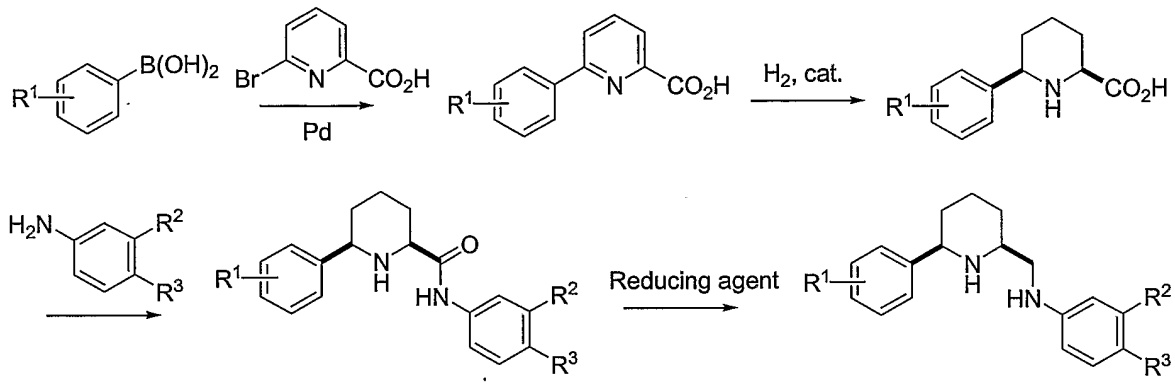
SCHEME A. SUZUKI SYNTHESIS OF 2-ARYL-N-(2-ARYLAMINO)ETHYLPIPERIDINE DERIVATIVES




Briefly, 2-chloropyridine or 2-bromopyridine is submitted to a Suzuki reaction with an arylboronic acid or arylboronic ester (*e.g.*, 3,4-dimethoxyphenylboronic acid, 2,3-dimethyl-4-methoxyphenylboronic acid, 3,4-methylenedioxyphenylboronic acid or the like) in the presence of a palladium catalyst (*e.g.*, $Pd(PPh_3)_4$, $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$ or the like) and a base (*e.g.*, $K_3PO_4$, KOH, NaOH, $K_2CO_3$, $KHCO_3$, $Li_3PO_4$, etc.) in a single solvent (*e.g.*, toluene, water, dioxane, THF, and the like) or a mixture comprising such a solvent). The resulting 2-arlypyridine is then reduced to the corresponding 2-substituted piperidine derivative by catalytic hydrogenation, for example using hydrogen gas at 55 psi in the presence of an heterogeneous catalyst (*e.g.*, $PtO_2$) in the presence of an acid (*e.g.*, HCl, $H_2SO_4$ or AcOH) and using as a solvent (*e.g.*, methanol, ethanol, ethyl acetate or the like) at a temperature between room temperature and 80°C. The piperidine derivative is then alkylated by reaction with the corresponding chloro- or bromoacetanilide, which can be obtained by

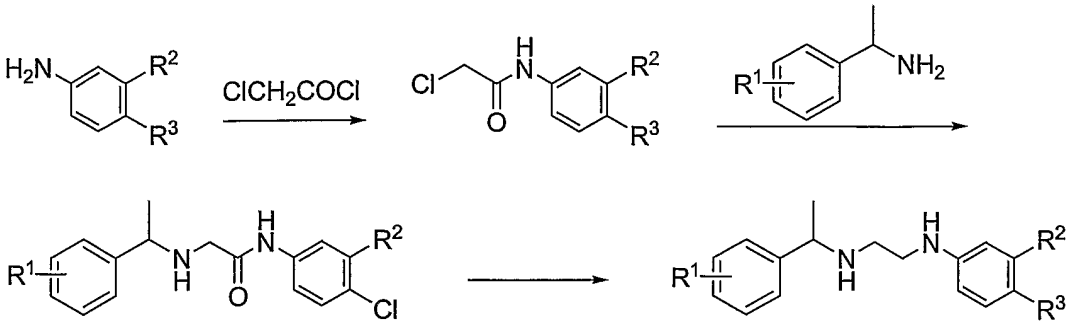
condensation reaction between chloroacetyl chloride or bromoacetyl bromide and the corresponding substituted aniline under Schotten-Baumann reaction conditions. These alkylation reactions take place at temperatures between 0°C and 120°C, more preferably between 40°C and 80°C in solvent(s) (*e.g.*, acetone, butanone, acetonitrile, THF or DMF). Finally, the amide is reduced to the desired diamine target by reaction with reducing agent (*e.g.*, alane, borane, LAH, $BF_3/NaBH_4$ or the like) in solvent(s) (*e.g.*, THF, $Et_2O$, MTBE or dibutyl ether) and at reaction temperatures between -78°C and 120°C, more preferably between room temperature and 70°C.

SCHEME B. SUZUKI SYNTHESIS OF *CIS*-2-ARYL-6-ARYLAMINOMETHYLPIPERIDINE DERIVATIVES




Briefly, 6-chloropicolinic acid or 2-bromopicolinic acid is submitted to a Suzuki reaction with an appropriately substituted arylboronic acid or arylboronic ester (*e.g.*, 3,4-dimethoxyphenylboronic acid, 2,3-dimethyl-4-methoxyphenylboronic acid, 3,4-methylenedioxyphenylboronic acid or the like) in the presence of a palladium catalyst (*e.g.*, $Pd(PPh_3)_4$, $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$ or the like) and a base (*e.g.*, $K_3PO_4$, KOH, NaOH, $K_2CO_3$, $KHCO_3$, $Li_3PO_4$, etc.) in a single solvent (*e.g.*, toluene, water, dioxane, THF or the like) or a mixture of such solvents. The resulting 2-arlypicolinic acid is then reduced to the corresponding *cis*-2,6-disubstituted piperidine derivative by catalytic hydrogenation (*e.g.*, using hydrogen gas at 55 psi in the presence of an heterogeneous catalyst such as, but not limited to, $PtO_2$) in the presence of an acid (*e.g.*, HCl, $H_2SO_4$ or AcOH) and using as a solvent (*e.g.*, methanol, ethanol, ethyl acetate or the like) at a temperature between room temperature and 80°C. The arylpiperidine carboxylic acid derivative is then transformed to the appropriate anilide by reaction with the corresponding aniline in the presence of a condensing agent (*e.g.*, DCC, BOP or pyBrop) in a solvent (*e.g.*, $CH_2Cl_2$, $CHCl_3$, THF, acetonitrile or the like) at a temperature between -78°C and 100°C, more preferably between 0°C and 50°C, in the presence of a base such as $NEt_3$, DIPEA, Py or the like, in amounts between 0 and 2 equivalents. Finally, the amide is reduced to the target diamine by reaction with reducing agents (*e.g.*, alane, borane, LAH, $BF_3/NaBH_4$ or the like) in solvent(s) (*e.g.*, THF, $Et_2O$, MTBE or dibutyl ether) and at reaction temperatures between -78°C and 120°C, more preferably between room temperature and 70°C.

SCHEME C. SYNTHESIS OF N-BENZYL-N'-ARYL-ETHYLENEDIAMINES




Briefly, an appropriately substituted aniline is obtained by condensation reaction between chloroacetyl chloride or bromoacetyl bromide and the corresponding substituted aniline under Schotten-Baumann reaction conditions. The chloroacetanilide is then reacted with appropriately substituted benzylamine or 1-aryl-ethylamine. These alkylation reactions take place at temperatures between 0°C and 120°C, more preferably between 40°C and 80°C, in solvent (*e.g.*, acetone, butanone, acetonitrile, THF or DMF) to furnish the desired N-benzyl acetanilide. For chiral 1-(aryl)-ethylamines, an optically pure form can be obtained by resolution of the racemic amine using chiral resolving agents (*e.g.*, (R)-mandelic acid, essentially as reported by Koju Hagitani, Sumitomo Chem. Co. Ltd. (1997), JP 09278718 A). Finally, the amide is reduced to the target diamine by reaction with reducing agent (*e.g.*, alane, borane, LAH, $BF_3/NaBH_4$ or the like) in solvent (*e.g.*, THF, $Et_2O$, MTBE or dibutyl ether) and at a reaction temperature between -78°C and 120°C, more preferably between room temperature and 70°C.

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

Compounds may be labeled by carrying out their synthesis using precursors comprising at least one atom that is an isotope. Each isotope is preferably carbon (*e.g.*, $^{14}C$), hydrogen (*e.g.*, $^{3}H$ or $^{2}H$), fluorine (*e.g.*, $^{18}F$), 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 exchange with tritium gas under heterogeneous catalysis 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.

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.

## EXAMPLES

Mass spectra (MS) reported in the following Examples are collected using electrospray MS, obtained in positive ion mode using a Waters ZMD II Mass Spectrometer. MS conditions are as follows:

Capillary voltage: 3.5 kV

Cone voltage: 30 V

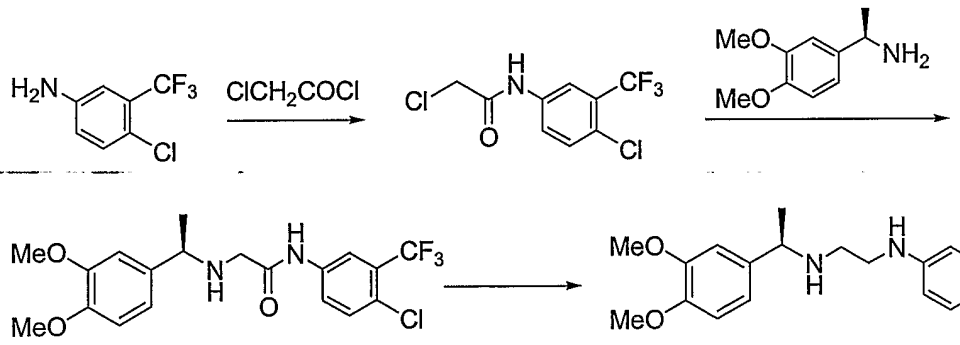
Desolvation and source temperature: 250°C and 120°C respectively

Mass range: 100-750

Scan time: 0.5 second

Inter scan delay: 0.1 minute

### EXAMPLE 1. SYNTHESIS OF N-(4-CHLORO-3-TRIFLUOROMETHYLPHENYL)-N'-[(R)-1-(3,4-DIMETHOXYPHENYL)-ETHYL]-ETHANE-1,2-DIAMINE (Compound 2)




*Step 1. 2-chloro-N-(4-chloro-3-trifluoromethylphenyl)-acetamide*

Chloroacetylchloride (1.1 g, 10 mmol) is added dropwise to a mixture of 4-chloro-3-trifluoromethylaniline (1.96 g, 10 mmol), ethyl ether (30 mL), and $NaHCO_3$ (saturated solution, 30 mL) at room temperature and under vigorous stirring. After 1 h at room temperature the layers are separated, the organic layer is washed with $NaHCO_3$ (saturated solution, 2 x 30 mL), brine (2 x 30 mL), aqueous HCl (1M, 30 mL), and brine (2 x 30 mL), and then dried ($MgSO_4$). The solvent is removed under reduced pressure to produce the title compound as a solid. LC/MS: 271(M+1).

