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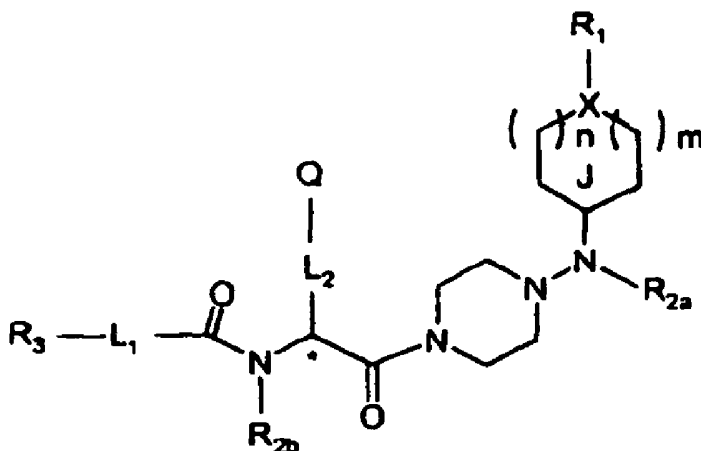
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(54) Title: AMINE SUBSTITUTED PIPERAZINE MELANOCORTIN RECEPTOR-SPECIFIC COMPOUNDS



(57) Abstract: A compound of the formula where R<sub>1</sub>, R<sub>2a</sub>, R<sub>2b</sub>, R<sub>3</sub>, L<sub>1</sub>, L<sub>2</sub>, Q, J, X, m and n are as defined, or an enantiomer, stereoisomer or diastereoisomer thereof, or a pharmaceutically acceptable salt thereof, and the use thereof in the treatment of diseases, syndromes and conditions modulated by melanocortin receptors.;

## Amine Substituted Piperazine Melanocortin Receptor-Specific Compounds

### 5 CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of the filing of U.S. Provisional Patent Application Serial No. 61/119,901 entitled "Amine Substituted Piperazine Melanocortin Receptor-Specific Compounds", filed on December 4, 2008, and the specification and claims thereof are incorporated herein by reference.

### 10 BACKGROUND OF THE INVENTION

Field of the Invention (Technical Field):

This invention provides amine substituted piperazine compounds that are specific for one or more melanocortin receptors, and which may be used in the treatment of a wide variety of diseases, syndromes and conditions.

### 15 Background:

A family of melanocortin receptor types and subtypes have been identified. Melanocortin-1 receptors (MCR-1) are expressed in normal human melanocytes and melanoma cells, and are reported to be expressed in various other cells, including those involved in immune responses, such as monocytes, neutrophils, lymphocytes, dendritic cells, natural killer (NK) cells and endothelial cells.

20 Melanocortin-2 receptors (MCR-2) for ACTH (adrenocorticotropin) are expressed in cells of the adrenal gland. Melanocortin-3 and melanocortin-4 receptors (MCR-3 and MCR-4) are expressed primarily in cells in the hypothalamus, mid-brain and brainstem, but are reported to be expressed in other cells. Melanocortin-5 receptors (MCR-5) are expressed in a wide distribution of central nervous system and peripheral tissues.

25 A wide variety of diseases, conditions and syndromes have been identified for which compounds specific for one or more melanocortin receptors may have utility. For example, compounds that are specific for MCR-1, particularly agonists, may be useful as tanning agents by increasing melanin production. Compounds specific for MCR-1 or MCR-3 may be useful in regulation of inflammatory processes, and thus applicable to treatment or prevention of a wide variety of diseases. Compounds  
30 specific for MCR-3 or MCR-4 are believed to be useful in regulation of energy homeostasis, including use as agents for attenuating food intake and body weight gain, for use in treatment of anorexia, as a weight gain aid, for treatment of obesity, and treatment of other food intake and metabolism-related purposes. Compounds specific for MCR-3 and MCR-4 can further be used as agents for treatment of sexual dysfunction, including male erectile dysfunction and female sexual dysfunction. Compounds specific for  
35 MCR-4 can further be used as agents for treatment of alcohol abuse, anxiety and related conditions.

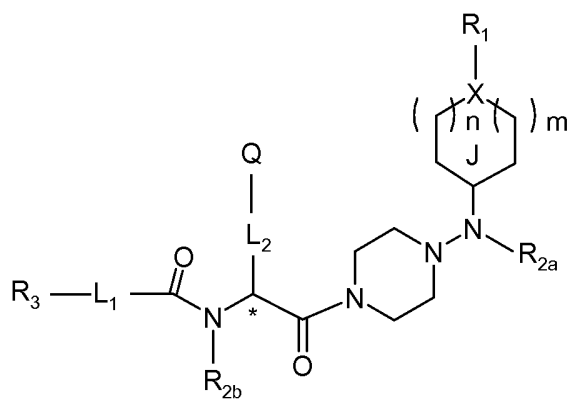
Melanocortin receptor-specific compounds have been developed and explored for treatment of certain of the foregoing and other conditions. However, to date no melanocortin receptor-specific compound has been approved for any clinical indication, and very few have been tested in human clinical trials.

There is a significant need for compounds with high specificity for discrete melanocortin receptors, as well as for compounds that are either agonists or antagonists for specific melanocortin receptors. High affinity compounds for melanocortin receptors can be used to exploit varied physiological responses associated with the melanocortin receptors, either as agonists or antagonists. In addition, melanocortin receptors, particularly MCR-1 or MCR-3, have an effect on the activity of various cytokines, and high affinity compounds for melanocortin receptors can be used to regulate cytokine activity.

There also remains a significant need for compounds specific for MCR-4 for treatment of conditions relating to sexual dysfunction, including female sexual dysfunction and male erectile dysfunction, and regulation of energy homeostasis, including use as agents for attenuating food intake and body weight gain, for treatment of obesity, and treatment of other food intake and metabolism-related purposes.

#### SUMMARY OF THE INVENTION (DISCLOSURE OF THE INVENTION)

In one aspect, the invention provides compounds of formula I:



or an enantiomer, stereoisomer or diastereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

$R_1$  is not present if X is O or N forming a double bond with another ring atom, and otherwise  $R_1$  is H,

a  $C_1$  to  $C_{17}$  linear or branched alkyl, cycloalkyl, or alkylcycloalkyl, optionally substituted with a terminal amide, amino, monosubstituted amino, disubstituted amino, or nitrile,

a  $C_1$  to  $C_7$  acyl group, optionally substituted with a terminal amide, amino, monosubstituted amino, disubstituted amino, or nitrile,

an amide,

an amino,

a monosubstituted amino,

a disubstituted amino or

nitrile;

$R_{2a}$  and  $R_{2b}$  are each independently

H,

a  $C_1$  to  $C_{17}$  linear or branched alkyl, cycloalkyl, or alkylcycloalkyl,

a  $C_1$  to  $C_7$  acyl group,

sulfonyl,  
 carbamoyl or  
 urea,

in each instance optionally substituted with one or more substituents, and when one or more substituents are present, such substituents are the same or different and independently halo, amino, monosubstituted amino, disubstituted amino, hydroxy, or carboxy;

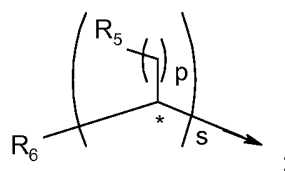
$L_1$  and  $L_2$  are each independently

a bond or

a  $C_1$  to  $C_6$  aliphatic chain,

and if a  $C_1$  to  $C_6$  aliphatic chain, optionally wherein one or more carbon atoms in the  $C_1$  to  $C_6$  aliphatic chain are replaced by oxygen or nitrogen atoms, and further optionally wherein the  $C_1$  to  $C_6$  aliphatic chain is substituted with one or more substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl;

$R_3$  is one or two cyclic radicals, and if two cyclic radicals, fused cyclic radicals or cyclic radicals joined by  $L_3$ , the one or two cyclic radicals optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl, or  $R_3$  is a group of the structure



$Q$  is a monocyclic or polycyclic aryl or heteroaryl group, optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, oxo, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl;

$L_3$  is a bond or  $-CH_2-$ ,  $-CH_2-CH_2-$ ,  $-CH=CH-$ ,  $-CH_2-O-$ ,  $-O-CH_2-$ ,  $-CH_2-S-$ ,  $-S-CH_2-$ ,  $-C(=O)-NH-$ ,  $-NH-C(=O)-$ ,  $-C(=O)-O-$ , or  $-O-C(=O)-$ ;

$R_5$  is H or one or two cyclic radicals, and if two cyclic radicals, fused cyclic radicals or cyclic radicals joined by  $L_3$ , the one or two cyclic radicals optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl;

R<sub>6</sub> is

an amine,

an amine substituted with one or two linear or branched C<sub>1</sub> to C<sub>17</sub> alkyl, cycloalkyl, aryl, heteroaryl, alkylaryl, alkene, alkenyl, or aralkyl chains,

5 a C<sub>1</sub> to C<sub>7</sub> acyl group,

a C<sub>1</sub> to C<sub>7</sub> alkylamine group, wherein the alkyl is linear, branched or cyclic and the amine is optionally substituted with one or two C<sub>1</sub> to C<sub>17</sub> linear or branched alkyl, cycloalkyl, aryl, heteroaryl, alkylaryl, alkene, alkenyl, or aralkyl chains, or

10 an N-acylated linear or branched C<sub>1</sub> to C<sub>17</sub> alkyl, aryl, heteroaryl, alkene, alkenyl, or aralkyl chain,

wherein any cyclic radical in R<sub>6</sub> is optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl;

15 X is N, O, C or CH;

m is from 0 to 2;

n is 1 or 2;

p is from 0 to 3; and

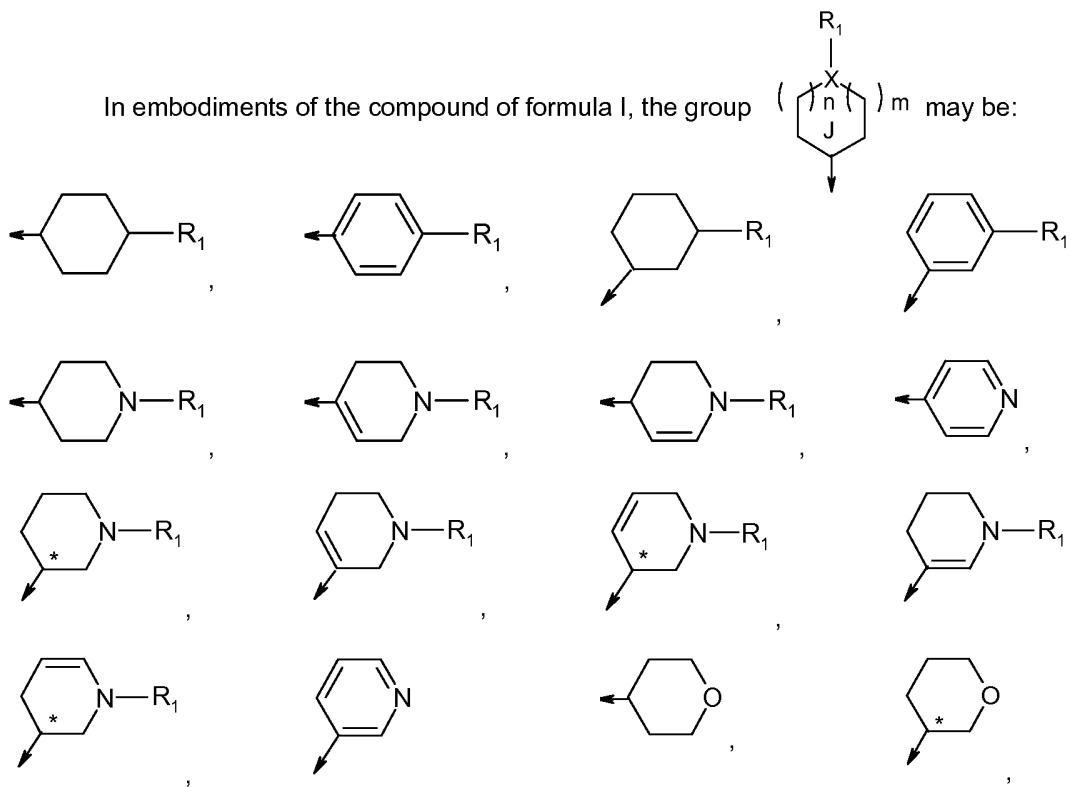
s is 0 or 1, and if 0, then the bracketed group is absent;

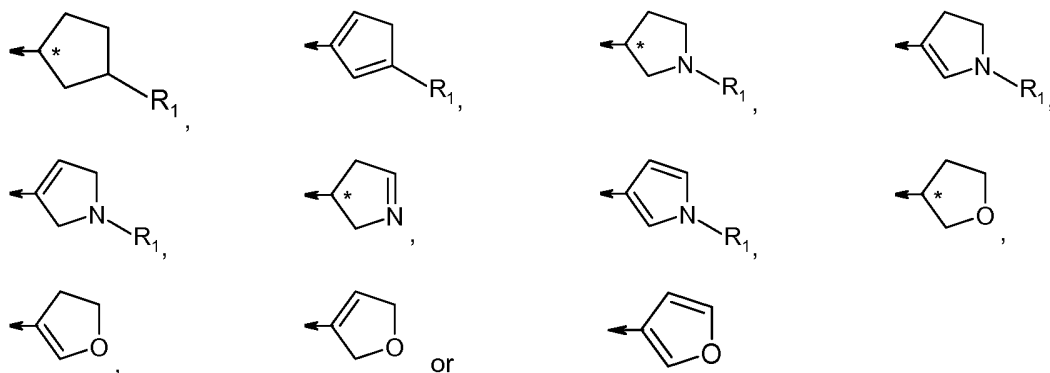
20 wherein the ring atoms of the ring marked J comprise from 0 to 3 double bonds; and

wherein the carbon atoms marked with an asterisk can have any stereochemical configuration.

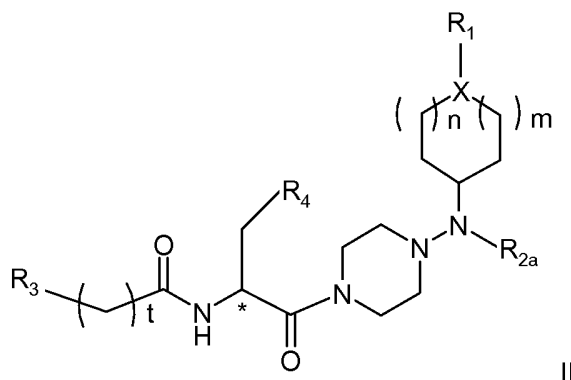
In embodiments of the compound of formula I, the group  $\left( \begin{array}{c} R_1 \\ | \\ \text{X} \\ | \\ \text{J} \end{array} \right)_m$  may be:

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In another aspect, the invention provides compounds of formula II:

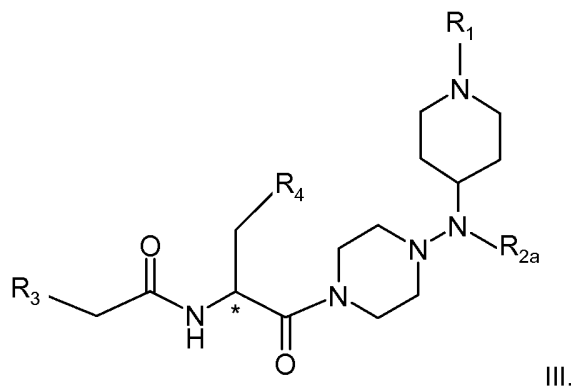


or an enantiomer, stereoisomer or diastereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

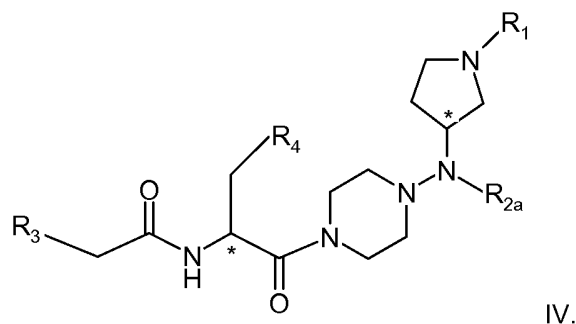
- 5  $R_4$  is heteroaryl, phenyl or naphthyl, optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl; and

- 10  $t$  is from 0 to 4.

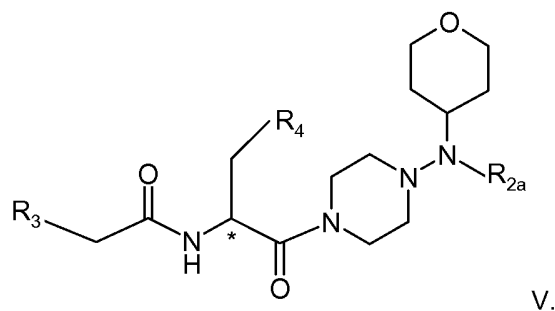
In another aspect, the invention provides compounds of formula III:



In another aspect, the invention provides compounds of formula IV:



In another aspect, the invention provides compounds of formula V:



5 In any of the foregoing compounds of formulas I, II, III or IV R<sub>1</sub> may be:

- H,
- CH<sub>3</sub>,
- CH<sub>2</sub>-CH<sub>3</sub>,
- CH-(CH<sub>3</sub>)<sub>2</sub>,
- C(=O)-CH<sub>3</sub>, or
- C(=O)-CH-(CH<sub>3</sub>)<sub>2</sub>.

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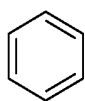
In any of the foregoing compounds of formulas I, II, III, IV or V, R<sub>2a</sub> may be:

- H,
- CH<sub>3</sub>,
- CH<sub>2</sub>-CH<sub>3</sub>,
- CH-(CH<sub>3</sub>)<sub>2</sub>,
- C(=O)-CH<sub>3</sub>,
- C(=O)-O-CH<sub>2</sub>-CH<sub>3</sub>,
- C(=O)-NH-CH<sub>2</sub>-CH<sub>3</sub>,
- C(=O)-CH-(CH<sub>3</sub>)<sub>2</sub>, or
- methyl-cyclopropane.

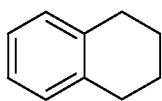
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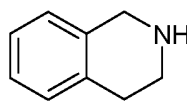
In any of the foregoing compounds of formulas I, II, III, IV or V, R<sub>13</sub> may be:



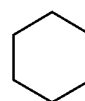
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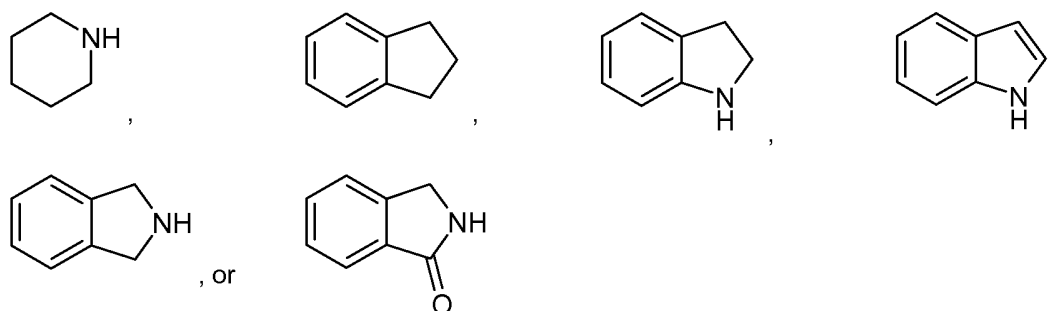
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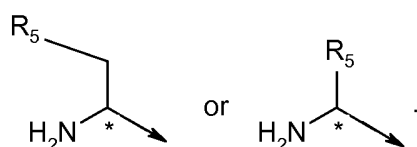


In any of the foregoing compounds of formulas II, III, IV or V,  $R_4$  may be phenyl, optionally substituted with one or more ring substituents, and when one or more substituents are present, are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl.

In any of the foregoing compounds of formulas II, III, IV or V,  $R_4$  may be naphthyl, optionally substituted with one or more ring substituents, and when one or more substituents are present, are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl.

In any of the foregoing compounds of formulas II, III, IV or V,  $R_4$  may be heteroaryl which is pyridine, pyrimidine, thiophene, thiazole, oxazole or imidazole, optionally substituted with one or more ring substituents, and when one or more substituents are present, are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl.

In any of the foregoing compounds of formulas I, II, III, IV or V,  $R_3$  may alternatively be a group of the formula:



The invention further provides a pharmaceutical composition comprising a compound of any of formulas I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. This pharmaceutical composition may further comprise at least one additional active pharmaceutical agent. The invention further provides a method of treating a patient with a disease, disorder, condition or syndrome responsive to modulation of a melanocortin receptor, comprising administration to the patient of a pharmaceutically effective amount of the pharmaceutical composition as provided.

The invention further comprises a method for stimulating sexual response in a mammal, comprising administering a pharmaceutically sufficient amount of a composition including a compound of this invention or pharmaceutically acceptable salt thereof. In this method, the mammal may be a male or



a female. The composition may further comprise a pharmaceutically acceptable carrier. In the method, administering may include administering by any method of administration, such as administration by injection, administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration, parenteral administration, pulmonary administration, ocular administration, sublingual administration and vaginal administration. In the event of nasal administration, it may be nasal administration of a metered amount of a formulation comprising an aqueous buffer.

The invention further comprises a method for inhibiting food uptake in a mammal, comprising administering a pharmaceutically sufficient amount of a composition comprising a compound of this invention or pharmaceutically acceptable salt thereof, and particularly an MCR-3 and/or MCR-4 selective agonist or partial agonist. The composition may further comprise a pharmaceutically acceptable carrier. In the method, administering may include administering by any method of administration, such as administration by injection, administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration, parenteral administration, pulmonary administration, ocular administration and sublingual administration. In the event of nasal administration, it may be nasal administration of a metered amount of a formulation comprising an aqueous buffer.

The invention further comprises a method for increasing weight gain in a mammal, comprising administering a pharmaceutically sufficient amount of a composition comprising a compound of this invention or pharmaceutically acceptable salt thereof, and particularly an MCR-3 and/or MCR-4 selective antagonist. The composition may further comprise a pharmaceutically acceptable carrier. In the method, administering may include administering by any method of administration, such as administration by injection, administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration, parenteral administration, pulmonary administration, ocular administration and sublingual administration. In the event of nasal administration, it may be nasal administration of a metered amount of a formulation comprising an aqueous buffer.

One object of this invention is a melanocortin receptor-specific pharmaceutical for use in treatment of sexual dysfunction.

Another object is to provide a melanocortin receptor-specific pharmaceutical for use in treatment of male sexual dysfunction, including erectile dysfunction.

Another object is to provide a melanocortin receptor-specific pharmaceutical for use in treatment of female sexual dysfunction.

Another object is to provide a melanocortin receptor-specific pharmaceutical for use in treatment of eating disorders.

Another object is to provide a melanocortin receptor-specific pharmaceutical which is effective by oral administration.

Another object of this invention is to provide compounds which are specific for melanocortin receptors MCR-1 and/or MCR-3 and/or MCR-4 and/or MCR-5 and which are agonists, partial agonists, inverse agonists or antagonists.

Other objects, advantages and novel features, and the further scope of applicability of this invention, will be set forth in part in the detailed description to follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of this invention. The objects and advantages of this invention may be realized and attained by means of the

5 instrumentalities and combinations particularly pointed out in the appended claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS  
(BEST MODES FOR CARRYING OUT THE INVENTION)

1. DEFINITIONS

As used herein, the term "alkyl" or "alkyl group" means a saturated unbranched or branched hydrocarbon chain. (C<sub>1</sub>-C<sub>6</sub>) alkyl means an alkyl having from 1 to 6 carbon atoms. Non-limiting examples of (C<sub>1</sub>-C<sub>6</sub>) alkyl groups include methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, and hexyl. Alkyl includes longer alkyl groups, such as heptyl and octyl. An alkyl group can be unsubstituted or optionally substituted with one or two suitable substituents.

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As used herein, the term "aliphatic" means compounds with hydrocarbon chains, such as for example alkanes, alkenes, alkynes, and derivatives thereof.

As used herein, the term "alkenyl" or "alkenyl group" means an unbranched or branched hydrocarbon chain having one or more double bonds therein (i.e., comprising an alkene or olefin). The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to (C<sub>2</sub>-C<sub>6</sub>) alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or optionally substituted with one or two suitable substituents.

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As used herein, the term "alkynyl" or "alkynyl group" means an unbranched or branched hydrocarbon chain having one or more triple bonds therein. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkynyl groups include, but are not limited to, (C<sub>2</sub>-C<sub>6</sub>) alkynyl groups, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl. An alkynyl group can be unsubstituted or optionally substituted with one or two suitable substituents.

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As used herein, the term "aralkyl" means a radical -R<sup>a</sup>R<sup>b</sup> where R<sup>a</sup> is an alkylene (a bivalent alkyl) group and R<sup>b</sup> is an aryl group as defined above. Examples of aralkyl groups include benzyl, phenylethyl, 3-(3-chlorophenyl)-2-methylpentyl, and the like.

As used herein, the term "aryl" or "aryl group" means a monocyclic or polycyclic (e.g., bicyclic) aromatic ring system comprising carbon and hydrogen atoms. The term "aryl" also includes polycyclic aromatic ring systems wherein at least one ring is aromatic and one or more rings are non-aromatic (including saturated or partially saturated rings). Non-limited examples include phenyl, tolyl, anthacenyl, fluorenyl, indenyl, azulenyl, naphthyl, 1-naphthyl, 2-naphthyl, and biphenyl as well as benzo-fused

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carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. An aryl group can be unsubstituted or optionally substituted with one or more suitable substituents as defined below. An aryl group may be fused to a cycloalkyl group, fused to another aryl group, fused to a heteroaryl group, or fused to a heterocycloalkyl group. Preferred aryl groups include, but are not limited to, monocyclic or bicyclic aromatic hydrocarbon radicals of 6 to 12 ring atoms, and optionally substituted independently with one or more substituents selected from alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl.

As used herein, the term "heteroaryl" or "heteroaryl group" means a monocyclic or polycyclic aromatic ring comprising carbon atoms, hydrogen atoms, and one or more heteroatoms, preferably 1 to 4 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. Non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazyl, indolyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,-)triazolyl, (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, thiadiazolyl, furyl, phenyl, isoxazolyl, oxazolyl, pyrazolyl, tetrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, triazinyl, and pyrazinyl. Bicyclic heteroaromatic rings include, but are not limited to, benzothiadiazolyl, indolyl, benzothiophenyl, benzofuryl, benzimidazolyl, benzisoxazolyl, benzothiazolyl, quinolinyl, benzotriazolyl, benzoxazolyl, isoquinolinyl, purinyl, furopyridinyl and thienopyridinyl. A heteroaryl can be unsubstituted or optionally substituted with one or more suitable substituents as defined below. A heteroaryl group optionally may be fused to another heteroaryl group, fused to an aryl group, fused to a cycloalkyl group, or fused to a heterocycloalkyl group.

As used herein, the term "cycloalkyl" or "cycloalkyl group" means a monocyclic or polycyclic saturated ring comprising carbon and hydrogen atoms and having no carbon-carbon multiple bonds. Examples of cycloalkyl groups include, but are not limited to, (C<sub>3</sub>-C<sub>7</sub>) cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl group can be unsubstituted or optionally substituted with one or more suitable substituents as defined below. A cycloalkyl group optionally may be fused to another cycloalkyl group, fused to an aryl group, fused to a heteroaryl group, or fused to a heterocycloalkyl group.

As used herein, the term "heterocycloalkyl" or "heterocycloalkyl group" means a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. A heterocycloalkyl group may be fused to an aryl or heteroaryl group. Examples of heterocycloalkyl groups include, but are not limited to, pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group can be unsubstituted or optionally substituted with one or more suitable substituents as defined below. A heterocycloalkyl group optionally may be fused to a cycloalkyl group, fused to an aryl group, fused to a heteroaryl group, or fused to another heterocycloalkyl group. For example, a heterocycloalkyl group can be fused to or substituted with an aryl group or heteroaryl group, for example, but not limited to, 1,2,3,4-tetrahydroisoquinolinyl and 1,2,3,4-tetrahydroquinolinyl, tetrahydronaphthyridinyl, phenylpiperidinyl, and piperidinylpyridinyl. A heterocycloalkyl group may be a monocyclic or bicyclic ring, such as a monocyclic ring comprising from 3

to 6 carbon atoms and from 1 to 3 heteroatoms, referred to herein as (C<sub>3</sub>-C<sub>6</sub>) heterocycloalkyl. A heterocycloalkyl group may also be fused to or substituted with an aryl group or a heteroaryl group.

As used herein, the terms "heterocyclic radical" or "heterocyclic ring" mean a heterocycloalkyl group or a heteroaryl group.

5 As used herein, the term "cyclic radical" means an aryl group, a cycloalkyl group, a heterocycloalkyl group, a heteroaryl group or a combination of two or more thereof.

As used herein, the term "alkoxy" means an -O-alkyl group, wherein alkyl is as defined above. An alkoxy group can be unsubstituted or optionally substituted with one or two suitable substituents.

10 Preferably, the alkyl chain of an alkoxy group is from 1 to 6 carbon atoms in length, referred to herein as "(C<sub>1</sub>-C<sub>6</sub>) alkoxy".

As used herein, the term "aryloxy" means an -O-aryl group, wherein aryl is as defined above. An aryloxy group can be unsubstituted or optionally substituted with one or two suitable substituents. Preferably, the aryl ring of an aryloxy group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C<sub>6</sub>)aryloxy".