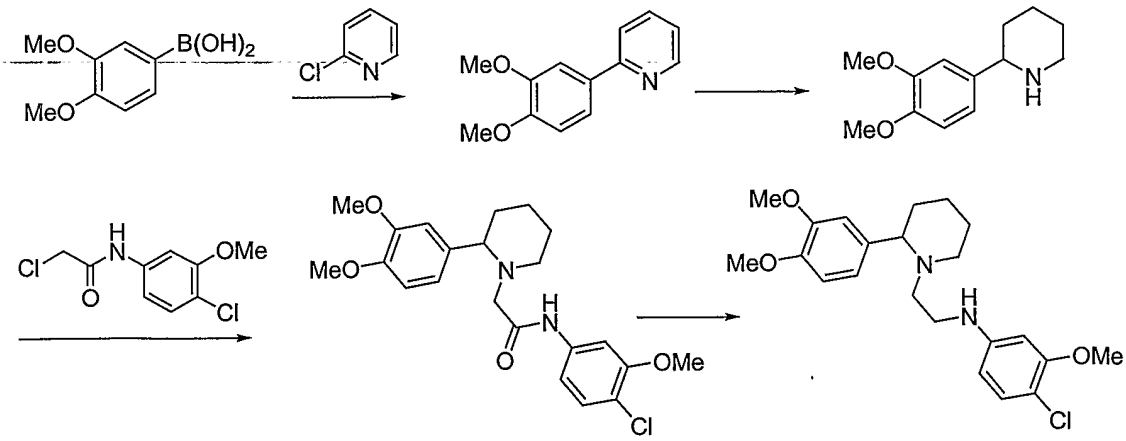
*Step 2. N-(4-chloro-3-trifluoromethylphenyl)-2-[(R)-1-(3,4-dimethoxyphenyl)-ethylamino]-acetamide*

A mixture of (R)-1-(3,4-dimethoxyphenyl)-ethylamine (1.5 g, 8.1 mmol, obtained by resolution of the racemic amine with (R)-mandelic acid), 2-chloro-N-(4-chloro-3-trifluoromethylphenyl)-acetamide (2.1g, 7.7 mmol) and triethylamine (3.4 mL, 24 mmol) in toluene (30 mL) is heated at 90°C (oil bath temperature) for 3 h. After cooling to room temperature the mixture is poured into water (200 mL) and partitioned into 100 mL of ethyl acetate. The organic layer is dried with $MgSO_4$ and filtered and the solvent removed under reduced pressure. Flash chromatography on silicagel eluting with 5% methanol in ethyl acetate furnishes the title compound as a dry foam. LC/MS: 417 (M+1).

*Step 3. N-(4-chloro-3-trifluoromethylphenyl)-N'-[(R)-1-(3,4-dimethoxyphenyl)-ethyl]-ethane-1,2-diamine*

A solution of the compound obtained in step 2 (1.5 g, 3.6 mmol) in dry toluene (30 mL) is treated dropwise with a solution of $AlH_3$ (0.5 N in toluene, 14.4 mL, 7.2 mmol) under an atmosphere of nitrogen (balloon). The solution is stirred at room temperature for 3 h. The reaction is quenched by slow addition of excess $Na_2CO_3.10H_2O$ and filtered through a celite pad, washing with EtOAc. The title compound is obtained as an oil. H-1 NMR: 7.20 (m, 1H); 7.80 (m, 4H); 6.60 (d, 1H); 3.84 (s, 3H); 3,82 (s, 3H); 3.70 (q, 1H); 3.10 (br, 2H); 2.60-2.80 (m, 2H); 1.40 (d, 3H). LC/MS: 403 (M+1).

EXAMPLE 2. SYNTHESIS OF (4-CHLORO-3-METHOXYPHENYL)-{2-[2-(3,4-DIMETHOXYPHENYL)-PIPERIDIN-1-YL]-ETHYL}-AMINE




*Step 1. 2-(3,4-Dimethoxyphenyl)-pyridine*

A mixture of 2-chloropyridine (2.6 g, 22.9 mmol), 3,4-dimethoxyphenylboronic acid (4.0 g, 22.0 mmol), toluene (100 mL), $NaHCO_3$ (saturated solution in water, 30 mL) and $Pd(PPh_3)_4$ (100 mg,

86 μmol) is heated in a pressure tube at 90°C (oil bath temperature) for 16 h. The reaction mixture is cooled down to room temperature and the aqueous layer separated. The organic layer is washed with aqueous NaOH (1 M, 50 mL) and brine (3 x 50 mL). The solution is dried with $MgSO_4$ and the solvent evaporated under reduced pressure to produce the crude product as an oil. Purification is carried out by flash chromatography using silicagel and eluting with 50% ethyl ether in hexanes. The desired compound is obtained as a clear oil. H-1 NMR: 3.94 (s, 3H); 4.00 (s, 3H); 7.19 (m, 1H); 7.51 (dd, 1H); 7.60-7.75 (m, 3H); 8.66 (m, 1H). LC/MS: 216 (M+1).

*Step 2. 2-(3,4-Dimethoxyphenyl)-piperidine*

The product from step 1 is dissolved in a mixture of MeOH (50 mL) and concentrated aqueous HCl (2 mL) and hydrogenated at 60 psi in the presence of $PtO_2$ (10%/C, 250 mg) for 16 h. The catalyst is filtered off through a pad of celite, the product is washed with MeOH/EtOAc and the solvent is removed under reduced pressure to afford the title product (HCl salt) as a yellow solid. H-1 NMR (dmso-$d_6$): 1.60-2.00 (m, 6H); 2.98 (dd, 1H); 3.25 (br, 1H); 3.73 (s, 3H); 3.77 (s, 3H); 4.1 (t, 1H); 6.90-7.00 (m, 2H); 7.32 (s, 1H); 9.05 (br, 1H); 9.40 (br, 1H).

*Step 3. 2-Chloro-N-(4-chloro-3-methoxyphenyl)-acetamide*

Chloroacetyl chloride (10 mmol) is added dropwise to a mixture of 4-chloro-3-methoxyaniline (1.57 g, 10 mmol), ethyl ether (30 mL) and $NaHCO_3$ (saturated solution, 30 mL) at room temperature and under vigorous stirring. After 1 h at room temperature the layers are separated, the organic layer is washed with $NaHCO_3$ (saturated solution, 2 x 30 mL), brine (2 x 30 mL), aqueous HCl (1M, 30 mL), and brine (2 x 30 mL), and dried ($MgSO_4$). The solvent is removed under reduced pressure to produce the title compound as an off-white solid. H-1 NMR: 3.91 (s, 3H); 4.18 (s, 2H); 6.90 (dd, 1H); 7.30 (d, 1H); 7.46 (d, 1H); 8.22 (broad, 1H).

*Step 4. N-(4-Chloro-3-methoxyphenyl)-2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-acetamide*

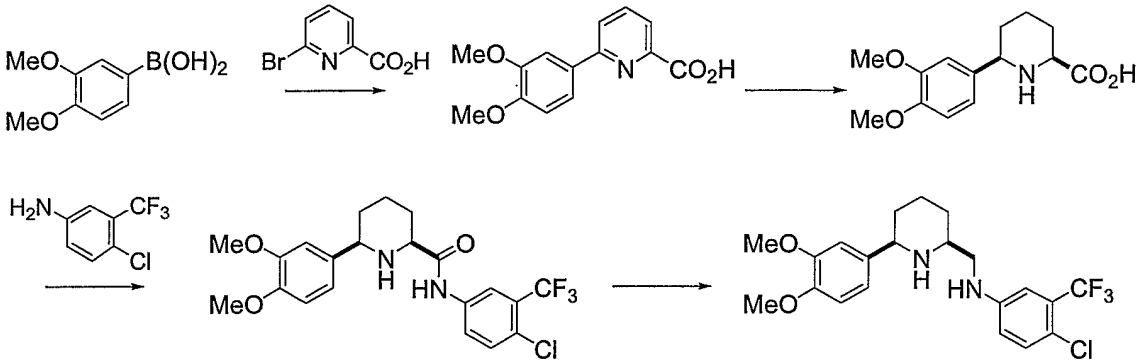
A mixture of 2-chloro-N-(4-chloro-3-methoxyphenyl)-acetamide (from step 3, 234 mg, 1.0 mmol), 2-(3,4-dimethoxyphenyl)-piperidine hydrochloride (from step 2, 258 mg, 1.0 mmol) and $K_2CO_3$ (207 mg, 1.5 mmol) in acetonitrile (6 mL) is heated at 90°C (oil bath temperature) for 16 h. The solvent is evaporated at reduced pressure and the desired product is obtained as a white solid after flash chromatography on silicagel eluting with 50% EtOAc in hexanes. H-1 NMR: 1.4-1.9 (br, 6H); 2.3 (dt, 1H); 2.62 (d, 1H); 3.06 (d, 1H); 3.22 (dd, 1H); 3.29 (d, 1H); 3.77 (s, 3H); 3.83 (s, 3H); 3.89 (s, 3H); 6.7-6.85 (m, 5H); 7.25 (d, 1H); 7.65 (d, 1H) 9.32 (broad, 1H). LC/MS: 419 (M+1).

*Step 5. (4-Chloro-3-methoxyphenyl)-{2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine*

A solution of the compound obtained in step 4 (42 mg, 0.1 mmol) in dry toluene (3 mL) is treated dropwise with a solution of $AlH_3$ (0.5 N in toluene, 1 mL, 0.5 mmol) under an atmosphere of

nitrogen (balloon). The solution is stirred at room temperature for 16 h. The reaction is quenched by slow addition of aqueous NaOH (1M, 1 mL) and partitioned between ethyl ether (30 mL) and brine (30 mL). The organic layer is dried with $MgSO_4$ and the solvent removed under reduced pressure. The title compound is obtained as an oil after purification by PTLC, eluting with 50% EtOAc in hexanes. H-1 NMR: 1.60-2.15 (m, 6H); 2.70-3.20 (m, 6H); (3.82 (s, 3H); 3.85 (s, 3H); 3.88 (s, 3H); 4.10 (br, 1H); 6.00-6.10 (m, 2H); 6.74-6.85 (m, 2H); 6.89 (d, 1H); 7.05 (d, 1H). LC/MS: 405 (M+1).

EXAMPLE 3. (4-CHLORO-3-TRIFLUOROMETHYLPHENYL)-[6-(3,4-DIMETHOXYPHENYL)-PIPERIDIN-2-YLMETHYL]-AMINE



*Step 1. Cis-6-(3,4-dimethoxyphenyl)-pyridine-2-carboxylic acid*

A mixture of 6-bromopicolinic acid (2.02 g, 10 mmol), 3,4-dimethoxyphenylboronic acid (1.8 g, 10.0 mmol), toluene (50 mL), $NaHCO_3$ (saturated solution in water, 10 mL) and $Pd(PPh_3)_4$ (50 mg, 43 μmol) is heated in a pressure tube at 90°C (oil bath temperature) for 16 h. The reaction mixture is cooled to room temperature and the aqueous layer separated. The organic layer is washed with $NaHCO_3$ (saturated solution, 25 mL) and brine (3 x 50 mL). The solution is dried with $MgSO_4$ and the solvent evaporated under reduced pressure to produce the crude title compound. LC/MS: 260 (M+1).

*Step 2. Cis- 6-(3,4-dimethoxyphenyl)-piperidine-2-carboxylic acid*

The product from step 1 is dissolved in MeOH (50 mL) and concentrated aqueous HCl (2 mL) and hydrogenated at 60 psi in the presence of $PtO_2$ (10%/C, 250 mg) for 16 h. The catalyst is filtered off through a pad of celite and the solvent removed under reduce pressure to afford the title product (HCl salt) as a yellow solid. LC/MS: 266 (M+1).

*Step 3. Cis-6-(3,4-dimethoxyphenyl)-piperidine-2-carboxylic acid (4-chloro-3-trifluoromethylphenyl)-amide*

The piperidine-carboxylic acid hydrochloride salt obtained in step 2 (157 mg, 0.52 mmol), 4-chloro-3-trifluoromethylaniline (105 mg, 0.52 mmol) and BOP (460 mg, 1.04 mmol) are dissolved in

N,N-dimethylacetamide (5 mL) at 50°C (oil bath temperature) under an atmosphere of dry nitrogen (balloon). The reaction mixture is stirred overnight and the PTLC (50% EtOAc in hexanes) affords the title compound as an orange oil. H-1 NMR: 8.83 (s, 1H); 7.88 (s, 1H); 7.80 (d, 1H); 7.42 (d, 1H); 6.82-7.00 (m, 3H); 3.96 (s, 3H); 3.92 (s, 3H); 3.66 (d, 1H); 3.58 (d, 1H); 1.60-1.90 (m, 6H). LC/MS: 443 (M+1).