15 As used herein, the term "alkoxycarbonyl" group means a monovalent group of the formula -C(=O)-alkoxy. Preferably, the hydrocarbon chain of an alkoxycarbonyl group is from 1 to 8 carbon atoms in length, referred to herein as a "lower alkoxycarbonyl" group.

As used herein, the term "carbamoyl" group means the radical -C(=O)N(R')<sub>2</sub>, wherein R' is chosen from the group consisting of hydrogen, alkyl, and aryl.

20 As used herein, a "carbonyl" group means a divalent group of the formula C(=O).

As used herein, an "oxo" group means a group of the formula (=O).

As used herein, the term "acyl" means a group R-C(=O)-, where R is an organic group, including but not limited to a C<sub>1</sub> to C<sub>7</sub> alkyl. An example is the acetyl group CH<sub>3</sub>-C(=O)-, referred to herein sometimes as "Ac". A moiety is "acylated" when an aryl, alkyl or substituted alkyl group as defined above is bonded through one or more carbonyl {-C(=O)-} groups.

As used herein, an "amide" means compounds that have a trivalent nitrogen attached to a carbonyl group (-C(=O)-NH<sub>2</sub>), such as for example methanamide, ethanamide, propanamide, and the like.

As used herein, an "imide" means compounds containing an imido group (-C(=O)-NH-C(=O)-).

As used herein, an "amine" means compounds that contain an amino group (-NH<sub>2</sub>),  
30 monosubstituted amino group (-NHR) or disubstituted amino group (-NRR), where each R is independently a suitable substituent.

As used herein, an "alkylamine" means a saturated, monovalent, unbranched or branched hydrocarbon chain with a terminal amine. Examples of alkylamine groups include, but are not limited to, (C<sub>1</sub>-C<sub>6</sub>) alkyl-amino groups, such as methanamine, ethanamine, propanamine, butanamine, pentanamine and  
35 hexanamine, branched groups such as isopropanamine, sec-butanamine and so on, (C<sub>1</sub>-C<sub>6</sub>) alkyl-monosubstituted amino groups, such as dimethanamine, and (C<sub>1</sub>-C<sub>6</sub>) alkyl-disubstituted amino groups, such as trimethanamine. An alkylamine group can be unsubstituted or optionally substituted with one or two suitable substituents.

As used herein a "nitrile" means compounds that are carboxylic acid derivatives and contain a (-C≡N) group bound to an organic group.

As used herein, the term "halogen" means fluorine, chlorine, bromine, or iodine. Correspondingly, the meaning of the terms "halo" and "Hal" encompass fluoro, chloro, bromo, and iodo.

5 As used herein, the term "sulfonamide" means compounds of the formula -R-S(=O)<sub>2</sub>-NH<sub>2</sub>, where R any organic group, including but not limited to alkyl, and where sulfonamide is a suitable substituent, where R is a portion of the substituted group.

As used herein, the term "sulfonyl" means compounds of the formula -R-S(=O)<sub>2</sub>-R', and where sulfonyl is a suitable substituent, where R is a portion of the substituted group and R' is hydrogen or an organic group including but not limited to alkyl, O-alkyl, aryl, alkenyl or aralkyl.

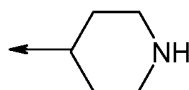
As used herein, the term "urea" means compounds of the formula formula -R-C(=O)-O-R', and where urea is a suitable substituent, where R is a portion of the substituted group and where R' is hydrogen or an organic group including but not limited to alkyl, aryl, alkenyl or aralkyl.

As used herein, the term "nitrogen protecting group" means a group that replaces an amino hydrogen for the purpose of protecting against side reactions and degradation during a reaction sequence. Nitrogen protecting groups useful in the invention include nitrogen protecting groups well known in the synthetic arts, including, but not limited to, boc, Fmoc, 2-chlorobenzyloxycarbonyl, alloc, benzyloxycarbonyl (Z), 2-(4-biphenyl)propyl-2-oxycarbonyl (Bpoc), 1-adamantyloxycarbonyl, triphenylmethyl (trityl), and toluene sulphonyl.

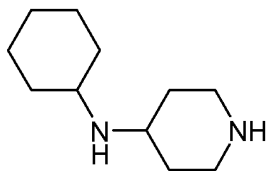
20 As used herein, the term "suitable substituent" means a group that does not nullify the synthetic, therapeutic or pharmaceutical utility of the compounds of the invention or the intermediates useful for preparing them. Examples of suitable substituents include, but are not limited to: alkyl; haloalkyl; cycloalkyl; alkoxy; alkylthio; halo; nitro; acyl; cyano; aryl; alkylaryl; aryloxy; amino; monosubstituted amino; disubstituted amino; carbamoyl, urea; sulfonamide; sulfonyl; oxo, hydroxyl; carboxy; alkoxy-carbonyl; alkenyl; alkynyl; heteroaryl; heterocycloalkyl; O-alkenyl; O-alkynyl; oxo; CF<sub>3</sub>; NO<sub>2</sub>; NH<sub>2</sub>; NH(alkyl); N(alkyl)<sub>2</sub>; NH(aryl); N(aryl)<sub>2</sub>; C(=O)NH<sub>2</sub>; C(=O)NH(alkyl); C(=O)N(alkyl)<sub>2</sub>; C(=O)NH(aryl); C(=O)N(aryl)<sub>2</sub>; OC(=O)NH<sub>2</sub>; C(=O)NH(heteroaryl); C(=O)N(heteroaryl)<sub>2</sub>; C(=O)NH(aralkyl); C(=O)N(aralkyl)<sub>2</sub>; OC(=O)NH(alkyl); OC(=O)N(alkyl)<sub>2</sub>; OC(=O)NH(aryl); OC(=O)N(aryl)<sub>2</sub>; OC(=O)NH(aralkyl); OC(=O)N(aralkyl)<sub>2</sub>; C(=O)(alkyl); C(=O)(aryl); C(=O)(aralkyl); C(=O)O(alkyl); C(=O)O(aryl); C(=O)O(aralkyl); OC(=O)(alkyl); OC(=O)(aryl); OC(=O)(aralkyl); OC(=O)O(alkyl); OC(=O)O(aryl); OC(=O)O(aralkyl); S-alkyl; S-alkenyl; S-alkynyl; S-aryl, S(=O)<sub>2</sub>-alkyl; S(=O)<sub>2</sub>-O-alkyl; S(=O)<sub>2</sub>-alkenyl; S(=O)<sub>2</sub>-aralkyl; and S(=O)<sub>2</sub>-aryl. One of skill in art can readily choose a suitable substituent based on the synthesis, stability and pharmacological activity of the compound of the invention.

35 The "  "

As used herein in the chemical structure drawings, the above arrow when drawn from an atom in a chemical group indicates the point of attachment of that chemical group to another chemical group, without specifying the other chemical group. Thus, according to this definition,



represents the point of attachment of the depicted piperidine to another chemical group, such as for example the following:



The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of this invention encompass any composition made by admixing a compound of this invention and a pharmaceutically acceptable carrier.

The term "EC<sub>50</sub>" is intended to include the molar concentration of an agonist which produced 50% of the maximum possible response for that agonist. By way of example, a compound which, at a concentration of 72 nM, produces 50% of the maximum possible response for that compound as determined in a cAMP assay, has an EC<sub>50</sub> of 72 nM. Unless otherwise specified, the molar concentration associated with an EC<sub>50</sub> determination is in nanomoles (nM).

The term "K<sub>i</sub> (nM)" is intended to include the equilibrium receptor binding affinity representing the molar concentration of a competing compound that binds to half the binding sites of a receptor at equilibrium in the absence of a competitor. In general, the K<sub>i</sub> is inversely correlated to the affinity of the compound for the receptor, such that if the K<sub>i</sub> is low, the affinity is high. K<sub>i</sub> may be determined using the equation of Cheng and Prusoff (Cheng Y., Prusoff W. H., *Biochem. Pharmacol.* 22: 3099-3108, 1973):

$$K_i = \frac{IC_{50}}{1 + \frac{[ligand]}{K_d}}$$

where "ligand" is the concentration of ligand, which may be a radioligand, and K<sub>d</sub> is an inverse measure of receptor affinity which produces 50% receptor occupancy. Unless otherwise specified, the molar concentration associated with a K<sub>i</sub> determination is nM. IC<sub>50</sub> is the concentration of ligand at which 50% of receptor-bound radioligand or other ligand is displaced from the receptor sites in a competitive receptor binding displacement assay.

The terms "treat," "treating" and "treatment," as used herein, contemplate an action that occurs while a patient is suffering from the specified disease or disorder, which reduces the severity of the disease or disorder.

As used herein, the term "pharmaceutically effective amount" means the amount of a compound of the invention that will elicit a biological or medical response in the mammal that is being treated by a medical doctor or other clinician.

As used herein, the term "prophylactically effective" or "preventive" means the amount of a compound of the invention that will prevent or inhibit affliction or mitigate affliction of a mammal with a medical condition that a medical doctor or other clinician is trying to prevent, inhibit, or mitigate before a patient begins to suffer from the specified disease or disorder.

The term "pharmaceutically acceptable salt(s)", as used herein includes salts prepared from pharmaceutically acceptable non-toxic inorganic or organic bases or acids, thereby constituting pharmaceutically acceptable acid and base addition salts (see Handbook of Pharmaceutical Salts: Properties, Selection and Use, P. H. Stahl, P. G. Wermuth, IUPAC, Wiley-VCH, 2002). Acid addition salts are formed from inorganic or organic acids. Examples of suitable non-toxic acid addition salts are acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Hemisalts of the acids may also be formed, for example, hemisulphate. Base-addition salts are formed from inorganic or organic bases. Examples of suitable non-toxic base-addition salts are salts derived from aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, TEA, trimethylamine, tripropylamine, and tromethamine.

The chemical naming protocol and structure diagrams used herein employ and rely on the chemical naming features as utilized by the ChemDraw program (available from CambridgeSoft Corp.) or ISIS Draw (available from MDL Information Systems Inc.). In particular, certain compound names were derived from the structures using the *Autonom* program as utilized by Chemdraw Ultra or ISIS Draw. In general, structure diagrams do not depict hydrogen atoms other than on heteroatoms, in terminal groups and other special circumstances.

## 2. ISOMERIC PURITY, PRODRUGS AND ISOTOPICALLY-SUBSTITUTED COMPOUNDS

*Isomeric Purity and Isolation.* The compounds of the invention can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., cis-trans isomers or geometric isomers), enantiomers (optical isomers), or diastereomers. According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention,

encompass the racemic form of compounds as well as all enantiomers and stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures.

A compound is considered optically active or enantiomerically pure (i.e., substantially the R-form or substantially the S-form) with respect to a chiral center when the compound is about 90% ee (enantiomeric excess) or greater, preferably, equal to or greater than 95% ee with respect to a particular chiral center. A compound of the invention is considered to be in enantiomerically enriched form when the compound has an enantiomeric excess of greater than about 80% ee, preferably greater than about 85% ee. As used herein, a racemic mixture means about 50% of one enantiomer and about 50% of its corresponding enantiomer relative to all chiral centers in the molecule. Thus, the invention encompasses all enantiomerically pure, enantiomerically enriched, and racemic mixtures of compounds of the invention.

Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

The compounds of the invention also include, where possible, all tautomeric isomers thereof, such as prototropic tautomerism (e.g. hydroxypyridine – pyridone, ketone – enol, amide – imidic acid, amine – imine), annular tautomerism, ring-chain tautomerism and valence tautomerism.

*Prodrugs.* The invention is further intended to include prodrugs of the compounds of the invention, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological compounds. In general, such prodrugs will be functional derivatives of compounds of the invention, which are readily convertible in vivo into a compound of formula (I). Prodrugs are any covalently bonded compounds, which release the active parent compound drug of formula (I) in vivo. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985 and Rautio, J., et al., "Prodrugs: design and clinical applications," *Nat. Rev. Drug Disc.* 7:255-270 (2008). Typical examples of prodrugs have biologically labile protecting groups on a functional moiety, such as for example by esterification of hydroxyl, carboxyl or amino functions. Broadly speaking, prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated or dephosphorylated to produce an active parent drug of formula (I) in vivo.

*Isotopically-Substituted Compounds.* The subject invention also includes compounds which are identical to those recited in formula (I), but for the fact that one or more atoms depicted in formula (I) are replaced by an atom 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 incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen and fluorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,



$^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$  or  $^{19}\text{F}$ . Compounds of this invention and pharmaceutically acceptable salts or solvates of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of this invention, for example those into which radioactive isotopes such as  $^3\text{H}$  and  $^{14}\text{C}$  are incorporated, may have use in a variety of assays, such as drug and/or substrate tissue distribution assays. Substitution with heavier isotopes, such as substitution of one or more hydrogen atoms with deuterium ( $^2\text{H}$ ), can provide pharmacological advantages in some instances, including increased metabolic stability. Isotopically labeled compounds of formula (I) can generally be prepared by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

### 3. FORMULATION AND USE OF COMPOUNDS OF THE INVENTION

Compounds of the invention can be used for both medical applications and animal husbandry or veterinary applications. Typically, the compound, or a pharmaceutical composition including the compound, is used in humans, but may also be used in other mammals. The term "patient" is intended to denote a mammalian individual, and is so used throughout the specification and in the claims. The primary applications of this invention involve human patients, but this invention may be applied to laboratory, farm, zoo, wildlife, pet, sport or other animals.

The compounds disclosed herein, or made by methods disclosed herein, may be used for the treatment of any condition, syndrome or disease, and in particular for any condition, syndrome or disease for which a melanocortin receptor-specific molecule has some efficacy. The compounds disclosed herein, or made by methods disclosed herein, can have one or more advantages relative to melanocortin receptor-specific peptides, including but not limited to advantages such as increased resistance to enzymatic degradation, increased circulation half life, increased bioavailability, increased efficacy, increased specificity, prolonged duration of effect and combinations of the foregoing.

*Salt Form of Compounds.* The compounds of this invention may be in the form of any pharmaceutically acceptable salt. The pharmaceutically acceptable salts may be salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include salts of aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of this invention is basic, acid addition salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, carboxylic, citric, ethanesulfonic, formic, fumaric,

gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pantoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Acid addition salts of the compound of this invention are prepared in a suitable solvent from the compound and an excess of an acid, such as

5 hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic, citric, tartaric, maleic, succinic or methanesulfonic acid. The acetate salt form is especially useful. Where the compound of embodiments of this invention include an acidic moiety, suitable pharmaceutically acceptable salts may include alkali metal salts, such as sodium or potassium salts, or alkaline earth metal salts, such as calcium or magnesium salts.