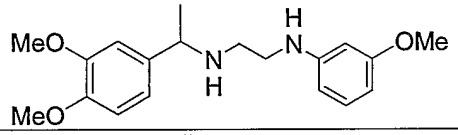
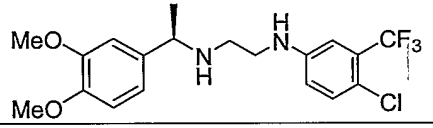
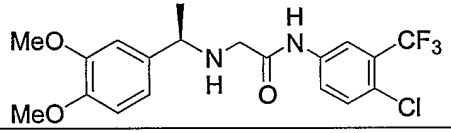
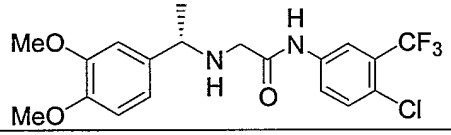
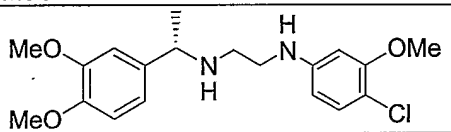
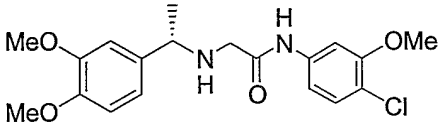
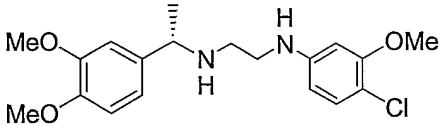
*Step 4. (4-Chloro-3-trifluoromethylphenyl)-[6-(3,4-dimethoxyphenyl)-piperidin-2-ylmethyl]-amine*

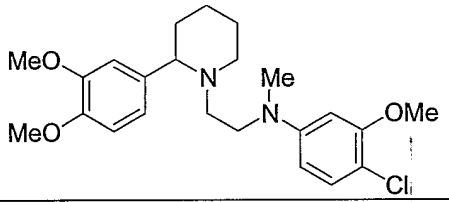
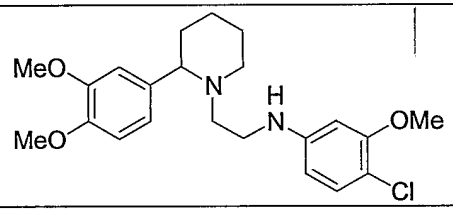
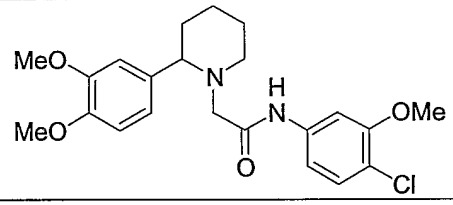
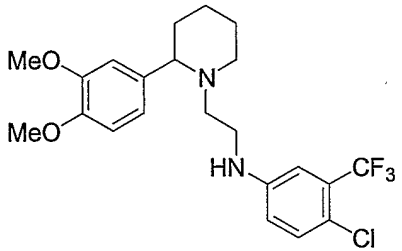
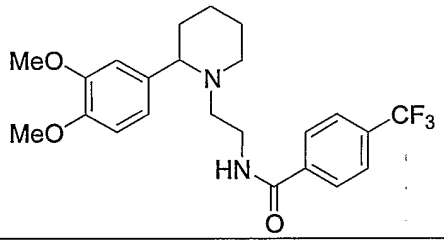
The amide obtained in step 3 (30 mg, 0.068 mmol) is dissolved in anhydrous THF (3 mL) under a nitrogen atmosphere (balloon). $AlH_3$ (0.5 N, 1 mL) is added dropwise. The solution is stirred at room temperature for 16 h. The reaction is quenched by slow addition of aqueous NaOH (1M, 1 mL) and partitioned between ethyl ether (10 mL) and brine (10 mL). The organic layer is dried with $MgSO_4$ and the solvent removed under reduced pressure. The title compound is obtained as an oil after purification by PTLC, eluting with 50% EtOAc in hexanes. H-1 NMR: 7.22 (d, 1H); 6.90-6.96 (m, 3H); 6.82 (d, 1H); 6.64 (d, 1H); 4.26 (br, 1H); 3.90 (s, 3H); 3,84 (s, 3H); 3.60 (d, 1H); 2.90-3.20 (m, 3H); 1.20-2.00 (m, 6H). LC/MS: 429 (M+1).

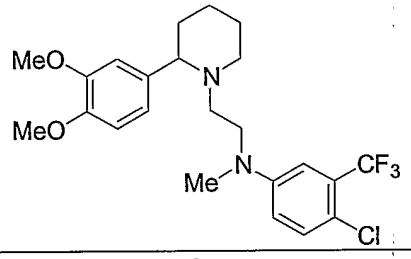
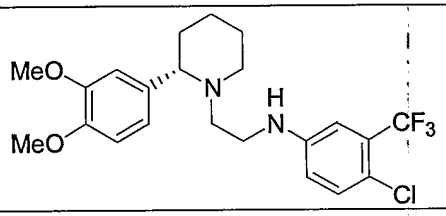
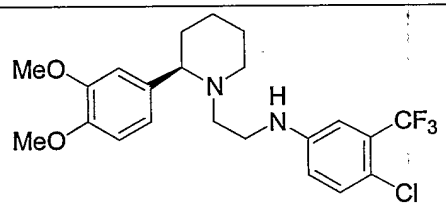
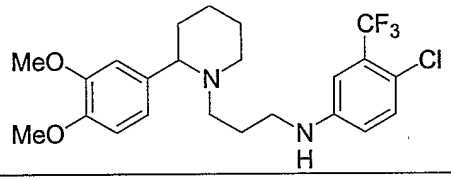
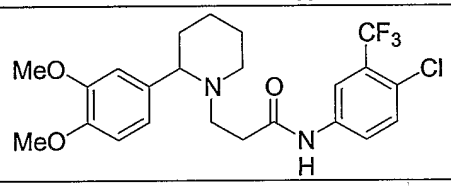
EXAMPLE 4. ADDITIONAL HETEROCYCLIC DIAMINE COMPOUNDS

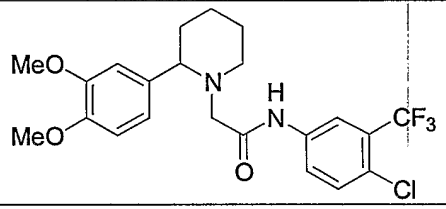
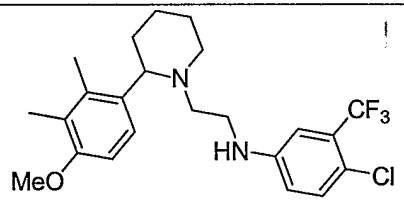
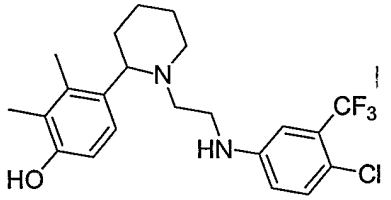
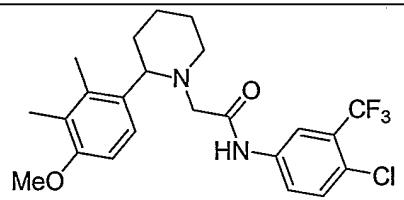
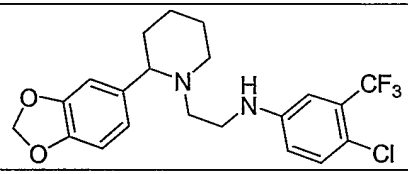
The following compounds are synthesized according to the methods given in Examples 1-3. In Table I, an asterisk "*" in the column labeled "$K_i$" indicates that the compound exhibits a $K_i$ of less than 1 micromolar in the calcium mobilization assay of Example 10. Mass spectroscopy data in the "LC/MS" column is obtained as described above and presented as (M+1).

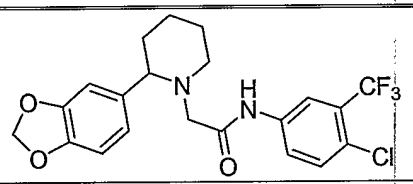
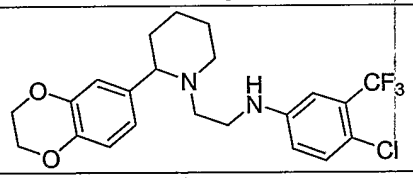
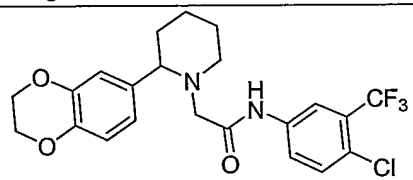
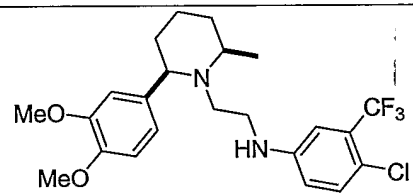
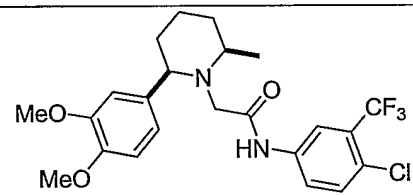
TABLE I

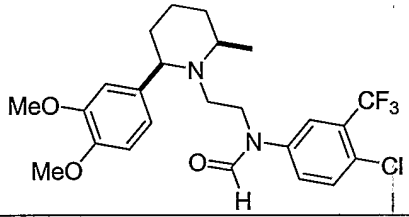
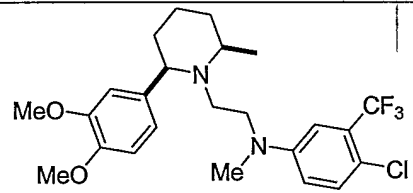
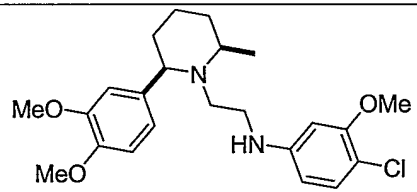
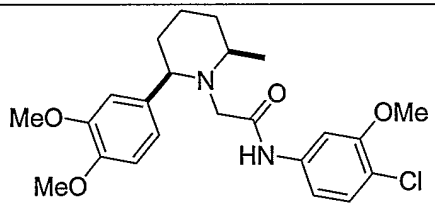
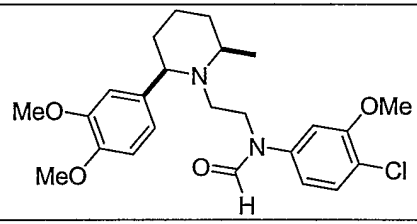
| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 1.  | N-[1-(3,4-Dimethoxyphenyl)-ethyl]-N'-(3-methoxyphenyl)-ethane-1,2-diamine | | 345 | |
| 2.  | N-(4-Chloro-3-trifluoromethylphenyl)-N'-[(R)-1-(3,4-dimethoxyphenyl)-ethyl]-ethane-1,2-diamine | 7.20 (m, 1H); 7.80 (m, 4H); 6.60 (d, 1H); 3.84 (s, 3H); 3.82 (s, 3H); 3.70 (q, 1H); 3.10 (br, 2H); 2.60-2.80 (m, 2H); 1.40 (d, 3H). | 403 | * |
| 3.  | N-(4-Chloro-3-trifluoromethylphenyl)-2-[(*R*)-1-(3,4-dimethoxyphenyl)-ethylamino]-acetamide | 9.39 (br, 1H); 7.78 (m, 2H); 7.40 (d, 1H); 6.80 (m, 3H); 3.84 (s, 3H); 3.82 (s, 3H); 3.78 (q, 1H); 3.30 (dd, 2H); 2.05 (s, 1H); 1.4 (d, 3H). | 417 | * |
| 4.  | N-(4-Chloro-3-trifluoromethylphenyl)-2-[(*S*)-1-(3,4-dimethoxyphenyl)-ethylamino]-acetamide | | 417 | |
| 5.  | N-(4-Chloro-3-methoxyphenyl)-N'-[(*R*)-1-(3,4-dimethoxyphenyl)-ethyl]-ethane-1,2-diamine | 7.09 (d, 1H); 6.80-6.90 (m, 3H); 6.18 (s, 1H); 6.22 (d, 1H); 3.95 (s, 3H); 3.94 (s, 3H); 3.92 (s, 3H); 3.73 (q, 1H); 3.16 (br, 2H); 2.60-2.80 (m, 2H); 1.60 (br, 2H); 1.38 (d, 1H). | 365 | * |
| 6.  | N-(4-Chloro-3-methoxyphenyl)-2-[(*R*)-1-(3,4-dimethoxyphenyl)-ethylamino]-acetamide | | 379 | |
| 7.  | N-(4-Chloro-3-methoxyphenyl)-N'-[(*S*)-1-(3,4-dimethoxyphenyl)-ethyl]-ethane-1,2-diamine | | 365 | |