10 *Pharmaceutical Compositions.* Another embodiment of this invention provides a pharmaceutical composition that includes a compound of this invention and a pharmaceutically acceptable carrier. The carrier may be a liquid formulation, and is preferably a buffered, isotonic, aqueous solution. Pharmaceutically acceptable carriers also include excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like, as hereafter

15 described.

The compounds of the several embodiments of this invention may be formulated or compounded into pharmaceutical compositions that include at least one compound of this invention together with one or more pharmaceutically acceptable carriers, including excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like, as may

20 be desired. Formulation excipients may include polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride and sodium citrate. For injection or other liquid administration formulations, water containing at least one or more buffering constituents is preferred, and stabilizing agents, preservatives and solubilizing agents may also be employed. For solid administration formulations, any of a variety of thickening, filler, bulking and carrier additives may be employed, such as

25 starches, sugars, amino acids, fatty acids and the like. For topical administration formulations, any of a variety of creams, ointments, gels, lotions and the like may be employed. For most pharmaceutical formulations, non-active ingredients will constitute the greater part, by weight or volume, of the preparation. For pharmaceutical formulations, it is also contemplated that any of a variety of measured-release, slow-release or time-release formulations and additives may be employed, so that the dosage

30 may be formulated so as to effect delivery of a compound of this invention over a period of time.

In general, the actual quantity of compounds administered to a patient will vary between fairly wide ranges depending on the mode of administration, the formulation used, and the response desired.

In practical use, the compounds can be combined as the active ingredient in an admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier

35 may take a wide variety of forms depending on the form of preparation desired for administration, for example, oral, parenteral (including intravenous), urethral, vaginal, nasal, dermal, transdermal, pulmonary, deep lung, inhalation, buccal, sublingual, or the like. In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral

liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets.

5           Because of their ease of administration, tablets and capsules represent an advantageous oral dosage unit form. If desired, a composition including a compound of this invention may be coated by standard aqueous or nonaqueous techniques. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. In another advantageous dosage unit form, sublingual pharmaceutical compositions may be employed, such as sheets, wafers, tablets or  
10   the like. The active compound can also be administered intranasally as, for example, by liquid drops or spray.

          The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch or alginic acid; a lubricant such as magnesium stearate; and a sweetening  
15   agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

          Various other materials may be utilized as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as  
20   preservatives, a dye and a flavoring such as cherry or orange flavor.

          Compounds may also be administered parenterally. Solutions or suspensions of active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. These preparations may optionally contain a preservative to prevent the growth of microorganisms.  
25   Lyophilized single unit formulations may also be employed, such as are reconstituted with saline prior to administration, and thus do not require a preservative.

          The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders, such as lyophilized formulations, for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the  
30   extent that it may be administered by syringe. The form must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, a polyol, for example glycerol, propylene glycol or liquid polyethylene glycol, suitable mixtures thereof, and vegetable oils.

35           Compounds as disclosed herein may be therapeutically applied by means of nasal administration. By "nasal administration" is meant any form of intranasal administration of any of the compounds of this invention. The compounds may be in an aqueous solution, such as a solution including saline, citrate or other common excipients or preservatives. The compounds may also be in a dry or powder formulation.

In an alternative embodiment, compounds may be administered directly into the lung. Intrapulmonary administration may be performed by means of a metered dose inhaler, a device allowing self-administration of a metered bolus of a compound of this invention when actuated by a patient during inspiration. Both dry powder inhalation and nebulized aerosols may be employed.

5 According to another embodiment of this invention, compounds of this invention may be formulated with any of a variety of agents that increase effective nasal absorption of drugs, including peptide drugs. These agents should increase nasal absorption without unacceptable damage to the mucosal membrane. U.S. Patents 5,693,608, 5,977,070 and 5,908,825, among others, teach a number of pharmaceutical compositions that may be employed, including absorption enhancers, and the  
10 teachings of each of the foregoing, and all references and patents cited therein, are incorporated by reference.

If in an aqueous solution, certain compounds of this invention may be appropriately buffered by means of saline, acetate, phosphate, citrate, acetate or other buffering agents, which may be at any physiologically acceptable pH, generally from about pH 4 to about pH 7. A combination of buffering  
15 agents may also be employed, such as phosphate buffered saline, a saline and acetate buffer, and the like. In the case of saline, a 0.9% saline solution may be employed. In the case of acetate, phosphate, citrate, acetate and the like, a 50 mM solution may be employed. In addition to buffering agents, a suitable preservative may be employed, to prevent or limit bacteria and other microbial growth. One such preservative that may be employed is 0.05% benzalkonium chloride.

20 It is also possible and contemplated that the compound may be in a dried and particulate form. In a preferred embodiment, the particles are between about 0.5 and 6.0  $\mu\text{m}$ , such that the particles have sufficient mass to settle on the lung surface, and not be exhaled, but are small enough that they are not deposited on surfaces of the air passages prior to reaching the lung. Any of a variety of different techniques may be used to make dry powder microparticles, including but not limited to micro-milling,  
25 spray drying and a quick freeze aerosol followed by lyophilization. With micro-particles, the compounds may be deposited to the deep lung, thereby providing quick and efficient absorption into the bloodstream. Further, with such approach penetration enhancers are not required, as is sometimes the case in transdermal, nasal or oral mucosal delivery routes. Any of a variety of inhalers can be employed, including propellant-based aerosols, nebulizers, single dose dry powder inhalers and multidose dry  
30 powder inhalers. Common devices in current use include metered dose inhalers, which are used to deliver medications for the treatment of asthma, chronic obstructive pulmonary disease and the like. Preferred devices include dry powder inhalers, designed to form a cloud or aerosol of fine powder with a particle size that is always less than about 6.0  $\mu\text{m}$ .

35 Microparticle size, including mean size distribution, may be controlled by means of the method of making. For micro-milling, the size of the milling head, speed of the rotor, time of processing and the like control the microparticle size. For spray drying, the nozzle size, flow rate, dryer heat and the like control the microparticle size. For making by means of quick freeze aerosol followed by lyophilization, the nozzle size, flow rate, concentration of aerosoled solution and the like control the microparticle size. These parameters and others may be employed to control the microparticle size.

The compounds of this invention may be therapeutically administered by means of an injection, typically a deep intramuscular injection, such as in the gluteal or deltoid muscle, of a time release injectable formulation. In one embodiment, a compound of this invention is formulated with a PEG, such as poly(ethylene glycol) 3350, and optionally one or more additional excipients and preservatives, including but not limited to excipients such as salts, polysorbate 80, sodium hydroxide or hydrochloric acid to adjust pH, and the like. In another embodiment a compound of this invention is formulated with a poly(ortho ester), which may be an auto-catalyzed poly(ortho ester) with any of a variable percentage of lactic acid in the polymeric backbone, and optionally one or more additional excipients. In one embodiment poly (D,L-lactide-co-glycolide) polymer (PLGA polymer) is employed, preferably a PLGA polymer with a hydrophilic end group, such as PLGA RG502H from Boehringer Ingelheim, Inc. (Ingelheim, Germany). Such formulations may be made, for example, by combining a compound of this invention in a suitable solvent, such as methanol, with a solution of PLGA in methylene chloride, and adding thereto a continuous phase solution of polyvinyl alcohol under suitable mixing conditions in a reactor. In general, any of a number of injectable and biodegradable polymers, which are preferably also adhesive polymers, may be employed in a time release injectable formulation. The teachings of U.S. Patents 4,938,763, 6,432,438, and 6,673,767, and the biodegradable polymers and methods of formulation disclosed therein, are incorporated here by reference. The formulation may be such that an injection is required on a weekly, monthly or other periodic basis, depending on the concentration and amount of compound, the biodegradation rate of the polymer, and other factors known to those of skill in the art.

*Routes of Administration.* If it is administered by injection, the injection may be intravenous, subcutaneous, intramuscular, intraperitoneal or other means known in the art. The compounds of this invention may be formulated by any means known in the art, including but not limited to formulation as tablets, capsules, caplets, suspensions, powders, lyophilized preparations, suppositories, ocular drops, skin patches, oral soluble formulations, sprays, aerosols and the like, and may be mixed and formulated with buffers, binders, excipients, stabilizers, anti-oxidants and other agents known in the art. In general, any route of administration by which the compounds of this invention are introduced across an epidermal layer of cells may be employed. Administration means may thus include administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, pulmonary administration, nasal administration, urethral administration, vaginal administration, and the like.

In one aspect, a compound of this invention is administered by means of a time release injectable formulation, such as a compound of this invention in a formulation with a PEG, poly(ortho ester) or PLGA polymer. In another aspect, a compound of this invention is administered by means of an automated delivery device providing subcutaneous delivery, either continuous or intermittent. A compound of this invention may also be administered by transdermal administration.

*Therapeutically Effective Amount.* In general, the actual quantity of compound of this invention administered to a patient will vary between fairly wide ranges depending upon the mode of administration, the formulation used, and the response desired. The dosage for treatment is

administration, by any of the foregoing means or any other means known in the art, of an amount sufficient to bring about the desired therapeutic effect. Thus a therapeutically effective amount includes an amount of a compound or pharmaceutical composition of this invention that is sufficient to induce a desired effect.

5 In general, the compounds of this invention are highly active. For example, for systemic applications the compound can be administered at about 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 50, or 100 µg/kg body weight, depending on the specific compounds selected, the desired therapeutic response, the route of administration, the formulation and other factors known to those of skill in the art.

*Therapeutic Application.* In one embodiment, compounds of this invention that are MCR-1  
10 specific can be used as chemoprevention agents against sun-induced, such as by UV radiation, neoplastic activity in human skin. MCR-1 agonist compounds of this invention may be employed to stimulate epidermal melanocytes to produce melanin as well as to convert pheomelanin to eumelanin. Eumelanin, which is dark brown or black pigmentation, is considered more photo-protective than pheomelanin, which is yellow or red pigmentation. The process of melanogenesis is believed to involve  
15 stimulation of MCR-1 in epidermal melanocytes, thereby mediating the stimulation of tyrosinase enzymes within these pigment cells, inducing the conversion of tyrosine to dopa and then through dopaquinone to eumelanin. Sun tanning due to direct sun exposure is proposed to result from the same pathway by local production of melanotropic peptide from a POMC gene in the epidermis. Thus, stimulation of eumelanin production and conversion of pheomelanin to eumelanin may be a desirable chemoprevention modality in  
20 blocking sun- or UV-induced neoplastic activity in skin. A potent, high-affinity and highly selective MCR-1 agonist compound of this invention can accordingly be used as a therapeutic chemoprevention agent for combating harmful sun or UV exposure that induces neoplastic activity in skin melanocytes.

MCR-1 agonist compounds and/or MCR-3 agonist compounds may be used to treat, prevent or ameliorate the effects of a number of inflammatory diseases and inflammatory conditions. In one aspect,  
25 the inflammatory condition results from a disease including a form of arthritis, including but not limited to osteoarthritis, rheumatoid arthritis, septic arthritis, gout and pseudogout, juvenile idiopathic arthritis, Still's disease and ankylosing spondylitis, as well as arthritis secondary to other diseases, such as arthritis secondary to lupus erythematosus, Henoch-Schönlein purpura, psoriatic arthritis, reactive arthritis, haemochromatosis, hepatitis, Wegener's granulomatosis, vasculitis syndromes, Lyme disease, familial  
30 Mediterranean fever, hyperimmunoglobulinemia D with recurrent fever, TNF receptor-associated periodic syndrome and inflammatory bowel disease, including Crohn's disease and ulcerative colitis. In another aspect, the inflammatory condition results from a disease including a form of inflammatory bowel disease, such as Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischemic colitis, diversion colitis, Behçet's syndrome, infective colitis and indeterminate colitis. In another aspect, the  
35 inflammatory condition results from an autoimmune disease, including but not limited to systemic syndromes such as systemic lupus erythematosus, Sjögren's syndrome, scleroderma, rheumatoid arthritis and polymyositis, or a syndrome affecting only a local body system, such as the endocrine system (diabetes mellitus type 1, Hashimoto's thyroiditis, Addison's disease, etc.), dermatologic system (pemphigus vulgaris), hematologic system (autoimmune hemolytic anemia), or neural system (multiple

sclerosis). Thus autoimmune diseases include, in addition to the general syndromes discussed above, such diseases and conditions as acute disseminated encephalomyelitis, Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, autoimmune oophoritis, celiac disease, Crohn's disease, gestational pemphigoid, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome, Hashimoto's disease, idiopathic thrombocytopenic purpura, Kawasaki disease, lupus erythematosus, mixed connective tissue disease, multiple sclerosis, myasthenia gravis, opsoclonus myoclonus syndrome, optic neuritis, Ord's thyroiditis, pemphigus, pernicious anaemia, primary biliary cirrhosis, Reiter's syndrome, Sjögren's syndrome, Takayasu's arteritis, temporal arteritis, autoimmune hemolytic anemia and Wegener's granulomatosis.

In another aspect, the inflammatory condition results from or is related to chronic obstructive pulmonary disease (COPD), also known as chronic obstructive airway diseases, including but not limited to diseases characterized by the pathological limitation of airflow in the airway that is not fully reversible, such as for example chronic bronchitis, emphysema, pneumoconiosis, pulmonary neoplasms and other lung disorders. Other inflammatory conditions include upper or lower airway diseases and disorders, such as allergic asthma, non-allergic asthma, allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, non-allergic conjunctivitis, and the like, as well as airway diseases related to external toxins or substances, such as various forms of pneumoconiosis (coalworker's pneumoconiosis, asbestosis, silicosis, bauxite fibrosis, berylliosis, or siderosis), byssinosis or hypersensitivity pneumonitis (farmer's lung or bird fancier's lung). Other lung diseases involving an inflammatory condition include acute respiratory distress syndrome. The compounds and compositions of this invention are of particular utility for treatment of conditions wherein glucocorticoids are either ineffectual or inadequate to bring about the desired pharmacological response, such as COPD, asthma in individuals who smoke, and other conditions characterized, in whole or in part, by eosinophil accumulation in the lung, neutrophil infiltration and activation, alveolar macrophage recruitment and activation, epithelial cell expression of IL-8 or increased expression of TNF- $\alpha$ . For airway or lung disorders, in one aspect the compounds of this invention are delivered systemically; in another aspect the compounds of this invention are delivered locally, such as by inhalation administration.