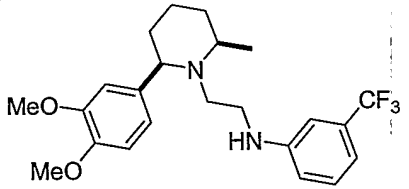
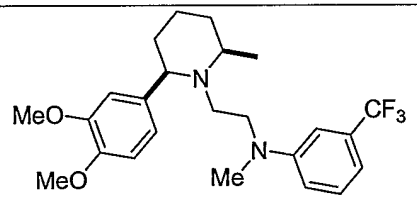
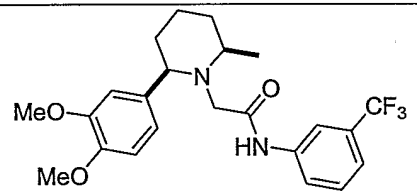
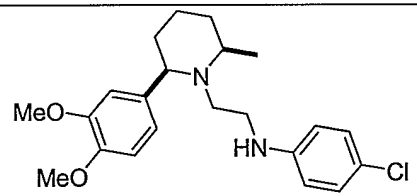
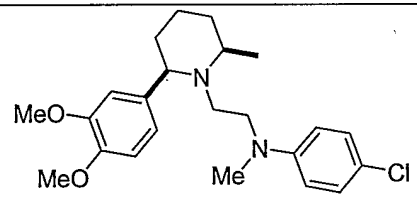
| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 8.  | (4-Chloro-3-methoxyphenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-methyl-amine | | 419 | |
| 9.  | (4-Chloro-3-methoxyphenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine | | 405 | |
| 10.  | N-(4-Chloro-3-methoxyphenyl)-2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-acetamide | | 419 | |
| 11.  | (4-Chloro-3-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine | 7.20 (d, 1H); 6.78-6.90 (m, 4H); 6.50 (d, 1H); 4.38 (br, 1H); 3.85 (s, 3H); 3.83 (s, 3H); 2.70-3.20 (m, 6H); 2.00-2.08 (m, 2H); 1.60-1.80 (5H); 1.40 (m, 1H). | 443 | * |
| 12.  | N-{2-[2-(3,4-Dimethoxyphenyl)-piperidin-1-yl]-ethyl}-4-trifluoromethyl-benzamide | | 437 | |

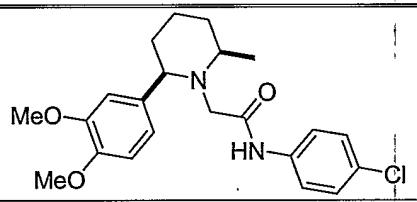
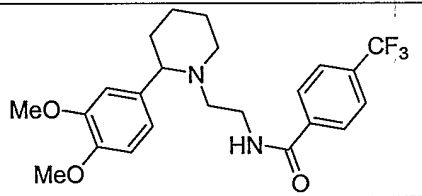
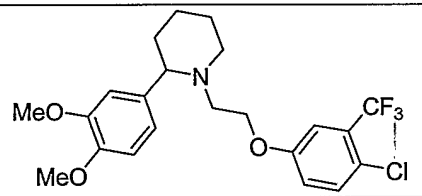
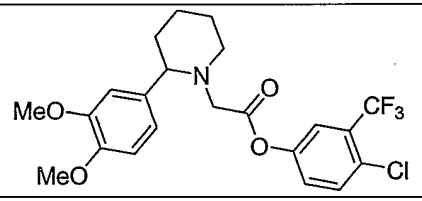
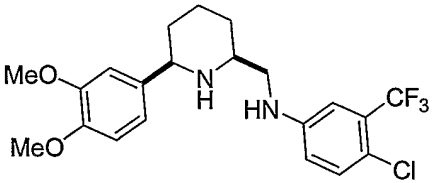
| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 13.  | (4-Chloro-3-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-methyl-amine | | 457 | |
| 14.  | Postulated absolute stereochemistry (4-Chloro-3-trifluoromethylphenyl)-{2-[(*S*)-2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine | | 443 | * |
| 15.  | Postulated absolute stereochemistry (4-Chloro-3-trifluoromethylphenyl)-{2-[(*R*)-2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine | 7.20 (d, 1H); 6.78-6.90 (m, 4H); 6.50 (d, 1H); 4.38 (br, 1H); 3.85 (s, 3H); 3.83 (s, 3H); 2.70-3.20 (m, 6H); 2.00-2.08 (m, 2H); 1.60-1.80 (5H); 1.40 (m, 1H). | 443 | * |
| 16.  | (4-Chloro-3-trifluoromethylphenyl)-{3-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-propyl}-amine | 7.20 (d, 1H); 6.78 (m, 4H); 6.57 (d, 1H); 5.4 (br, 1H); 3.82 (s, 6H); 3.61 (s, 3H); 3.34 (d, 1H); 3.13 (m, 1H); 2.95 (m, 2H); 2.60 (m, 1H); 1.40-2.00 (m, 6H) | 457 | * |
| 17.  | N-(4-Chloro-3-trifluoromethylphenyl)-3-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-propionamide | 11.78 (br, 1H); 7.95 (s, 1H); 7.82 (d, 1H); 7.43 (d, 1H); 6.78 (s, 2H); 6.64 (s, 1H); 3.81 (s, 6H); 3.46 (s, 2H); 3.39 (d, 1H); 3.05 (d, 1H); 2.96 (t, 1H); 2.64 (dt, 1H); 1.50-2.10 (m, 8H) | 471 | * |

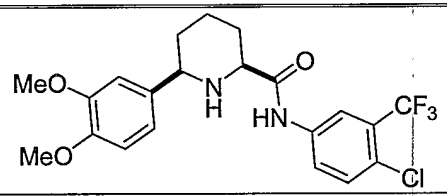
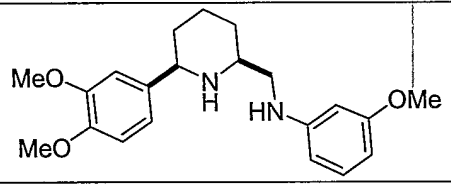
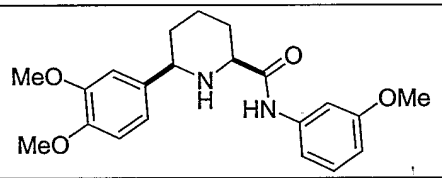
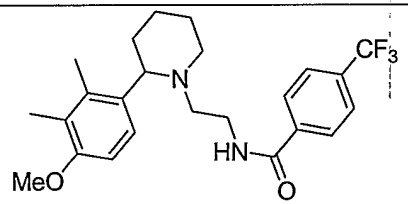
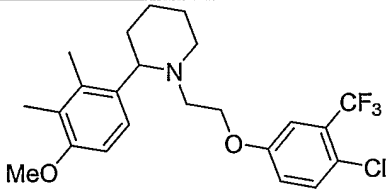
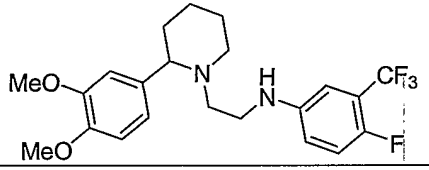
| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 18.  | N-(4-Chloro-3-trifluoromethylphenyl)-2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-acetamide | | 457 | |
| 19.  | (4-Chloro-3-trifluoromethylphenyl)-{2-[2-(4-methoxy-2,3-dimethylphenyl)-piperidin-1-yl]-ethyl}-amine | 7.22 (br, 1H); 7.18 (d, 1H); 6.79 (s, 1H); 6.64 (d, 1H); 6.50 (d, 1H); 4.38 (br, 1H); 3.79 (s, 3H); 3.38 (d, 1H); 3.18 (d, 1H); 3.05 (m, 1H); 2.88 (m, 1H); 2.78 (m, 1H); 2.24 (br, 3H); 2.18 (s, 3H); 2.0 (m, 2H); 1.40-1.80 (m, 5H). | 441 | * |
| 20.  | 4-{1-[2-(4-Chloro-3-trifluoromethyl-phenylamino)-ethyl]-piperidin-2-yl}-2,3-dimethyl-phenol | | 427 | * |
| 21.  | N-(4-Chloro-3-trifluoromethylphenyl)-2-[2-(4-methoxy-2,3-dimethylphenyl)-piperidin-1-yl]-acetamide | 9.38 (br, 1H); 7.82 (1H); 7.79 (d, 1H); 7.41 (d, 1H); 7.20 (d, 1H); 6.68 (d, 1H); 3.77 (s, 3H); 3.60 (d, 1H); 3.23 (d, 1H); 3.08 (d, 1H); 2.62 (d, 1H); 2.38 (t, 1H); 2.28 (s, 3H); 2.16 (s, 3H); 1.40-1.90 (m, 6H). | 455 | * |
| 22.  | [2-(2-Benzo[1,3]dioxol-5-yl-piperidin-1-yl)-ethyl]-(4-chloro-3-trifluoromethylphenyl)-amine | | 427 | * |

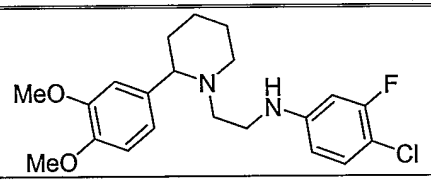
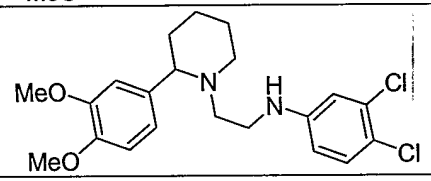
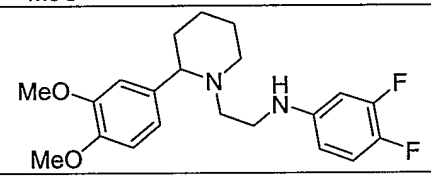
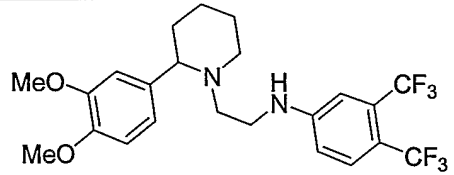
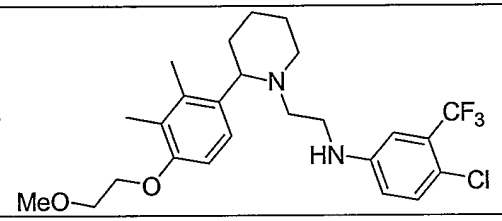
| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 23.  | 2-(2-Benzo[1,3]dioxol-5-yl-piperidin-1-yl)-N-(4-chloro-3-trifluoromethylphenyl)-acetamide | | 441 | |
| 24.  | (4-Chloro-3-trifluoromethylphenyl)-{2-[2-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-piperidin-1-yl]-ethyl}-amine | | 441 | * |
| 25.  | N-(4-Chloro-3-trifluoromethylphenyl)-2-[2-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-piperidin-1-yl]-acetamide | | 455 | |
| 26.  | (4-Chloro-3-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-ethyl}-amine | 7.08 (d, 1H); 6.92 (s, 1H); 6.80 (m, 2H); 6.62 (s, 1H); 6.19 (d, 1H); 3.95 (s, 3H); 3.93 (s, 3H); 3.78 (br, 1H); 3.46 (s, 2H); 3.26 (d, 1H); 2.40-3.00 (m, 5H); 1.30-1.90 (m, 6H); 1.20 (d, 3H). | 457 | * |
| 27.  | N-(4-Chloro-3-trifluoromethylphenyl)-2-[2-(3,4-dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-acetamide | | 471 | |

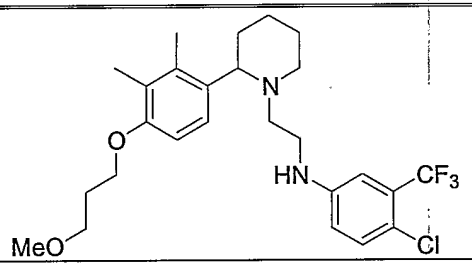
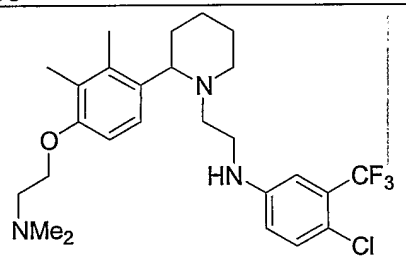
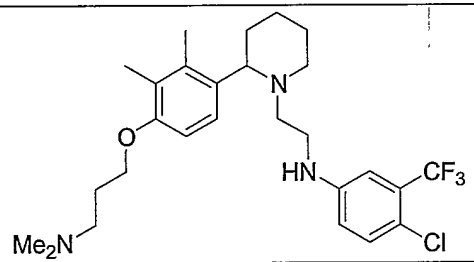
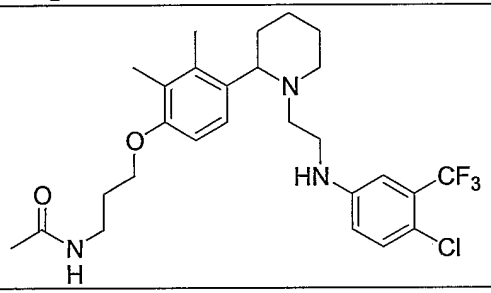
| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 28.  | N-(4-Chloro-3-trifluoromethylphenyl)-N-{2-[2-(3,4-dimethoxyphenyl)-6-methyl-piperidin-1-yl]-ethyl}-formamide | | 485 | |
| 29.  | (4-Chloro-3-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxyphenyl)-6-methyl-piperidin-1-yl]-ethyl}-methyl-amine | | 471 | |
| 30.  | (4-Chloro-3-methoxyphenyl)-{2-[2-(3,4-dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-ethyl}-amine | | 419 | |
| 31.  | N-(4-Chloro-3-methoxyphenyl)-2-[2-(3,4-dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-acetamide | | 433 | |
| 32.  | N-(4-Chloro-3-methoxyphenyl)-N-{2-[2-(3,4-dimethoxyphenyl)-6-methyl-piperidin-1-yl]-ethyl}-formamide | | 447 | |

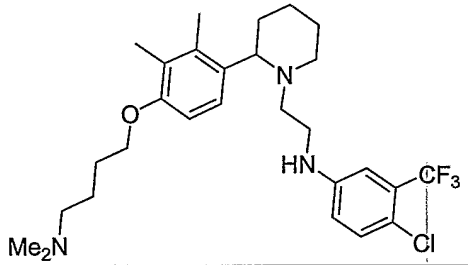
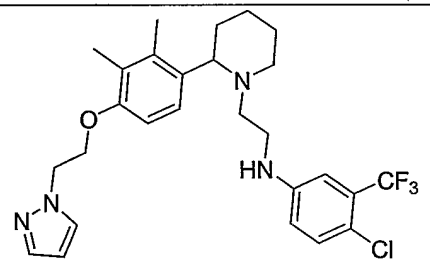
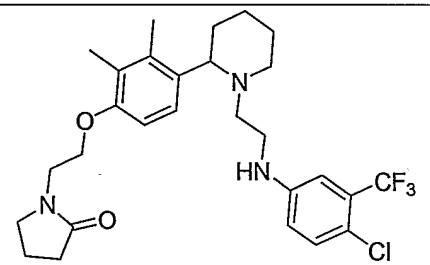
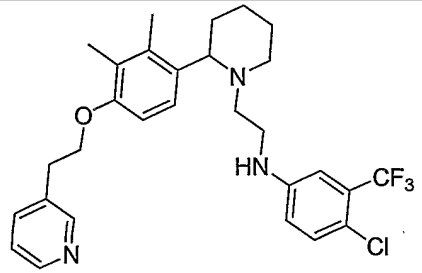
| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 33.  | {2-[2-(3,4-Dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-ethyl}-(3-trifluoromethylphenyl)-amine | | 423 | |
| 34.  | {2-[2-(3,4-Dimethoxyphenyl)-6-methyl-piperidin-1-yl]-ethyl}-methyl-(3-trifluoromethylphenyl)-amine | | 437 | |
| 35.  | 2-[2-(3,4-Dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-N-(3-trifluoromethylphenyl)-acetamide | | 437 | |
| 36.  | {2-[2-(3,4-Dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-ethyl}-(4-chlorophenyl)-amine | | 389 | |
| 37.  | (4-Chlorophenyl)-{2-[2-(3,4-dimethoxyphenyl)-6-methyl-iperidin-1-yl]-ethyl}-methyl-amine | | 403 | |

| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 38.  | 2-[2-(3,4-Dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-N-(4-chlorophenyl)-acetamide | | 403 | |
| 39.  | N-{2-[2-(3,4-Dimethoxyphenyl)-piperidin-1-yl]-ethyl}-4-trifluoromethyl-benzamide | | 437 | |
| 40.  | 1-[2-(4-Chloro-3-trifluoromethyl-phenoxy)-ethyl]-2-(3,4-dimethoxy-phenyl)-piperidine | | 444 | * |
| 41.  | [2-(3,4-Dimethoxy-phenyl)-piperidin-1-yl]-acetic acid 4-chloro-3-trifluoromethylphenyl ester | | 458 | |
| 42.  | (4-Chloro-3-trifluoromethylphenyl)-[6-(3,4-dimethoxyphenyl)-piperidin-2-ylmethyl]-amine | | 429 | * |

| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 43.  | 6-(3,4-Dimethoxyphenyl)-piperidine-2-*cis*-carboxylic acid (4-chloro-3-trifluoromethylphenyl)-amide | | 443 | |
| 44.  | [6-(3,4-Dimethoxyphenyl)-piperidin-2-ylmethyl]-(3-methoxyphenyl)-amine | | 357 | |
| 45.  | 6-(3,4-Dimethoxyphenyl)-piperidine-2-*cis*-carboxylic acid (3-methoxyphenyl)-amide | | 371 | |
| 46.  | N-{2-[2-(4-Methoxy-2,3-dimethylphenyl)-piperidin-1-yl]-ethyl}-4-trifluoromethyl-benzamide | | 435 | |
| 47.  | 1-[2-(4-Chloro-3-trifluoromethyl-phenoxy)-ethyl]-2-(4-methoxy-2,3-dimethylphenyl)-piperidine | | 442 | |
| 48.  | {2-[2-(3,4-Dimethoxyphenyl)-piperidin-1-yl]-ethyl}-(4-fluoro-3-trifluoromethylphenyl)-amine | | 427 | |

| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 49.  | (4-Chloro-3-fluorophenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine | | 393 | |
| 50.  | (3,4-Dichlorophenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine | | 409 | |
| 51.  | (3,4-Difluorophenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine | | 377 | |
| 52.  | (3,4-Bis-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxy-phenyl)-piperidin-1-yl]-ethyl}-amine | | 477 | |
| 53.  | (4-Chloro-3-trifluoromethylphenyl)-(2-{2-[4-(2-methoxy-ethoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine | | 485 | |

| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 54.  | (4-Chloro-3-trifluoromethylphenyl)-{2-{2-[4-(3-methoxy-propoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine | | 499 | |
| 55.  | (4-Chloro-3-trifluoromethylphenyl)-(2-{2-[4-(2-dimethylamino-ethoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine | | 498 | |
| 56.  | (4-Chloro-3-trifluoromethylphenyl)-(2-{2-[4-(3-dimethylamino-propoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine | | 512 | |
| 57.  | N-[3-(4-{1-[2-(4-Chloro-3-trifluoromethylphenylamino)-ethyl]-piperidin-2-yl}-2,3-dimethylphenoxy)-propyl]-acetamide | | 526 | |

| COMPOUND | NAME | NMR | LC/MS | $K_i$ |
|---|---|---|---|---|
| 58.  | (4-Chloro-3-trifluoromethylphenyl)-(2-{2-[4-(4-dimethylamino-butoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine | | 526 | |
| 59.  | (4-Chloro-3-trifluoromethylphenyl)-(2-{2-[2,3-dimethyl-4-(2-pyrazol-1-yl-ethoxy)-phenyl]-piperidin-1-yl}-ethyl)-amine | | 521 | |
| 60.  | 1-[2-(4-{1-[2-(4-Chloro-3-trifluoromethylphenylamino)-ethyl]-piperidin-2-yl}-2,3-dimethylphenoxy)-ethyl]-pyrrolidin-2-one | | 538 | |
| 61.  | (4-Chloro-3-trifluoromethylphenyl)-(2-{2-[2,3-dimethyl-4-(2-pyridin-3-yl-ethoxy)-phenyl]-piperidin-1-yl}-ethyl)-amine | | 532 | |

EXAMPLE 5. 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 6. 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 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 7. PURIFIED RECOMBINANT CHO CELL MEMBRANES EXPRESSING MONKEY MCH1R

Cynomolgus macaque hypothalamus MCH1R 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 8. 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 above) 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 9. 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 MCH1R 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 min 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 h 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 h 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 with the aid of the computer program FitP™ (BIOSOFT, Ferguson, MO). For preferred compounds, $K_i$ values are below 1 micromolar, preferably below 500 nanomolar, more preferably below 100 nanomolar.

EXAMPLE 10. 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 h. 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 is 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 h. It is important that the incubation not continue beyond 6 h. 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. $IC_{50}$ values for MCHR antagonists are determined using SIGMAPLOT software (SPSS Inc., Chicago, IL) and standard techniques. The $IC_{50}$ is then used to generate $K_i$ as described by Cheng and Prusoff (1973) *Biochem Pharmacol. 22(23)*:3099-108.

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 (background autofluorescence of the test compound may be assessed using standard methods). Compounds that induce no detectable increase in the basal activity of the MCH receptor have no detectable agonist activity and are preferred.

EXAMPLE 11. 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 $0.1 \times 10^6$ 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 h 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 min.

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 min. 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 min. 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 12. 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 min.

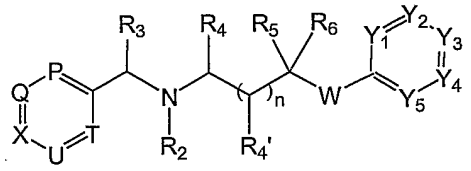
Cofactor mixture is prepared by diluting 16.2 mg NADP and 45.4 mg glucose-6-phosphate in 4 mL 100 mM $MgCl_2$. Glucose-6-phosphate dehydrogenase solution is prepared by diluting 214.3 μL glucose-6-phosphate dehydrogenase suspension (Roche Molecular Biochemicals; Indianapolis, IN) into 1285.7 μL distilled 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 min), 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 min 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 LC/MS profile (internal standard) per well. LC/MS 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 min and less than 4 h, preferably between 30 min and 1 h, 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.