In yet another aspect, the inflammatory condition results from or is related to some form of transplant-related condition or syndrome, such as graft-versus-host disease, hyperacute rejection, acute rejection, or chronic rejection. Graft-versus-host disease is a common complication of allogeneic bone marrow transplantation, but can occur with other transplantations, and particularly those with T cells present in the graft, either as contaminants or intentionally introduced. Hyperacute, acute or chronic rejection can occur with bodily organs such as kidneys, liver, pancreas, spleen, uterus, heart or lungs, as well as transplantation of bone, cornea, face, hand, penis or skin. In one embodiment, a pharmaceutical composition including one or more of the compounds of this invention is given prophylactically to limit or prevent a transplant-related condition or syndrome, such as immediately before, during or after transplantation of a bodily fluid, organ or part. In another embodiment, the bodily fluid, organ or part being transplanted is perfused with a solution of a pharmaceutical composition including one or more of the compounds of this invention. In yet another embodiment, one or more of the compounds of this invention

are administered in conjunction with, combination with or series with one or more other agents for transplant rejection, such as calcineurin inhibitors including cyclosporin or tacrolimus, mTOR inhibitors including sirolimus or everolimus, anti-proliferatives including azathioprine or mycophenolic acid, corticosteroids including prednisolone or hydrocortisone, antibodies such as monoclonal anti-IL-2R $\alpha$  receptor antibodies, basiliximab or daclizumab, or polyclonal anti-T-cell antibodies such as anti-thymocyte globulin or anti-lymphocyte globulin.

Compounds of this invention may also be directed towards the treatment of fibrotic and sclerotic diseases, indications, conditions and syndromes in a subject. There are a number of fibrotic and sclerotic diseases, indications, conditions and syndromes which may be so treated. Fibrotic and sclerotic diseases, indications, conditions and syndromes frequently include an inflammatory component, and thus many may similarly be categorized as an inflammatory disease or condition. Fibrotic and sclerotic diseases and conditions, in addition to including an inflammatory component, may also be idiopathic, toxic, hereditary and/or pharmacologically-induced disorders. In general, fibrotic disorders are characterized by excessive production of extracellular matrix, primarily type I collagen, which may result in loss of organ function. It is believed, without wishing to be bound by theory, that agonism of MCR-1 can result in suppression of transforming growth factor- $\beta_1$ -induced collagen synthesis by human dermal fibroblasts, thereby providing therapeutic and/or prophylactic benefit for fibrotic and sclerotic diseases, indications, conditions and syndromes. Representative fibrotic and sclerotic diseases and conditions that can be so treated include, but are not limited to, localized scleroderma, systemic sclerosis, sclerodermic graft-versus-host disease of the skin, idiopathic lung fibrosis, bleomycin-induced lung fibrosis, cyclosporine-induced nephropathy, cirrhosis of the liver, hypertrophic scars, keloids and the like.

Expression of various cytokines is increased during an inflammatory process, including an inflammatory process secondary to circulatory shock, ischemia, reperfusion injury and the like. TNF- $\alpha$  is a pleiotropic cytokine produced mainly by macrophages, and also by other types of cells. Other cytokines which increase during an inflammatory process, including an inflammatory process secondary to circulatory shock, ischemia, reperfusion injury and the like, include IL-1 and IL-6. While cytokines such as TNF- $\alpha$  have beneficial effects in many instances, significantly increased levels, such as secondary to circulatory shock, ischemia, reperfusion injury and the like, can have pathological effects. In one embodiment, the invention is directed to methods of using one or more of the compounds of this invention to decrease pro-inflammatory cytokine production and expression, including decreasing pro-inflammatory cytokine production and expression secondary to circulatory shock, ischemia, reperfusion injury and the like. The decrease in pro-inflammatory cytokine production and expression, including without limitation one or more of TNF- $\alpha$ , IL-1 and IL-6, occurs instantaneously or within a short time period following administration of a composition comprising one or more of the compounds of this invention. The invention is further directed to methods of using one or more of the compounds of this invention to increase anti-inflammatory cytokine production and expression. The increase in anti-inflammatory cytokine production and expression, including without limitation IL-10, occurs instantaneously or within a short time period following administration of a composition comprising one or more of the compounds of this invention.



Certain cancers, such as mesothelioma, are reported to be very sensitive to growth-promoting influences of cytokines and growth factors, and may be treatable by means of compounds selective for MCR-1. Canania, A., et al., "Autocrine inhibitory influences of  $\alpha$ -melanocyte-stimulating hormone in malignant pleural mesothelioma," *J. Leukoc. Biol.* 75:253-259 (2004). Cancers that may be so treated include pleural mesothelioma, known to express mRHA for MCR-1 and the receptor protein, as well as other tumors that express MCR-1, including but not limited to adenocarcinoma, such as pulmonary adenocarcinoma.

There are a number of ocular diseases, indications, conditions and syndromes characterized by inflammation, including but not limited to increased cytokine production. One example is dry eye disease, an ocular disease affecting approximately 10-20% of the population. There are many possible variables that can influence a patient's signs or symptoms of dry eye including levels of circulating hormones, various autoimmune diseases (e.g. Sjogren's syndrome and systemic lupus erythematosus), ocular surgeries including PRK or LASIK, many medications, environmental conditions, visual tasking such as computer use, ocular fatigue, contact lens wear, and mechanical influences such as corneal sensitivity, partial lid closure, surface irregularities (e.g. pterygium), and lid irregularities (e.g. ptosis, entropion/ectropion, pinguecula). Another inflammatory disease of the eye is uveitis, an ocular disease involving inflammation of the middle layer or uvea of the eye, which may also be understood to include any inflammatory process involving the interior of the eye. Uveitis includes anterior, intermediate, posterior and panuveitic forms, with the majority of uveitis cases anterior in location, involving inflammation of the iris and anterior chamber. This condition can occur as a single episode and subside with proper treatment or may take on a recurrent or chronic nature. Symptoms include red eye, injected conjunctiva, pain and decreased vision. Signs include dilated ciliary vessels, presence of cells and flare in the anterior chamber, and keratic precipitates on the posterior surface of the cornea. Intermediate uveitis includes inflammation and the presence of inflammatory cells in the vitreous cavity, and posterior uveitis include the inflammation of the retina and choroid. Uveitis may be secondary to any of a number of diseases and disorders, including acute posterior multifocal placoid pigment epitheliopathy, ankylosing spondylitis, Behçet's disease, birdshot retinochoroidopathy, brucellosis, herpes simplex, herpes zoster, inflammatory bowel disease, juvenile rheumatoid arthritis, Kawasaki disease, leptospirosis, Lyme disease, multiple sclerosis, psoriatic arthritis, Reiter's syndrome, sarcoidosis, syphilis, systemic lupus erythematosus, toxocariasis, toxoplasmosis, tuberculosis, Vogt-Koyanagi-Harada syndrome, Whipple disease or polyarteritis nodosa. In one embodiment, the invention is directed to methods of using one or more of the compounds of this invention for treatment of any of the foregoing ocular diseases, indications, conditions and syndromes. Such treatment may include treatment by means of eye drops, ointments, gels, washes, implants, plugs or other means and methods for delivering one or more of the compounds of this invention to an ocular surface.

Compounds of this invention that are ligands of MCR-4 are believed to be useful in treating diseases, disorders and/or conditions responsive to modulation of the MCR-4, more particularly activation of the MCR-4, i.e. diseases, disorders and/or conditions which would benefit from agonism (including full or partial agonism) at the MCR-4, including energy homeostasis and metabolism related (such as

diabetes, in particular type 2 diabetes; dyslipidemia; fatty liver; gout; hypercholesterolemia; hypertriglyceridemia; hyperuricacidemia; impaired glucose tolerance; impaired fasting glucose; insulin resistance syndrome; and metabolic syndrome), food intake related (such as hyperphagia; binge eating; bulimia; and compulsive eating) and/or energy balance and body weight related diseases, disorders and/or conditions, more particularly such diseases, disorders and conditions characterized by excess body weight and/or excess food intake.

Compounds of this invention that are ligands of MCR-4 are particularly believed to be useful for treatment of body weight related diseases, disorders and/or conditions characterized by excess body weight, including obesity and overweight (by promotion of weight loss, maintenance of weight loss, and/or prevention of weight gain, including medication-induced weight gain or weight gain subsequent to cessation of smoking), and diseases, disorders and/or conditions associated with obesity and/or overweight, such as insulin resistance; impaired glucose tolerance; type 2 diabetes; metabolic syndrome; dyslipidemia (including hyperlipidemia); hypertension; heart disorders (e.g. coronary heart disease, myocardial infarction); cardiovascular disorders; non-alcoholic fatty liver disease (including non-alcoholic steatohepatitis); joint disorders (including secondary osteoarthritis); gastroesophageal reflux; sleep apnea; atherosclerosis; stroke; macro and micro vascular diseases; steatosis (e.g. in the liver); gall stones; and gallbladder disorders.

It will be understood that there are medically accepted definitions of obesity and overweight. A patient may be identified by, for example, measuring body mass index (BMI), which is calculated by dividing weight in kilograms by height in metres squared, and comparing the result with the definitions. The recommended classifications for BMI in humans, adopted by the Expert Panel on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults, and endorsed by leading organizations of health professionals, are as follows: underweight  $< 18.5 \text{ kg/m}^2$ , normal weight  $18.5\text{-}24.9 \text{ kg/m}^2$ , overweight  $25\text{-}29.9 \text{ kg/m}^2$ , obesity (class 1)  $30\text{-}34.9 \text{ kg/m}^2$ , obesity (class 2)  $35\text{-}39.9 \text{ kg/m}^2$ , extreme obesity (class 3)  $\geq 40 \text{ kg/m}^2$  (Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The North American Association for the Study of Obesity (NAASO) and the National Heart, Lung and Blood Institute (NHLBI) 2000). Modifications of this classification may be used for specific ethnic groups. Another alternative for assessing overweight and obesity is by measuring waist circumference. There are several proposed classifications and differences in the cut-offs based on ethnic group. For instance, according to the classification from the International Diabetes Federation, men having waist circumferences above 94 cm (cut off for europids) and women having waist circumferences above 80 cm (cut off for europids) are at higher risk of diabetes, dyslipidemia, hypertension and cardiovascular diseases because of excess abdominal fat. Another classification is based on the recommendation from the Adult Treatment Panel III where the recommended cut-offs are 102 cm for men and 88 cm for women. However, the compounds of this invention may also be used for reduction of self-diagnosed overweight and for decreasing the risk of becoming obese due to life style, genetic considerations, heredity and/or other factors. The term "diabetes" includes type 1 diabetes (insulin-dependent diabetes mellitus), latent autoimmune diabetes mellitus of adults (LADA), and type 2 diabetes.

It is believed that compounds of this invention which are MCR-4 agonists or partial agonists, upon administration to an animal, including man, will reduce food intake, body weight and/or body weight gain in that animal. Without being bound by any theory, it is believed that such compounds of this invention act by modulating appetite and/or satiety, increasing metabolic rate, reducing intake of and/or craving for fat and/or carbohydrates.

Without being bound by any theory, it is also believed that compounds of this invention which are MCR-4 agonists or partial agonists, act by enhancing glucose tolerance and/or decreasing insulin resistance. It is therefore believed that such compounds of this invention can be useful also for treatment of type 2 diabetes in underweight and normal weight individuals as well as in overweight and obese individuals.

Compounds of the invention might also be useful for (i) occlusive, haemorrhagic, traumatic or surgical organ and/or tissue damage, such as myocardial infarction and stroke or haemorrhagic or cardiogenic shock.

In another embodiment, compounds of this invention, including but not limited to MCR-4 antagonists, may be used as a therapeutic agent in eating disorders, such as treatment of anorexia and cachexia, which is malnutrition and wasting due to illness. In addition to use in treatment of patients diagnosed with anorexia or cachexia, compounds of this invention may be employed with persons who have below optimal body weight, and in particular with patients desiring to gain additional muscle mass.

In yet another embodiment, compounds of this invention can be used as therapeutic agents for treatment of sexual dysfunction, including treatment of both male erectile dysfunction and female sexual dysfunction.

In yet another embodiment, compounds of this invention may be used as therapeutic agents for treatment of inflammation, including specifically MCR-1, MCR-3 and MCR-5 agonists.

In yet another embodiment of the invention, compounds of this invention that are MCR-5 specific can be used as agents to decrease sebum production, and thus may be efficacious in the treatment of acne and related diseases. The compounds for this application may be conveniently formulated for local administration, as through a gel, lotion, cream or other topical formulation.

In yet another embodiment, compounds of this invention may be employed in the treatment of drug or alcohol dependence, depression, anxiety and related conditions and indications.

#### 4. SYNTHETIC METHODS FOR COMPOUNDS OF THE INVENTION

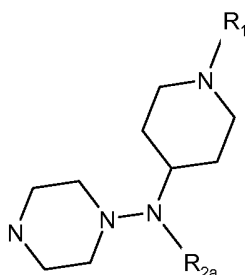
The following synthetic methods were employed in making compounds of this invention. It is to be understood that the invention and the compounds disclosed herein are not limited to those made by the following methods of synthesis, but that other or alternative methods of synthesis can be employed to make compounds within the scope of this invention.

The following abbreviations are employed in the synthetic schemes, and have the meanings given:

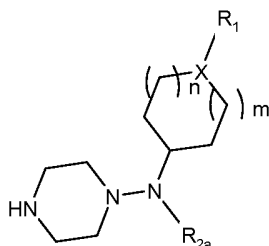
alloc	-	allyloxycarbonyl
boc	-	tert-butoxycarbonyl
cbz	-	carboxybenzyl

EDC	-	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Fmoc	-	9H-fluoren-9-ylmethoxycarbonyl
HATU	-	2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
HBTU	-	O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
PG	-	Refers to a protecting group, and specifically Fmoc, boc, cbz or alloc
TBTU	-	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TFA	-	trifluoroacetic acid

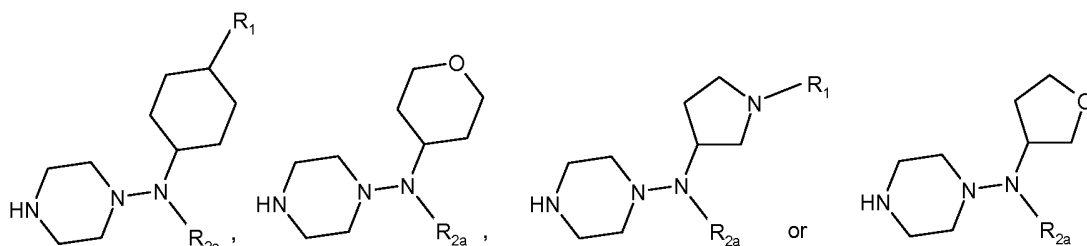
*Scheme A.* Scheme A may be employed to make the precursor compound  $R_1$  and  $R_{2a}$  substituted-piperazin-1-yl-piperidin-4-yl-amine of the following general structure:



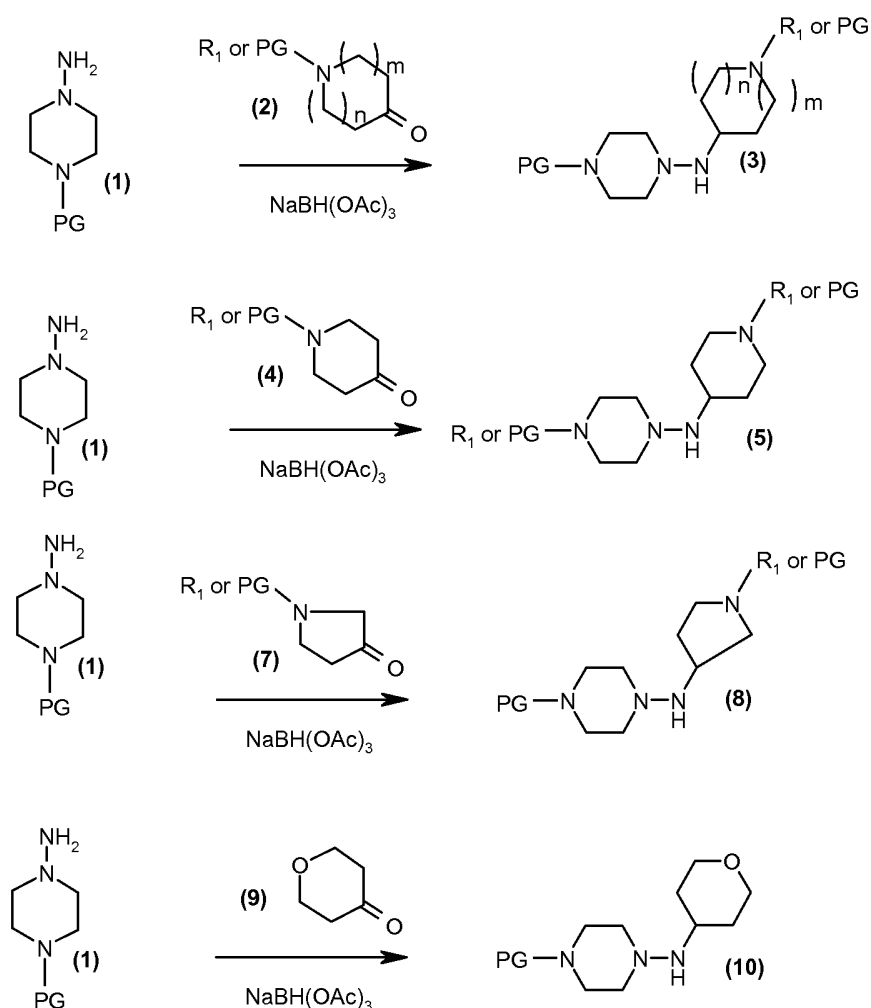
where  $R_1$  is a protecting group (PG) as defined herein, or is H, a  $C_1$  to  $C_{17}$  linear or branched alkyl, cycloalkyl, or alkylcycloalkyl, or a  $C_1$  to  $C_7$  acyl group, in each instance optionally substituted with a terminal amide, amino, monosubstituted amino, disubstituted amino, or nitrile, or is an amide, amino, monosubstituted amino, or disubstituted amino, and  $R_{2a}$  is a  $C_1$  to  $C_{17}$  linear or branched alkyl, cycloalkyl, or alkylcycloalkyl, or a  $C_1$  to  $C_7$  acyl group, in each instance optionally substituted with one or more substituents, and when one or more substituents are present, such substituents are the same or different and independently halo, amino, monosubstituted amino, disubstituted amino, hydroxy, or carboxy. More broadly, Scheme A may be employed to make an amine substituted piperazine precursor compound of the following general structure:



where  $n$  is 1 or 2,  $m$  is 0, 1 or 2,  $X$  is  $CH_2$ , N or O, and  $R_1$  and  $R_{2a}$  are as described above, on the proviso that if  $X$  is O, then  $R_1$  is not present. The foregoing general structure thus includes, by way of example and not limitation, amine substituted piperazine precursor compounds such as:



among other potential compounds resulting from substitution of X and m as set forth above. The foregoing amine substituted piperazine precursor compounds may be made by means of the following general scheme:

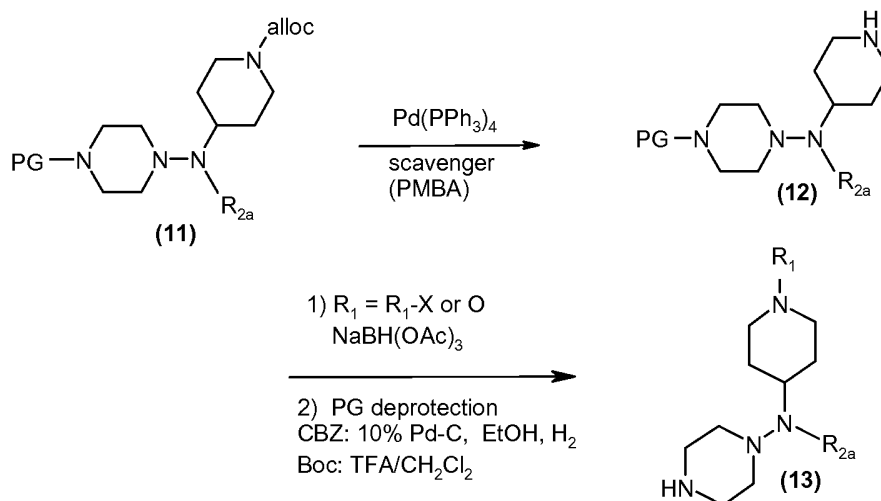


- 5 In the most general case, to equimolar concentrations of (1) and (2) in a solvent such as methylene chloride, dichloroethane or tetrahydrofuran is added  $\text{NaBH}(\text{OAc})_3$  portionwise (typically at 1.5 times the molar concentration of (1) or (2)). The resulting solution is stirred at room temperature for 16 hours, washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated to give amine substituted piperidine (3) which was used without further purification. Similar synthetic methods
- 10 may be employed with (7), yielding amine substituted piperidine (8), or with (9), yielding amine substituted piperidine (10). Similar methods may be employed utilizing any permissible substitutions in (1).

- 15 An  $\text{R}_{2a}$  group may be introduced to (3), (5), (8) or (10) by utilizing equimolar amounts of  $\text{R}_2$ -aldehyde and (3), (5), (8) or (10) in a solvent such as methylene chloride, dichloroethane or tetrahydrofuran and adding  $\text{NaBH}(\text{OAc})_3$  portionwise (typically at 1.5 times the molar concentration of the  $\text{R}_2$ -aldehyde). The resulting solution is stirred at room temperature for 16 hours, washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated to yield product. The  $\text{R}_{2a}$  group may also be introduced to (3), (5), (8) or (10) (1.0 mmol) by the coupling of an organic acid (1.1 mmol), a

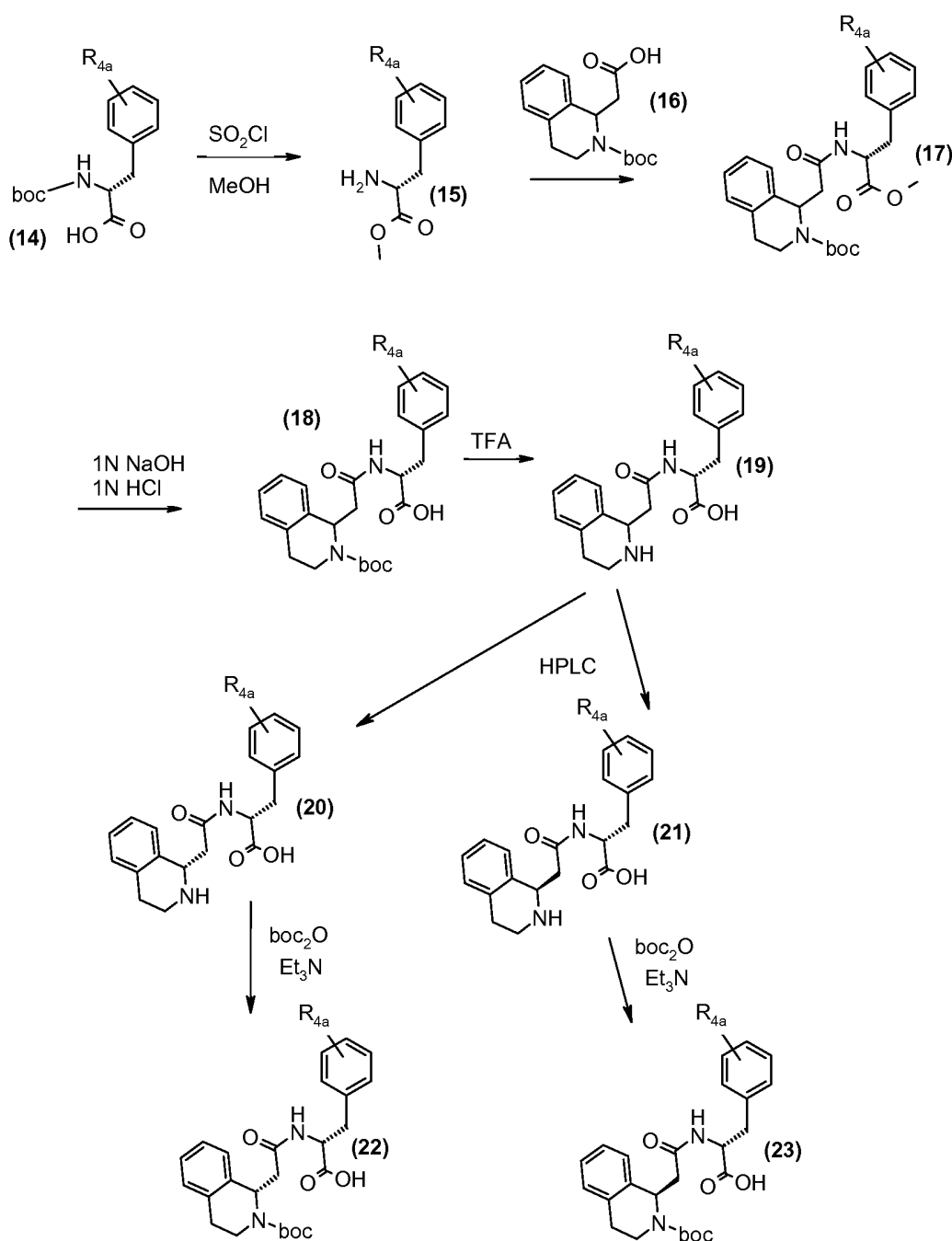
dehydrating reagent such as TBTU, EDC, HATU or HBTU (1.1 mmol) and an organic base such as N-methylmorpholine or diisopropyl ethyl amine (2.0 mmol) in a solvent such as methylene chloride, tetrahydrofuran or dioxane.

Alternatively, an R<sub>2a</sub> group may be introduced to **(3)**, **(5)**, **(8)** or **(10)** by stirring with an activated group (1.2 equivalents), such as an organic acid chloride, isocyanate, chloroformate or sulfonyl chloride (generically R<sub>1</sub>-X) and excess base such as pyridine, diisopropyl ethyl amine, triethylamine or 2,4 lutidine in a solvent such as methylene chloride, dichloroethane or tetrahydrofuran. Any R<sub>2a</sub> may be employed; typical R<sub>2a</sub> groups include methyl, isopropyl, isobutyl, acetyl, sulfonyl, carbamoyl and the like.



By way of example, use of boc as a PG for **(1)** and alloc as a PG for **(2)** results, following introduction of the R<sub>2a</sub> group, in compound **(11)**. Compound **(11)** is selectively deprotected, such as by removal of the alloc group to yield compound **(12)**. For example, to remove the alloc group compound **(11)** is treated at room temperature with catalytic tetrakis(triphenylphosphine)palladium in a solvent such as methylene chloride, tetrahydrofuran or dichloroethane in the presence of an excess (10X) of an allyl acceptor scavenger, such as phenylsilane or 1,3-dimethylbarbituric acid. Following addition of the R<sub>1</sub> group and removal of the protecting group PG (such as for example boc or cbz), the solution is dried over sodium sulfate and evaporated to give the R<sub>1</sub> and R<sub>2a</sub> substituted **(13)**.

Scheme B



Boc protected optionally substituted-phenylalanine (14) (10 mmol), where  $\text{R}_{4a}$  is from one to three permitted substituents, is dissolved in methanol and cooled to 0 °C in an ice bath. A solution of 2M thionyl chloride (5 mL, 10 mmol) is slowly added dropwise keeping the temperature below 5 °C. After 1 hour the solution is allowed to warm to room temperature overnight. The solution is then evaporated, triturated with ether and filtered to give the hydrochloride salt of the resulting ester (15).

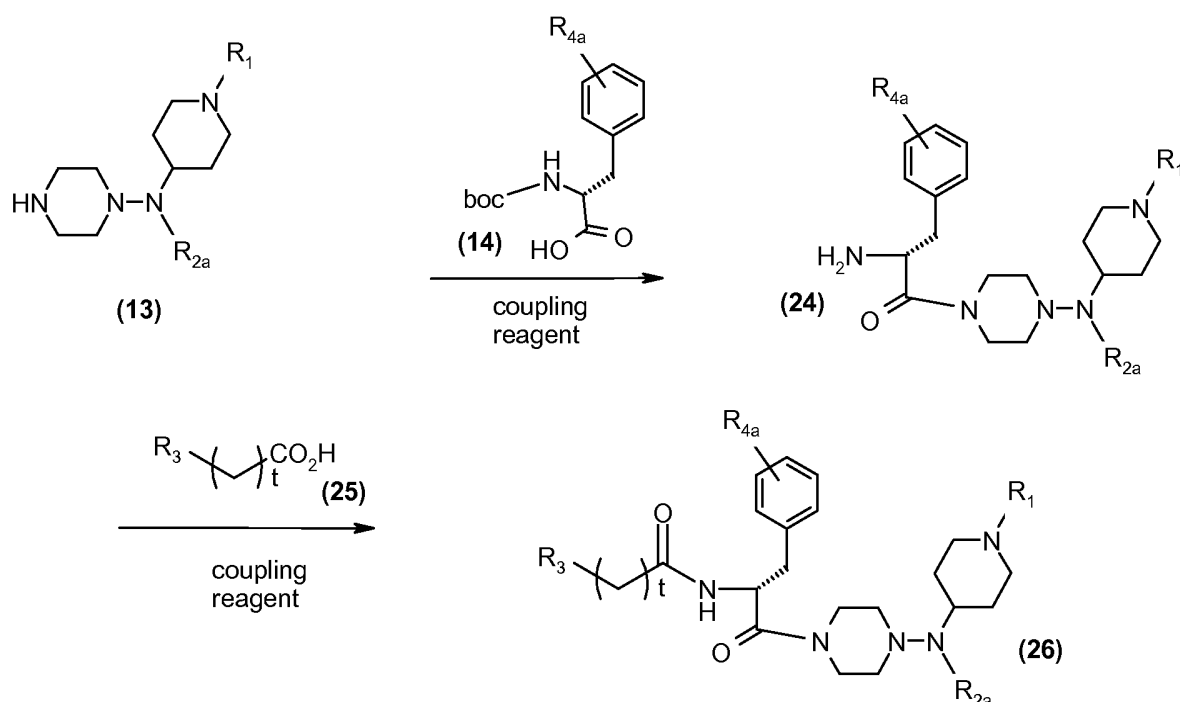
The substituted-phenylalanine (15) (2.0 mmol) is added slowly to a stirred mixture of Boc protected 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid (16) (2.1 mmol), a dehydrating reagent such as TBTU, EDC, HATU or HBTU (2.1 mmol) and an organic base such as N-methylmorpholine or diisopropyl

ethyl amine (6 mmol) in a solvent such as methylene chloride, tetrahydrofuran or dioxane. After stirring for 16 hours the solution is extracted and washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated. The resulting oil is purified on silica gel (40 g) eluted with 40-80% ethyl acetate in heptane.