WHAT IS CLAIMED IS:

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

W is NR, NR(C=O) or oxygen, wherein R is hydrogen or $C_1$-$C_2$alkyl that is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino and oxo;

n is 0 or 1;

$Y_1$ and $Y_5$ are independently CH or nitrogen;

$Y_2$, $Y_3$ and $Y_4$ are independently nitrogen or $CR_1$, such that:

(i) no more than 3 of $Y_1$, $Y_2$, $Y_3$, $Y_4$ and $Y_5$ are nitrogen; and

(ii) at least one of $Y_1$, $Y_2$, $Y_3$, $Y_4$ and $Y_5$ is not CH;

Each $R_1$ is independently:

(i) hydrogen, halogen, hydroxy, nitro, cyano, amino, aminocarbonyl, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, $C_1$-$C_6$alkoxy, halo$C_1$-$C_6$alkyl, halo$C_1$-$C_6$alkoxy, hydroxy$C_1$-$C_6$alkyl, $C_1$-$C_6$alkylthio, $C_2$-$C_8$alkyl ether, amino$C_1$-$C_6$alkyl, mono- or di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, mono- or di-($C_1$-$C_6$alkyl)aminocarbonyl, ($C_3$-$C_7$cycloalkyl)$C_0$-$C_6$alkyl or (4- to 7-membered heterocycloalkyl)$C_0$-$C_6$alkyl; or

(ii) taken together with an adjacent $R_1$ to form a fused 5- or 6-membered carbocycle or heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, nitro, cyano, amino, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_4$alkyl and halo$C_1$-$C_4$alkoxy;

such that $R_1$ of $Y_1$ and $R_1$ of $Y_5$ are not both $C_2$-$C_4$alkyl;

$R_2$ is:

(i) hydrogen or $C_1$-$C_4$alkyl; or

(ii) taken together with $R_3$ to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy;

$R_3$ is:

(i) $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, $C_2$-$C_4$alkenyl or halo$C_1$-$C_2$alkyl; or

(ii) taken together with $R_2$ to form an optionally substituted 5- to 7-membered heterocycloalkyl;

(iii) taken together with $R_4$ to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy; or

(iv) taken together with $R_{10}$ to form a fused 5- to 10-membered carbocycle or heterocycle;

$R_4$ is:

(i) hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy; or

(ii) taken together with $R_3$ to form an optionally substituted 5- to 7-membered heterocycloalkyl;

$R_4'$ is hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy;

$R_5$ and $R_6$ are:

(i) independently hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy; or

(ii) taken together to form an oxo group;

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 $CR_{11}$;

such that no more than three of P, Q, U, T and X are nitrogen, and at least two of P, Q, U, T and X are other than CH or 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;

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

(iii) taken together with $R_{11}$ to form a fused 5- to 10-membered carbocycle or heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, ($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy;

$R_9$ 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) hydrogen, halogen, hydroxy, nitro, cyano or –COOH;

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

(iii) taken together with $R_8$ to form a fused, optionally substituted carbocycle or heterocycle;

G is $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl or a 5- to 10-membered cycloalkyl, heterocycloalkyl, aryl or heteroaryl; each of which is substituted with from 0 to 5 substituents independently chosen from:

(a) oxo, halogen, amino, hydroxy, cyano, nitro, -COOH, -NH(C=O)H, aminosulfonyl, aminocarbonyl, -(C=N)OH and imino;

(b) $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, ($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkoxy, halo$C_1$-$C_6$alkyl, halo$C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_8$alkyl)amino$C_0$-$C_6$alkyl, $C_1$-$C_6$alkylsulfonyl, $C_1$-$C_6$alkylthio, mono- and di-($C_1$-$C_6$alkyl)aminosulfonyl, $C_1$-$C_6$alkoxycarbonyl, $C_2$-$C_4$alkanoyl, $C_2$-$C_6$alkanoylamino, mono- and di-($C_1$-$C_6$alkyl)aminocarbonyl and $C_1$-$C_6$alkyloxime; each of which is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkoxy, ($C_1$-$C_4$alkoxy)$C_1$-$C_4$alkyl, mono- and di-($C_1$-$C_4$alkyl)amino, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy; and

(c) (carbocycle)$C_0$-$C_6$alkyl, (heterocycle)$C_0$-$C_6$alkyl, (carbocycle)$C_0$-$C_6$alkoxy, (heterocycle)$C_0$-$C_6$alkoxy, (carbocycle)$C_0$-$C_6$alkylamino and (heterocycle)$C_0$-$C_6$alkylamino; each of which is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, ($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy;

each L is independently a single covalent bond, N($R_{13}$), O, S, C(=O), C(=O)O, OC(=O), SO, $SO_2$, $SO_2$N($R_{13}$), N($R_{13}$)$SO_2$, C(=O)N($R_{13}$) or N($R_{13}$)C(=O), wherein each $R_{13}$ is independently hydrogen, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl or halo$C_1$-$C_6$alkyl; and

each M is independently hydrogen, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_2$-$C_6$alkynyl, halo$C_1$-$C_6$alkyl, hydroxy$C_1$-$C_6$alkyl, $C_2$-$C_6$alkyl ether, amino$C_1$-$C_6$alkyl, ($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkyl, $C_5$-$C_{10}$cycloalkyl or 5- to 10-membered heterocycloalkyl.

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

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

4. A compound or salt of Claim 3, wherein R is methyl.

5. A compound or salt of Claim 1, wherein W is O.

6. A compound or salt of any one of Claims 1 to 5, wherein n is 0.

7. A compound or salt of any one of Claims 1 to 5, wherein n is 1.

8. A compound or salt of any one of Claims 1 to 7, wherein one and only one of $Y_1$, $Y_2$, $Y_3$, $Y_4$ and $Y_5$ is nitrogen.

9. A compound or salt of Claim 8, wherein one of $Y_1$, $Y_4$ and $Y_5$ is nitrogen.

10. A compound or salt of any one of Claims 1 to 7, wherein $Y_1$ and $Y_5$ are both CH, and $Y_2$, $Y_3$ and $Y_4$ are all $CR_1$.

11. A compound or salt of any one of Claims 1 to 10, wherein each $R_1$ is independently hydrogen, halogen, hydroxy, nitro, cyano, amino, $C_1$-$C_4$alkyl, $C_2$-$C_4$alkenyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl, halo$C_1$-$C_2$alkoxy, hydroxy$C_1$-$C_4$alkyl, $C_1$-$C_4$alkylthio, amino$C_1$-$C_6$alkyl, mono- or di-($C_1$-$C_4$alkyl)amino or ($C_3$-$C_7$cycloalkyl)$C_0$-$C_2$alkyl.

12. A compound or salt of Claim 11, wherein each $R_1$ is independently hydrogen, halogen, $C_1$-$C_2$alkyl, $C_2$-$C_4$alkenyl, $C_1$-$C_2$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

13. A compound or salt of Claim 12, wherein $Y_1$, $Y_4$ and $Y_5$ are each CH, and $Y_2$ and $Y_3$ are independently chosen from $CR_1$.

14. A compound or salt of Claim 13, 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.

15. A compound or salt of Claim 13, 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.

16. A compound or salt of any one of Claims 1 to 15, wherein $R_2$ is hydrogen or methyl.

17. A compound or salt of Claim 16, wherein $R_2$ is hydrogen.

18. A compound or salt of any one of Claims 1 to 15 wherein $R_2$ is taken together with $R_3$ to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy.

19. A compound or salt of Claim 18, wherein $R_2$ is taken together with $R_3$ to form piperidinyl that is substituted with from 0 to 2 methyl substituents.

20. A compound or salt of any one of Claims 1 to 19, wherein $R_3$ is hydrogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, $C_2$-$C_4$alkenyl or halo$C_1$-$C_2$alkyl.

21. A compound or salt of Claim 20, wherein $R_3$ is hydrogen.

22. A compound or salt of any one of Claim 1 to 19, wherein $R_3$ is taken together with $R_4$ to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy.

23. A compound or salt of Claim 22, wherein $R_3$ is taken together with $R_4$ to form a piperidinyl that is substituted with from 0 to 2 substituents independently chosen from halogen, methyl and methoxy.

24. A compound or salt of any one of Claims 1 to 21, wherein $R_4$ is hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

25. A compound or salt of Claim 24, wherein $R_4$ is hydrogen or methyl.

26. A compound or salt of any one of Claims 1 to 5 or 7 to 25, wherein $R_4'$ is hydrogen or methyl.

27. A compound or salt of any one of Claims 1 to 26, wherein $R_5$ and $R_6$ are independently hydrogen, halogen, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

28. A compound or salt of Claim 27, wherein $R_5$ and $R_6$ are independently hydrogen or methyl.

29. A compound or salt of any one of Claims 1 to 26, wherein $R_5$ and $R_6$ are taken together to form an oxo group.

30. A compound or salt of any one of Claims 1 to 29, wherein P is $CR_7$; Q is $CR_8$; U is $CR_9$; T is $CR_{10}$; and X is $CR_{11}$.

31. A compound or salt of any one of Claims 1 to 29, wherein P is $CR_7$; Q is nitrogen; U is $CR_9$; T is $CR_{10}$; and X is $CR_{11}$.

32. A compound or salt of any one of Claims 1 to 29, wherein P is $CR_7$; Q is $CR_8$; U is nitrogen; T is $CR_{10}$; and X is $CR_{11}$.

33. A compound or salt of any one of Claims 1 to 29, wherein P is $CR_7$; Q is $CR_8$; U is $CR_9$; T is nitrogen; and X is $CR_{11}$.

34. A compound or salt of any one of Claims 1 to 29, wherein $R_{11}$ is $C_1$-$C_2$alkoxy and $R_8$ or $R_9$ is $C_1$-$C_2$alkyl or $C_1$-$C_2$alkoxy.

35. A compound or salt of any one of Claims 1 to 34, wherein $R_7$, $R_8$, $R_9$, $R_{10}$ and $R_{11}$ are independently hydrogen, halogen, hydroxy, $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, mono- or di-($C_1$-$C_6$alkyl)amino, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

36. A compound or salt of Claim 35, wherein $R_7$ is hydrogen, $C_1$-$C_2$alkyl or $C_1$-$C_2$alkoxy; and $R_9$ and $R_{10}$ are hydrogen.

37. A compound or salt of Claim 36, wherein:
$R_7$ is hydrogen or methyl; and
$R_8$ and $R_{11}$ are independently hydroxy, halogen, methyl or methoxy.

38. A compound or salt of any one of Claims 1 to 30 or 32 to 34, wherein $R_{11}$ is taken together with $R_8$ to form a fused carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkyl, ($C_1$-$C_6$alkoxy)$C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

39. A compound or salt of Claim 38, wherein $R_7$, $R_9$ and $R_{10}$ are all hydrogen.

40. A compound or salt of Claim 39, wherein $R_{11}$ is taken together with $R_8$ to form a fused 5- or 6-membered heterocycloalkyl having 1 or 2 oxygen atoms; which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, methyl and methoxy.

41. A compound or salt of any one of Claims 1 to 34, wherein:
$R_7$, $R_8$, $R_9$ and $R_{10}$ are each independently hydrogen, halogen, hydroxy, nitro, cyano, -COOH or a group of the formula -L-M;
each L is independently a single covalent bond, N($R_{13}$) or O, wherein each $R_{13}$ is independently hydrogen or $C_1$-$C_6$alkyl; and
each M is independently hydrogen, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, halo$C_1$-$C_2$alkyl or amino$C_1$-$C_6$alkyl.

42. A compound or salt of Claim 41, wherein $R_7$, $R_8$, $R_9$ and $R_{10}$ are each independently hydrogen, halogen, $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl, $C_1$-$C_6$alkoxy, mono- or di-($C_1$-$C_6$alkyl)amino, halo$C_1$-$C_2$alkyl or halo$C_1$-$C_2$alkoxy.

43. A compound or salt of Claim 42, wherein $R_{10}$ is hydrogen.

44. A compound or salt of Claim 43, wherein $R_7$ and $R_8$ are independently hydrogen, methyl or methoxy; and $R_9$ and $R_{10}$ are each hydrogen.

45. A compound or salt of Claim 44, wherein $R_7$ and $R_8$ are both methyl.

46. A compound or salt of Claim 45, wherein $R_9$ and $R_{10}$ are hydrogen.

47. A compound or salt of any of Claims 1 to 46, wherein:

$R_{11}$ is a group of the formula -L-G;

G is $C_1$-$C_6$alkyl, $C_2$-$C_6$alkenyl or $C_2$-$C_6$alkynyl; each of which is substituted with from 0 to 5 substituents independently chosen from:

(a) oxo, halogen, hydroxy, amino, cyano, nitro, aminocarbonyl, aminosulfonyl, -COOH, -NH(C=O)H, -(C=N)OH and imino;

(b) $C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_8$alkyl)amino$C_0$-$C_6$alkyl, $C_1$-$C_6$alkylsulfonyl, $C_1$-$C_6$alkylthio, mono- or di-($C_1$-$C_6$alkyl)aminosulfonyl, $C_1$-$C_6$alkoxycarbonyl, $C_2$-$C_6$alkanoylamino, mono- and di-($C_1$-$C_6$alkyl)aminocarbonyl and $C_1$-$C_6$alkyloxime, each of which is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, ($C_1$-$C_4$alkoxy)$C_0$-$C_4$alkyl, mono- and di-($C_1$-$C_4$alkyl)amino, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy; and

(c) (carbocycle)$C_0$-$C_6$alkyl, (heterocycle)$C_0$-$C_6$alkyl, (carbocycle)$C_0$-$C_6$alkoxy, (heterocycle)$C_0$-$C_6$alkoxy, (carbocycle)$C_0$-$C_6$alkylamino and (heterocycle)$C_0$-$C_6$alkylamino, wherein the carbocycle is phenyl, naphthyl or $C_3$-$C_7$cycloalkyl, 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 is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino$C_0$-$C_6$alkyl, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

48. A compound or salt of Claim 47, wherein L is O.

49. A compound or salt of Claim 48, wherein:

G is $C_1$-$C_6$alkyl or amino$C_1$-$C_6$alkyl, each of which is substituted with from 0 to 5 substituents independently chosen from:

(a) oxo, hydroxy, amino, halogen, cyano, aminocarbonyl, -COOH or -NH(C=O)H;

(b) $C_1$-$C_6$alkoxy, mono- and di-($C_1$-$C_6$alkyl)amino, $C_1$-$C_6$alkylsulfonyl, $C_1$-$C_6$alkylthio, mono- or di-($C_1$-$C_6$alkyl)aminosulfonyl, $C_1$-$C_6$alkoxycarbonyl and $C_2$-$C_6$alkanoylamino, each of which is substituted with from 0 to 5 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_4$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy; and

(c) phenyl, naphthyl, $C_3$-$C_7$cycloalkyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, furanyl, thienyl, oxazolyl, thiazolyl, imidiazolyl, triazolyl, pyridinyl, pyrimidinyl and pyrazinyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, amino, cyano, hydroxy, oxo, $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, $C_2$-$C_4$alkanoyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_4$alkoxycarbonyl, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

50. A compound or salt of Claim 49, wherein G is $C_1$-$C_6$alkyl substituted with at least one substituent independently chosen from:

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

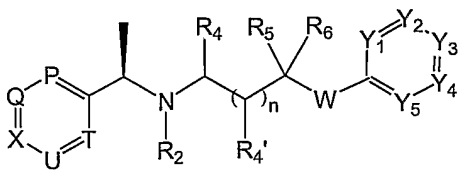
(b) $C_1$-$C_4$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, $C_1$-$C_4$alkoxycarbonyl and $C_2$-$C_4$alkanoylamino, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, $C_1$-$C_2$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

51. A compound or salt of Claim 49, wherein G is $C_1$-$C_6$alkyl substituted with at least one substituent independently chosen from:

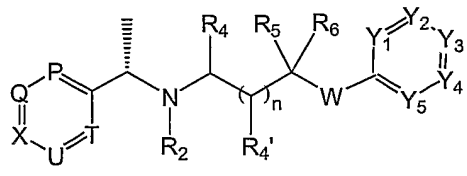
(a) oxo, hydroxy, cyano, aminocarbonyl, -COOH and -NH(C=O)H; and

(c) phenyl, $C_3$-$C_7$cycloalkyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, furanyl, thienyl, imidiazolyl, pyridinyl, pyrimidinyl or pyrazinyl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, oxo, $C_1$-$C_2$alkoxy, mono- and di-($C_1$-$C_4$alkyl)amino, halo$C_1$-$C_2$alkyl and halo$C_1$-$C_2$alkoxy.

52. A compound of salt any one of Claims 1 to 17, 20 to 21, or 24 to 51 of the Formula



or



.

53. A compound or salt of Claim 1, wherein the compound is:

N-(4-Chloro-3-trifluoromethylphenyl)-N'-[(R)-1-(3,4-dimethoxyphenyl)-ethyl]-ethane-1,2-diamine;

(4-Chloro-3-methoxyphenyl)-{2-[(R)-2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine;

(4-Chloro-3-trifluoromethylphenyl)-[6-(3,4-dimethoxyphenyl)-piperidin-2-ylmethyl]-amine;

N-[1-(3,4-Dimethoxyphenyl)-ethyl]-N'-(3-methoxyphenyl)-ethane-1,2-diamine;

N-(4-Chloro-3-trifluoromethylphenyl)-N'-[(R)-1-(3,4-dimethoxyphenyl)-ethyl]-ethane-1,2-diamine;

N-(4-Chloro-3-trifluoromethylphenyl)-2-[(*R*)-1-(3,4-dimethoxyphenyl)-ethylamino]-acetamide;

N-(4-Chloro-3-trifluoromethylphenyl)-2-[(*S*)-1-(3,4-dimethoxyphenyl)-ethylamino]-acetamide;

N-(4-Chloro-3-methoxyphenyl)-N'-[(*R*)-1-(3,4-dimethoxyphenyl)-ethyl]-ethane-1,2-diamine;

N-(4-Chloro-3-methoxyphenyl)-2-[(*R*)-1-(3,4-dimethoxyphenyl)-ethylamino]-acetamide;

N-(4-Chloro-3-methoxyphenyl)-N'-[(*S*)-1-(3,4-dimethoxyphenyl)-ethyl]-ethane-1,2-diamine;

(4-Chloro-3-methoxyphenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-methyl-amine;

(4-Chloro-3-methoxyphenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine;

N-(4-Chloro-3-methoxyphenyl)-2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-acetamide;

(4-Chloro-3-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine;

N-{2-[2-(3,4-Dimethoxyphenyl)-piperidin-1-yl]-ethyl}-4-trifluoromethyl-benzamide;

(4-Chloro-3-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-methyl-amine;

(4-Chloro-3-trifluoromethylphenyl)-{2-[(*S*)-2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine;

(4-Chloro-3-trifluoromethylphenyl)-{2-[(*R*)-2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine;

(4-Chloro-3-trifluoromethylphenyl)-{3-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-propyl}-amine;

N-(4-Chloro-3-trifluoromethylphenyl)-3-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-propionamide;

N-(4-Chloro-3-trifluoromethylphenyl)-2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-acetamide;

(4-Chloro-3-trifluoromethylphenyl)-{2-[2-(4-methoxy-2,3-dimethylphenyl)-piperidin-1-yl]-ethyl}-amine;

4-{1-[2-(4-Chloro-3-trifluoromethyl-phenylamino)-ethyl]-piperidin-2-yl}-2,3-dimethylphenol;

N-(4-Chloro-3-trifluoromethylphenyl)-2-[2-(4-methoxy-2,3-dimethylphenyl)-piperidin-1-yl]-acetamide;

[2-(2-Benzo[1,3]dioxol-5-yl-piperidin-1-yl)-ethyl]-(4-chloro-3-trifluoromethylphenyl)-amine;

2-(2-Benzo[1,3]dioxol-5-yl-piperidin-1-yl)-N-(4-chloro-3-trifluoromethylphenyl)-acetamide;

(4-Chloro-3-trifluoromethylphenyl)-{2-[2-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-piperidin-1-yl]-ethyl}-amine;

N-(4-Chloro-3-trifluoromethylphenyl)-2-[2-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-piperidin-1-yl]-acetamide;

(4-Chloro-3-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-ethyl}-amine;

N-(4-Chloro-3-trifluoromethylphenyl)-2-[2-(3,4-dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-acetamide;

N-(4-Chloro-3-trifluoromethylphenyl)-N-{2-[2-(3,4-dimethoxyphenyl)-6-methyl-piperidin-1-yl]-ethyl}-formamide;

(4-Chloro-3-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxyphenyl)-6-methyl-piperidin-1-yl]-ethyl}-methyl-amine;

(4-Chloro-3-methoxyphenyl)-{2-[2-(3,4-dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-ethyl}-amine;

N-(4-Chloro-3-methoxyphenyl)-2-[2-(3,4-dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-acetamide;

N-(4-Chloro-3-methoxyphenyl)-N-{2-[2-(3,4-dimethoxyphenyl)-6-methyl-piperidin-1-yl]-ethyl}-formamide;

{2-[2-(3,4-Dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-ethyl}-(3-trifluoromethylphenyl)-amine;

{2-[2-(3,4-Dimethoxyphenyl)-6-methyl-piperidin-1-yl]-ethyl}-methyl-(3-trifluoromethylphenyl)-amine;

2-[2-(3,4-Dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-N-(3-trifluoromethylphenyl)-acetamide;

{2-[2-(3,4-Dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-ethyl}-(4-chlorophenyl)-amine;

(4-Chlorophenyl)-{2-[2-(3,4-dimethoxyphenyl)-6-methyl-iperidin-1-yl]-ethyl}-methyl-amine;

2-[2-(3,4-Dimethoxyphenyl)-6-*cis*-methyl-piperidin-1-yl]-N-(4-chlorophenyl)-acetamide;

N-{2-[2-(3,4-Dimethoxyphenyl)-piperidin-1-yl]-ethyl}-4-trifluoromethyl-benzamide;

1-[2-(4-Chloro-3-trifluoromethyl-phenoxy)-ethyl]-2-(3,4-dimethoxy-phenyl)-piperidine;

[2-(3,4-Dimethoxy-phenyl)-piperidin-1-yl]-acetic acid 4-chloro-3-trifluoromethylphenyl ester;

(4-Chloro-3-trifluoromethylphenyl)-[6-(3,4-dimethoxyphenyl)-piperidin-2-ylmethyl]-amine;

6-(3,4-Dimethoxyphenyl)-piperidine-2-*cis*-carboxylic acid (4-chloro-3-trifluoromethylphenyl)-amide;

[6-(3,4-Dimethoxyphenyl)-piperidin-2-ylmethyl]-(3-methoxyphenyl)-amine;

6-(3,4-Dimethoxyphenyl)-piperidine-2-*cis*-carboxylic acid (3-methoxyphenyl)-amide;

N-{2-[2-(4-Methoxy-2,3-dimethylphenyl)-piperidin-1-yl]-ethyl}-4-trifluoromethyl-benzamide;

1-[2-(4-Chloro-3-trifluoromethyl-phenoxy)-ethyl]-2-(4-methoxy-2,3-dimethylphenyl)-piperidine;

{2-[2-(3,4-Dimethoxyphenyl)-piperidin-1-yl]-ethyl}-(4-fluoro-3-trifluoromethylphenyl)-amine;

(4-Chloro-3-fluorophenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine;

(3,4-Dichlorophenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine;

(3,4-Difluorophenyl)-{2-[2-(3,4-dimethoxyphenyl)-piperidin-1-yl]-ethyl}-amine;

(3,4-Bis-trifluoromethylphenyl)-{2-[2-(3,4-dimethoxy-phenyl)-piperidin-1-yl]-ethyl}-amine;

(4-Chloro-3-trifluoromethylphenyl)-(2-{2-[4-(2-methoxy-ethoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine;

(4-Chloro-3-trifluoromethylphenyl)-(2-{2-[4-(3-methoxy-propoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine;

(4-Chloro-3-trifluoromethylphenyl)-(2-{2-[4-(2-dimethylamino-ethoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine;

(4-Chloro-3-trifluoromethylphenyl)-(2-{2-[4-(3-dimethylamino-propoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine;

N-[3-(4-{1-[2-(4-Chloro-3-trifluoromethylphenylamino)-ethyl]-piperidin-2-yl}-2,3-dimethylphenoxy)-propyl]-acetamide;

(4-Chloro-3-trifluoromethylphenyl)-(2-{2-[4-(4-dimethylamino-butoxy)-2,3-dimethylphenyl]-piperidin-1-yl}-ethyl)-amine;

(4-Chloro-3-trifluoromethylphenyl)-(2-{2-[2,3-dimethyl-4-(2-pyrazol-1-yl-ethoxy)-phenyl]-piperidin-1-yl}-ethyl)-amine;

1-[2-(4-{1-[2-(4-Chloro-3-trifluoromethylphenylamino)-ethyl]-piperidin-2-yl}-2,3-dimethylphenoxy)-ethyl]-pyrrolidin-2-one; or

(4-Chloro-3-trifluoromethylphenyl)-(2-{2-[2,3-dimethyl-4-(2-pyridin-3-yl-ethoxy)-phenyl]-piperidin-1-yl}-ethyl)-amine.