The purified oil of compound **(17)** is dissolved in methanol (5 mL) and cooled to 0 °C. A solution of 4N sodium hydroxide (4 mL) is slowly added dropwise keeping the temperature below 5 °C. The reaction is stirred for 30 minutes at 0 °C, allowed to warm to room temperature and stirred an additional 2 hours. The resulting solution is concentrated under reduced pressure to remove methanol. The aqueous solution is then treated with 4N hydrochloric acid (4 mL) and brought to pH 1 with 1N hydrochloric acid.

The mixture is extracted into a solvent such as methylene chloride or ethyl acetate and washed with brine, and the organic layer dried over sodium sulfate and evaporated to a solid yielding compound **(18)**. De-protection is accomplished by stirring with excess TFA in a solvent such as methylene chloride for one hour followed by evaporation of the solvent, yielding compound **(19)**. The diastereomers **(20)** and **(21)** are separated by HPLC. Each resulting isomer (0.5 mmol) is boc protected by stirring with boc anhydride (0.5 mmol) and excess base such as triethylamine (0.2 mL) in a solvent such as methylene chloride. After evaporation of the solvent and excess base, the residue is dissolved in a solvent such as methylene chloride or ethyl acetate and washed with 1N hydrochloric acid and then brine. The resulting solution is dried over sodium sulfate and concentrated to a solid, yielding diastereomer compounds **(22)** and **(23)**.

*Scheme C*



R<sub>1</sub> and R<sub>2a</sub> substituted **(13)** (1.0 mmol) is added slowly to a stirred mixture of a boc protected optionally substituted-phenylalanine **(14)** (1.1 mmol), where R<sub>4a</sub> is from one to three permitted substituents, a dehydrating reagent such as TBTU, EDC, HATU or HBTU (1.1 mmol) and an organic base such as N-methylmorpholine or diisopropyl ethyl amine (2.0 mmol) in a solvent such as methylene

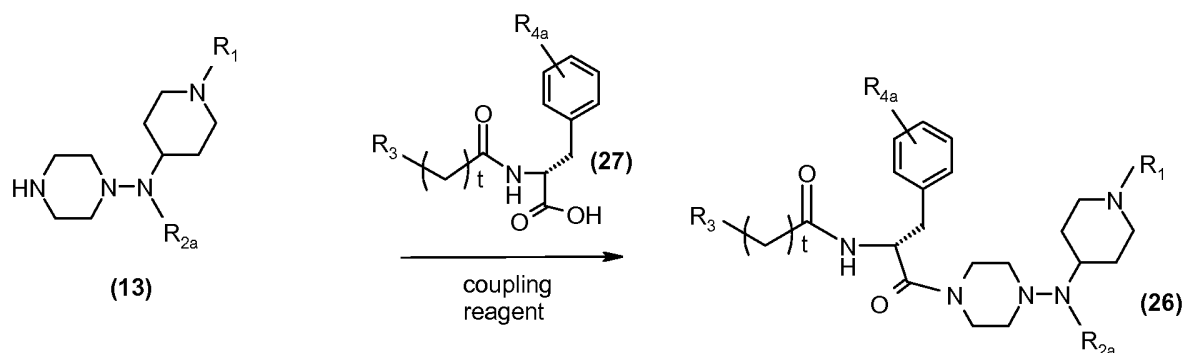


chloride, tetrahydrofuran or dioxane. After stirring for 16 hours the solution is extracted into a solvent such as methylene chloride or ethyl acetate and washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated. De-protection is accomplished by stirring with excess TFA in solvent such as methylene chloride for one hour followed by evaporation of the solvent. The resulting oil was  
5 basified to pH = 8 with sodium bicarbonate and extracted into a solvent such as methylene chloride or ethyl acetate. The solution was dried over sodium sulfate and evaporated to yield an oil as compound (24).

Compound (24) (1.0 mmol) is added slowly to a stirred mixture of a boc-protected R<sub>3</sub>-COOH (25) (1.1 mmol), a dehydrating reagent such as TBTU, EDC, HATU or HBTU (1.1 mmol) and an organic base  
10 such as N-methylmorpholine or diisopropyl ethyl amine (2.0 mmol) in a solvent such as methylene chloride, tetrahydrofuran or dioxane. After stirring for 16 hours the solution is extracted in a solvent such as methylene chloride or ethyl acetate and washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated. Deprotection is accomplished by stirring with excess TFA in a solvent such as methylene chloride for one hour followed by evaporation of the solvent. The compound (26) is purified by  
15 HPLC.

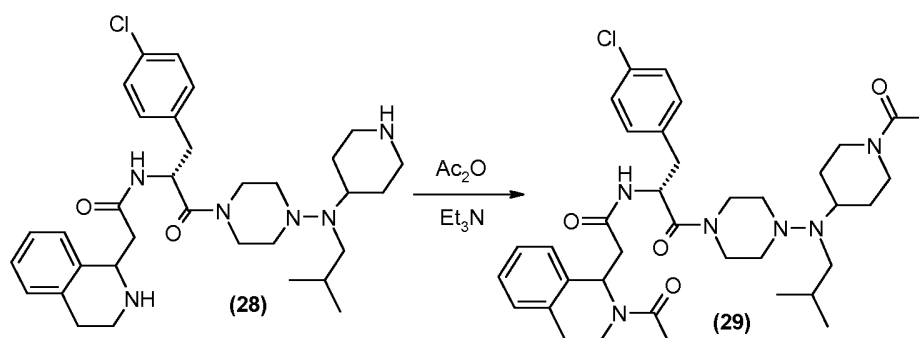
Similar methods may be employed utilizing deprotected and R<sub>2a</sub> substituted compounds derived from (8) or (10) or generally any compound of the general formula (3). The phenylalanine (14) may be optionally substituted with one or more substituents, including specifically substituents that are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, aryl,  
20 alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl. As appropriate, reactive substituents may include protecting groups, which are deprotected to yield final product. For (14), protecting groups other than boc, including specifically alloc, may be employed. In lieu of phenylalanine (14), it is possible to employ a protected and optionally substituted 1-naphthylalanine or 2-naphthylalanine. In compound (25), n may be from 0 to 4, and R<sub>3</sub> is one  
25 or two cyclic radicals, and if two cyclic radicals, optionally fused cyclic radicals or fused cyclic radicals joined by a group such as -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-, -CH<sub>2</sub>-S-, -S-CH<sub>2</sub>-, -C(=O)-NH-, -NH-C(=O)-, -C(=O)-O-, or -O-C(=O)-, the one or two cyclic radicals optionally substituted with one or more ring substituents, and when one or more substituents are present, are the same or different and  
30 independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl.

Scheme D



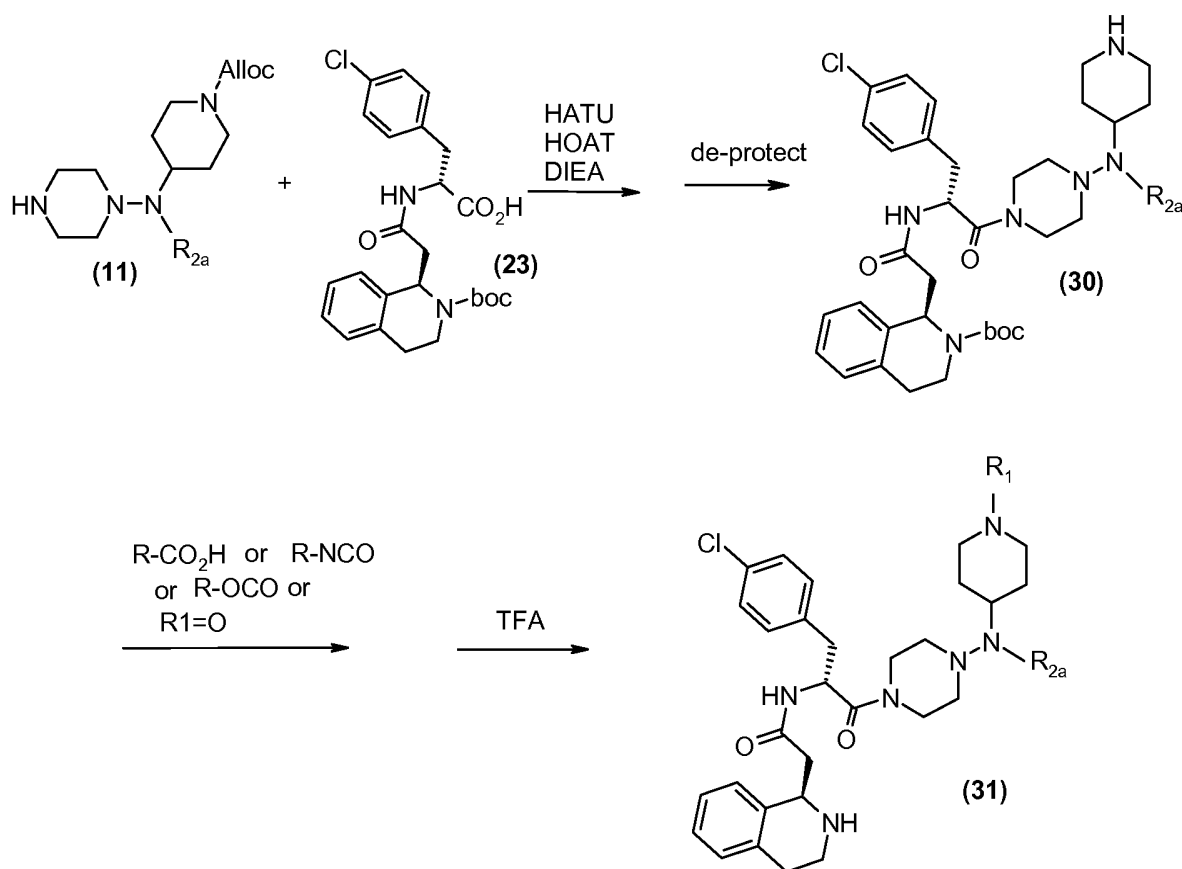
$R_1$  and  $R_{2a}$  substituted (13) (0.1 mmol) is added slowly to a stirred mixture of PG-compound (27) (0.11 mmol), which may, for example, be compound (22) or (23), a dehydrating reagent such as TBTU, EDC, HATU or HBTU (0.11 mmol) and an organic base such as N-methylmorpholine or diisopropyl ethyl amine (0.2 mmol) in a solvent such as methylene chloride, tetrahydrofuran or dioxane. After stirring for 16 hours the solution is extracted and washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated. De-protection is accomplished by stirring with excess TFA in solvent such as methylene chloride for one hour followed by evaporation of the solvent. The residue is dissolved in 35% aqueous methanol and purified by HPLC to yield compound (26).

Scheme E - Acetyl di-substitution



Di-substitution can be carried out on fully de-protected materials, such as compound (28) by stirring the TFA salt compound (28) (0.034 mmol) with acetic anhydride (0.034 mmol) and excess base such as triethylamine in a solvent such as methylene chloride, tetrahydrofuran or dioxane (2 mL). The solution is stirred at room temperature for 2 hours and then washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated. Purification is done by HPLC to yield compound (29).

Scheme F



To (11) and (23) is added a dehydrating reagent such as TBTU, EDC, HATU or HBTU (1.1 mmol) and an organic base such as N-methylmorpholine or diisopropyl ethyl amine (2.0 mmol) in a solvent such as methylene chloride, tetrahydrofuran or dioxane. After stirring for 16 hours the solution is extracted into a solvent such as methylene chloride or ethyl acetate and washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated. An R<sub>1</sub> is added to resulting compound (30), following by de-protection by stirring with excess TFA in solvent such as methylene chloride for one hour followed by evaporation of the solvent, yielding compound (31).

## 5. ASSAY SYSTEMS FOR COMPOUNDS

Selected compounds are tested in assays to determine binding and functional status, and are tested in animal models of feeding behavior as discussed below. The following assays and animal models are employed, with modifications, if any, as discussed in the examples.

**Competitive Inhibition Assay Using [<sup>125</sup>I]-NDP-α-MSH.** A competitive inhibition binding assay is performed using membrane homogenates prepared from HEK-293 cells that express recombinant hMCR-1a, hMCR-4, hMCR-3, or hMCR-5, and from B-16 mouse melanoma cells (containing endogenous MCR-1). In the examples that follow, all values are for human recombinant receptors unless otherwise noted. Assays are performed in 96 well GF/B Millipore multiscreen filtration plates (MAFB NOB10) pre-coated with 0.5% bovine serum albumin (Fraction V). Membrane homogenates are incubated with 0.2nM (for hMCR-4) 0.4 nM (for MCR-3 and MCR-5) or 0.1 nM (for mouse B16 MCR-1 or

hMCR-1a) [ $^{125}$ I]-NDP- $\alpha$ -MSH (Perkin Elmer) and increasing concentrations of test compounds in buffer containing 25 mM HEPES buffer (pH 7.5) with 100 mM NaCl, 2 mM  $\text{CaCl}_2$ , 2 mM  $\text{MgCl}_2$ , 0.3 mM 1,10-phenanthroline, and 0.2% bovine serum albumin. After incubation for 60 to 90 minutes at 37°C, the assay mixture is filtered and the membranes washed three times with ice-cold buffer. Filters are dried and  
5 counted in a gamma counter for bound radioactivity.

Non-specific binding is measured by inhibition of binding of [ $^{125}$ I]-NDP- $\alpha$ -MSH in the presence of 1  $\mu\text{M}$  NDP- $\alpha$ -MSH. Maximal specific binding (100%) is defined as the difference in radioactivity (cpm) bound to cell membranes in the absence and presence of 1  $\mu\text{M}$  NDP- $\alpha$ -MSH. Radioactivity (cpm) obtained in the presence of test compounds is normalized with respect to 100% specific binding to  
10 determine the percent inhibition of [ $^{125}$ I]-NDP- $\alpha$ -MSH binding. Each assay is conducted in duplicate or triplicate and the actual mean values are described, with results less than 0% reported as 0%.  $K_i$  values for test compounds are determined using Graph-Pad Prism® curve-fitting software.