54. A compound or salt of any one of claims 1 to 53, 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.

55. A pharmaceutical composition, comprising a compound or salt of any one of claims 1 to 53, in combination with at least one physiologically acceptable carrier or excipient.

56. The pharmaceutical composition of claim 55, wherein the composition is formulated as an injectible fluid, an aerosol, a cream, an oral liquid, a tablet, a gel, a pill, a capsule, a syrup or a transdermal patch.

57. 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 56, 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.

58. The method of claim 57, wherein the cells are present in an animal.

59. The method of claim 58, wherein the animal is a human, the cell is a brain cell, and the compound or salt is present in cerebrospinal fluid.

60. The method of claim 57, wherein the modulation is inhibition.

61. 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 53, under conditions and in an amount sufficient to detectably modulate MCH binding to the MCH receptor.

62. 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 53, 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.

63. The method of claim 62, wherein the cell is present in an animal.

64. The method of claim 63, wherein the animal is a human, the cell is a brain cell, and the compound or salt is present in cerebrospinal fluid.

65. The method of claim 62, wherein the signal-transducing activity of the MCH receptor in a cell is inhibited.

66. The method of claim 62, wherein the alteration in the electrophysiology of the cell is detected as a change in the animal's feeding behavior.

67. 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 or salt of any one of claims 1 to 53.

68. The method of claim 67, wherein the disease or disorder is an eating disorder, sexual disorder, diabetes, heart disease or stroke.

69. The method of claim 67 or 68, wherein the compound or salt is administered orally.

70. The method of claim 67 or 68, wherein the compound or salt is administered intranasally, intravenously or topically.

71. The method of claim 67 or 68, wherein the patient is a human.

72. The method of claim 67 or 68, wherein the patient is a dog or a cat.

73. A method for treating obesity, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or salt of any one of claims 1 to 53.

74. The method of claim 73, wherein the compound or salt is administered orally.

75. The method of claim 73 or 74, wherein the patient is a human.

76. The method of claim 73 or 74, wherein the patient is a dog or a cat.

77. A compound or salt of any one of claims 1 to 53, wherein the compound or salt is radiolabeled.

78. 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 53 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.

79. The method according to claim 78, 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.

80. The method of claim 78, wherein the sample is a tissue section.

81. A method for treating a patient, comprising diagnosing the patient as having a disease or disorder associated with MCH receptor activation, correlating the diagnosis of a disease or disorder associated with MCH receptor activation with the need for administration of a MCH receptor modulator, and administering to the patient an effective amount of a compound or salt of any one of claims 1 to 53.

82. A packaged pharmaceutical preparation, comprising: (i) a pharmaceutical composition of claim 55 in a container; and (ii) instructions for using the composition to treat a patient suffering from a disorder associated with MCH receptor activation.

83. The packaged pharmaceutical preparation of claim 82, wherein the disorder is an eating disorder, a sexual disorder, obesity, diabetes, heart disease or stroke.

84. The use of a compound or salt thereof according to any one of claims 1-53 for the manufacture of a medicament for the treatment of a condition responsive to MCH receptor modulation.

85. A use according to claim 84, wherein the condition is obesity, an eating disorder, a sexual disorder, diabetes, heart disease or stroke.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/027125

A. CLASSIFICATION OF SUBJECT MATTER
C07C217/54 C07C237/20 C07D211/26 C07D401/12 C07D405/04
A61K31/4523 A61P3/04 A61P3/10 A61P15/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/094799 A (NEUROGEN CORPORATION; HUTCHISON, ALAN; PETERSON, JOHN; DOLLER, DARIO;) 28 November 2002 (2002-11-28) | 1-51 |
| Y | RN: 477211-75-9, (2S, 5R) N-(4-chloro-3-methoxyphenyl)-'5-(3,4-dimethoxyphenyl)-pyrrolidine-2-ylmethyl!amine, p.68<br>RN: 477220-51-2 and 477220-52-3, (2S,5R) N-(4-chloro-3-methoxyphenyl)-5-(3,4-dimethoxyphenyl)-pyrrolidin-2-ylcarboxamide p.68 | 1-85 |
| X | DE 102 33 817 A1 (AVENTIS PHARMA DEUTSCHLAND GMBH) 12 February 2004 (2004-02-12) page 6, paragraph 38; compounds 51,69,85 | 1-85 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 18 November 2005 | 30/11/2005 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Schuemacher, A |

Form PCT/ISA/210 (second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/027125

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 6 362 231 B1 (SAKAI TERUYUKI ET AL) 26 March 2002 (2002-03-26) see figures1 -9figures 5,8,10,30; compounds 53,103,109,112,117,K-2030,S91, | 1-51 |
| X | US 6 376 491 B1 (AOKI YUHKO ET AL) 23 April 2002 (2002-04-23) examples 101,109,123 | 1-51 |
| X | WO 00/71520 A (TARGACEPT, INC; DULL, GARY, MAURICE; REICH, ERIN, E; WAGNER, JARED, MI) 30 November 2000 (2000-11-30) RN: 310881-29-9 5-''1-methyl-5-(3-pyridinyl)-2-pyrrolidiny l!methoxy!-pyrmidine claims 29 and 36 | 1-51 |
| X | US 5 149 704 A (SUMMERS ET AL) 22 September 1992 (1992-09-22) example 13 | 1-51 |
| X | US 5 120 751 A (SUMMERS ET AL) 9 June 1992 (1992-06-09) example 21 | 1-51 |
| X | US 6 048 900 A (CONNELL ET AL) 11 April 2000 (2000-04-11) N-(4-benzoylphenyl)-2-'(3-pyridinyl)-1-pyr rolidine!acetamide, RN: 212052-88-5, compound 77 | 1-51 |
| X | JARVEST, RICHARD L. ET AL: "Definition of the heterocyclic pharmacophore of bacterial methionyl tRNA synthetase inhibitors: potent antibacterially active non-quinolone analogues" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 14(15), 3937-3941 CODEN: BMCLE8; ISSN: 0960-894X, 19 June 2004 (2004-06-19), XP002354551 table 4, compounds 42, 43, 44, 47 and 48. | 1-51 |
| Y | WO 03/087045 A (7TM PHARMA A/S; HOEGBERG, THOMAS; BJURLING, ANNA, EMELIE; RECEVEUR, JE) 23 October 2003 (2003-10-23) claims 20,21; examples 157,160 | 1-85 |
| Y | WO 2004/005257 A (SYNAPTIC PHARMACEUTICAL CORPORATIONS; MARZABADI, MOHAMMAD; JIANG, ALLE) 15 January 2004 (2004-01-15) pages 95-96; claim 29; example 6; table I | 1-85 |
| Y | WO 2004/004726 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; RAY, ASIM, KUMAR; SIGFRIDSSON,) 15 January 2004 (2004-01-15) claims 1,14,17,18 | 1-85 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/027125

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 57 to 77 are directed to a method of treatment of the human/animal body and claims 78-81 directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/027125

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 02094799 A | 28-11-2002 | BR 0209932 A | 13-10-2004 |
| | | CA 2448080 A1 | 28-11-2002 |
| | | EP 1389189 A2 | 18-02-2004 |
| | | JP 2005515961 T | 02-06-2005 |
| | | MX PA03010612 A | 02-04-2004 |
| DE 10233817 A1 | 12-02-2004 | AU 2003251001 A1 | 16-02-2004 |
| | | AU 2003257465 A1 | 23-02-2004 |
| | | BR 0312916 A | 14-06-2005 |
| | | CA 2493924 A1 | 05-02-2004 |
| | | WO 2004012648 A2 | 12-02-2004 |
| | | WO 2004011438 A1 | 05-02-2004 |
| | | EP 1551810 A1 | 13-07-2005 |
| US 6362231 B1 | 26-03-2002 | AU 734710 B2 | 21-06-2001 |
| | | AU 3359797 A | 02-02-1998 |
| | | CA 2259922 A1 | 15-01-1998 |
| | | CN 1225083 A | 04-08-1999 |
| | | EP 0933354 A1 | 04-08-1999 |
| | | HK 1020942 A1 | 27-08-2004 |
| | | WO 9801417 A1 | 15-01-1998 |
| | | KR 2000023645 A | 25-04-2000 |
| | | TW 510896 B | 21-11-2002 |
| US 6376491 B1 | 23-04-2002 | AT 264855 T | 15-05-2004 |
| | | AU 754233 B2 | 07-11-2002 |
| | | AU 2660600 A | 12-07-2000 |
| | | BR 9916318 A | 14-08-2001 |
| | | CA 2355694 A1 | 29-06-2000 |
| | | CN 1333770 A | 30-01-2002 |
| | | DE 69916664 D1 | 27-05-2004 |
| | | DE 69916664 T2 | 31-03-2005 |
| | | DK 1149094 T3 | 16-08-2004 |
| | | WO 0037464 A2 | 29-06-2000 |
| | | ES 2217882 T3 | 01-11-2004 |
| | | JP 3435404 B2 | 11-08-2003 |
| | | JP 2002533340 T | 08-10-2002 |
| | | MX PA01006218 A | 17-04-2002 |
| | | TR 200101779 T2 | 21-12-2001 |
| | | ZA 200104410 A | 29-08-2002 |
| WO 0071520 A | 30-11-2000 | AU 4667800 A | 12-12-2000 |
| | | BR 0011534 A | 26-02-2002 |
| | | CA 2373789 A1 | 30-11-2000 |
| | | EP 1185513 A2 | 13-03-2002 |
| | | JP 2003500393 T | 07-01-2003 |
| | | MX PA01012202 A | 21-06-2002 |
| US 5149704 A | 22-09-1992 | IE 920801 A1 | 04-11-1992 |
| | | PT 100443 A | 31-08-1993 |
| | | WO 9219618 A1 | 12-11-1992 |
| US 5120751 A | 09-06-1992 | IE 920715 A1 | 07-10-1992 |
| | | PT 100314 A | 30-06-1993 |
| | | WO 9217476 A1 | 15-10-1992 |
| US 6048900 A | 11-04-2000 | NONE | |

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/027125

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 03087045 A | 23-10-2003 | AU 2003226926 A1 | 27-10-2003 |
| | | CA 2482341 A1 | 23-10-2003 |
| | | EP 1497260 A1 | 19-01-2005 |
| WO 2004005257 A | 15-01-2004 | AU 2003259098 A1 | 23-01-2004 |
| | | BR 0312257 A | 12-04-2005 |
| | | CA 2485379 A1 | 15-01-2004 |
| | | CN 1665786 A | 07-09-2005 |
| | | EP 1556351 A1 | 27-07-2005 |
| | | US 2005245743 A1 | 03-11-2005 |
| WO 2004004726 A | 15-01-2004 | AU 2003281194 A1 | 23-01-2004 |
| | | BR 0312312 A | 12-04-2005 |
| | | CA 2491835 A1 | 15-01-2004 |
| | | CN 1665502 A | 07-09-2005 |
| | | EP 1528924 A1 | 11-05-2005 |