*Competitive Binding Assay Using Eu-NDP- $\alpha$ -MSH.* Alternatively, a competitive inhibition binding assay was performed employing Eu-NDP- $\alpha$ -MSH (PerkinElmer Life Sciences catalog No. AD0225) with  
15 determination by time-resolved fluorometry (TRF) of the lanthanide chelate. In comparison studies with [ $^{125}$ I]-NDP- $\alpha$ -MSH, the same values, within experimental error ranges, were obtained for percent inhibition and  $K_i$ . Typically competition experiments to determine  $K_i$  values were conducted by incubating membrane homogenates prepared from HEK-293 cells that express recombinant hMCR-4 with 9 different concentrations of test compounds of interest and 2 nM of Eu-NDP- $\alpha$ -MSH in a solution containing 25 mM  
20 HEPES buffer with 100 mM NaCl, 2 mM  $\text{CaCl}_2$ , 2 mM  $\text{MgCl}_2$  and 0.3 mM 1,10-phenanthroline. After incubation for 90 minutes at 37°C, the reaction was stopped by filtration over AcroWell 96-well filter plates (Pall Life Sciences). The filter plates were washed 4 times with 200  $\mu\text{L}$  of ice-cold phosphate-buffered saline. DELFIA Enhancement solution (PerkinElmer Life Sciences) was added to each well. The plates were incubated on a shaker for 15 minutes and read at 340 nm excitation and 615 nm emission  
25 wavelengths. Each assay was conducted in duplicate and mean values were utilized.  $K_i$  values were determined by curve-fitting with Graph-Pad Prism® software using a one-site fixed-slope competition binding model.

*Competitive Binding Assay Using [ $^{125}$ I]-AgRP (83-132).* Competitive binding studies using [ $^{125}$ I]-AgRP (83-132) are carried out using membrane homogenates isolated from cells that express hMCR-4.  
30 The assays are performed in 96-well GF/B Millipore multiscreen filtration plates (MAFB NOB10) pre-coated with 0.5% bovine serum albumin (Fraction V). The assay mixture contained 25 mM HEPES buffer (pH 7.5) with 100 mM NaCl, 2 mM  $\text{CaCl}_2$ , 2 mM  $\text{MgCl}_2$ , 0.3 mM 1,10-phenanthroline, 0.5% bovine serum albumin, membrane homogenates, radioligand [ $^{125}$ I]-AgRP (83-132) (Perkin Elmer) and increasing concentrations of compounds in a total volume of 200  $\mu\text{L}$ . Binding is measured at radioligand  
35 concentrations of 0.2 nM. After incubating for 1 hour at 37 °C, the reaction mixture is filtered and washed with assay buffer containing 500 mM NaCl. The dried discs are punched out from the plate and counted on a gamma counter. The total binding of the radioligand did not exceed 10% of the counts added to the reaction mixture.  $K_i$  values for test compounds are determined using Graph-Pad Prism® curve-fitting software.

*Assay for Agonist Activity.* Accumulation of intracellular cAMP was examined as a measure of the ability of the compounds this invention to elicit a functional response in a human melanoma cell line, HBL, that express hMCR-1 (see Kang, L., et al., "A selective small molecule agonist of melanocortin-1 receptor inhibits lipopolysaccharide-induced cytokine accumulation and leukocyte infiltration in mice," *J. Leuk. Biol.* 80:897-904 (2006)) or HEK-293 cells that express hMCR-4. Confluent HBL cells that express hMCR-1 or HEK-293 cells that express recombinant hMCR-4 were detached from culture plates by incubation in enzyme-free cell dissociation buffer. Dispersed cells were suspended in Earle's Balanced Salt Solution containing 10 mM HEPES (pH 7.5), 1 mM MgCl<sub>2</sub>, 1mM glutamine, 0.5% albumin and 0.3 mM 3-isobutyl-1-methyl-xanthine (IBMX), a phosphodiesterase inhibitor. The cells were plated in 96-well plates at a density of  $0.4 \times 10^5$  cells per well for HBL cells and  $0.5 \times 10^5$  cells per well for HEK-293 cells and pre-incubated for 10 minutes. Cells were exposed for 15 minutes at 37 °C to peptides of the present invention dissolved in DMSO (final DMSO concentration of 1%) at a concentration range of 0.05 - 5000 nM in a total assay volume of 200  $\mu$ L. NDP- $\alpha$ -MSH was used as the reference agonist. cAMP levels were determined by an HTRF® cAMP cell-based assay system from Cisbio Bioassays utilizing cryptate-labeled anti-cAMP and d2-labeled cAMP, with plates read on a Perkin-Elmer Victor plate reader at 665 and 620 nm. Data analysis was performed by nonlinear regression analysis with Graph-Pad Prism® software. Maximum efficacy ( $E_{max}$ ) values were determined for each test compound of the present invention, compared to that achieved by the reference melanocortin agonist NDP- $\alpha$ -MSH.

#### 6. IN VIVO ANIMAL TESTS FOR COMPOUNDS

*Food intake after IN and IP dosing.* Changes in food intake are evaluated for selected compounds. Male C57BL/6 mice are obtained from Jackson labs (Bar Harbor, ME). Animals are individually housed in conventional plexiglass hanging cages and maintained on a controlled 12 hour on/off light cycle. Water and pelleted (Harlan Teklad 2018 18% Protein Rodent Diet) food is provided *ad libitum*. The mice are dosed IP (by intraperitoneal injection) after a 24 hour fast or IN (by intranasal administration) with vehicle or selected compounds (0.1–3 mg/kg, and in some cases up to 10 mg/kg). All animals are dosed once a day (or up to four consecutive days) at the start of the "lights off" period. The changes in food intake weight for the 4 hour and 20 hour period after dosing relative to control animals administered vehicle is determined.

*Diet-induced Obese (DIO) model.* Male diet-induced obese (DIO) C57BL/6 mice are obtained from Jackson labs (Bar Harbor, ME) where they were fed with a 60 Kcal% fat diet (Research Diets D12492i) until ~18 weeks of age. Upon arrival, animals are individually housed in conventional plexiglass hanging cages and maintained on a controlled 12 hour on/off light cycle with *ad libitum* access to water and pelleted food (Research Diets D12451 – 45 Kcal% Fat Rodent Diet). Mice are allowed 5 days to acclimate to the facility prior to experimentation. Mice are dosed orally with vehicle or selected compounds (0.1-50 mg/kg) by oral gavage injection using a 1mL BD Syringe and a 20G X 1-1/2" animal feeding needle (dose volumes up to 10 mL/kg). Animals are monitored immediately after dosing for signs of gasping, wheezing or presence of dose solution around the mouth. All animals are dosed once or twice daily, with changes in food intake weight monitored at 1, 7, 8 and 24 hours after dosing and

expressed relative to vehicle controls. Body weights are collected at 24 hours and daily thereafter and the percent change in body weight calculated from starting body weights.

*Induction of Spontaneous Penile Erection.* The ability of compounds to induce penile erections (PE) in sexually inexperienced male rats is evaluated via a spontaneous erection model. Male Sprague-Dawley rats weighing 250-300 g are pair-housed on a 12 hour on/off light cycle with food and water given *ad libitum*. Groups of 4-8 rats are acclimated to the testing area in their home cages for half an hour prior to being dosed. Compounds (at varying doses) are administered via one of the following routes: intravenous (IV), sub-cutaneous (SC), intra-cerebroventricular (ICV) or per oral (PO). Immediately after treatment, rats are placed into individual polystyrene observational cages (27 cm long, 16 cm wide and 25 cm high) and their behavior is recorded via a high resolution video camera system for 1-2 hours (depending on route of administration). The timing and type of erection (grooming related or sudden awareness) is recorded. Rats are also observed for abnormal behaviors such as gasping or writhing. After the observations are recorded the animals are returned to their home cages. The test sessions also include a negative control (vehicle) and, for IV, SC or ICV administration, a positive control (typically brexelanotide). Only those compounds that demonstrate mean statistically significant higher PE values than mean PE values with vehicle are considered efficacious. Compounds with oral bioavailability are evaluated by dosing via oral gavage, with a negative control (vehicle) also administered via oral gavage. The rats are gently restrained and the compound is introduced directly into the stomach using a bulb-tipped feeding needle attached to a syringe. The animals are then immediately transferred to the video observational cages and their behavior is recorded for 90 minutes, allowing the first 30 minutes for the absorption of the compound.

## 7. COMBINATION THERAPY WITH COMPOUNDS

*Combination Therapy for Sexual Dysfunction.* It is also possible and contemplated to use compounds of this invention in combination with other drugs or agents, such as for treatment of sexual dysfunction. These other drugs and agents may include agents that induce erectile activity, including phosphodiesterase-5 (PDE-5) inhibitors, testosterone, prostaglandin and the like. In a preferred embodiment of the invention, compounds of the invention are used in combination with a therapeutically effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. The teachings and disclosure of U.S. Patent No. 7,235,625, issued June 26, 2007, and entitled "Multiple Agent Therapy for Sexual Dysfunction", are incorporated here by reference as if set forth in full.

This invention thus provides methods of treating sexual dysfunction, the methods comprising the step of administering to the patient having or at risk of having sexual dysfunction a therapeutically effective amount of a compounds of this invention in combination with a therapeutically effective amount of a second sexual dysfunction pharmaceutical agent. The compounds of this invention may be administered simultaneously with, prior to or subsequent to administration with a therapeutically effective amount of a second sexual dysfunction pharmaceutical agent. Preferably the compounds of this invention is administered within one hour, preferably within less than one-half hour, of administration of a therapeutically effective amount of a second sexual dysfunction pharmaceutical agent. However, for

certain forms of combination therapy, such as for example in combination with a therapeutically effective amount of a hormone or hormone-related sexual dysfunction pharmaceutical agent, the hormone or hormone-related sexual dysfunction pharmaceutical agent may be administered on an independent schedule, such that there is no set or specific temporal relationship between administration of the compounds of this invention and the hormone or hormone-related sexual dysfunction pharmaceutical agent. Thus, for example, the hormone or hormone-related sexual dysfunction pharmaceutical agent may be administered on a daily or other dose, or by means of patches or other continuous administration schedules, with administration of the compounds of this invention when desired or needed by the patient. In one preferred embodiment of combination therapy the sexual dysfunction is female sexual dysfunction.

In another preferred embodiment of combination therapy the sexual dysfunction is erectile dysfunction.

This invention also provides pharmaceutical compositions that comprise a compound of this invention and a second compound useful for the treatment of sexual dysfunction. In an embodiment of the composition, the additional compounds useful for the treatment of sexual dysfunction are preferably selected from but not limited to the group consisting of a phosphodiesterase inhibitor; a cyclic-GMP-specific phosphodiesterase inhibitor; prostaglandins; apomorphine; oxytocin modulators;  $\alpha$ -adrenergic antagonists; androgens; selective androgen receptor modulators (SARMs); bupropion; vasoactive intestinal peptide (VIP); neutral endopeptidase inhibitors (NEP); and neuropeptide Y receptor antagonists (NPY).

In an embodiment of the method and composition, the second sexual dysfunction pharmaceutical agent is testosterone.

In another embodiment of combination therapy, the second sexual dysfunction pharmaceutical agent is a type V phosphodiesterase (PDE-5) inhibitor. For example, the PDE-5 inhibitor may be Viagra<sup>®</sup>, a brand of sildenafil, Levitra<sup>®</sup>, a brand of monohydrochloride salt of vardenafil, or Cialis<sup>®</sup>, a brand of tadalafil. Other PDE-5 inhibitors are disclosed in U.S. Patent No. 7,235,625, incorporated here by reference.

In another embodiment of the composition above, the second compound useful for the treatment of sexual dysfunction is an estrogen agonist/antagonist. In one embodiment, the estrogen agonist/antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol (also known as lasofoxifene) or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt; or a prodrug thereof. More preferably, the estrogen agonist/antagonist is in the form of a D-tartrate salt.

In yet another embodiment of the composition above, the estrogen agonist/antagonist is selected from the group consisting of tamoxifen, 4-hydroxy tamoxifen, raloxifene, droloxifene, toremifene, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiopehn-3-yl]-methanone, EM-652, EM-800, GW 5368, GW 7604, TSE-424 and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

In yet another embodiment, a compound of this invention may be used in combination with any known mechanical aids or devices.

This invention also provides kits for the treatment of sexual dysfunction (including erectile dysfunction), the kits comprising: a first pharmaceutical composition including a compound of this invention; a second pharmaceutical composition comprising a second compound useful for the treatment of sexual dysfunction; and, a container for the first and second compositions.

*Combination Therapy for Diabetes and/or Weight Regulation.* One or more compounds of this invention may be combined with at least one other pharmacologically active agent that is useful in the treatment of diabetes, such as other anti-diabetic drugs. One or more compounds of the invention may also be combined with at least one other pharmacologically active agent that is useful in the treatment of obesity and/or overweight, such as other anti-obesity drugs that affect energy expenditure, glycolysis, gluconeogenesis, glucogenolysis, lipolysis, lipogenesis, fat absorption, fat storage, fat excretion, hunger and/or satiety and/or craving mechanisms, appetite/motivation, food intake, or gastrointestinal motility.

One or more compounds of this invention may in addition or alternatively further be combined with at least one other pharmacologically active agent that is useful in the treatment of diseases, disorders and/or conditions associated with obesity and/or overweight, such as insulin resistance; impaired glucose tolerance; type 2 diabetes; metabolic syndrome; dyslipidemia (including hyperlipidemia); hypertension; heart disorders (e.g. coronary heart disease, myocardial infarction); cardiovascular disorders; non-alcoholic fatty liver disease (including non-alcoholic steatohepatitis); joint disorders (including secondary osteoarthritis); gastroesophageal reflux; sleep apnea; atherosclerosis; stroke; macro and micro vascular diseases; steatosis (e.g. in the liver); gall stones; and gallbladder disorders.

According to an additional aspect of the invention there is provided a combination treatment comprising the administration of a pharmacologically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

- insulin and insulin analogues;
- insulin secretagogues, including sulphonylureas (e.g. glipizide) and prandial glucose regulators (sometimes called "short-acting secretagogues"), such as meglitinides (e.g. repaglinide and nateglinide);
- agents that improve incretin action, for example dipeptidyl peptidase IV (DPP-4) inhibitors (e.g. vildagliptin, saxagliptin, and sitagliptin), and glucagon-like peptide-1 (GLP-1) agonists (e.g. exenatide);
- insulin sensitising agents including peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) agonists, such as thiazolidinediones (e.g. pioglitazone and rosiglitazone), and agents with any combination of PPAR alpha, gamma and delta activity;



- agents that modulate hepatic glucose balance, for example biguanides (e.g. metformin), fructose 1,6-bisphosphatase inhibitors, glycogen phosphorylase inhibitors, glycogen synthase kinase inhibitors, and glucokinase activators;
- 5     • agents designed to reduce/slow the absorption of glucose from the intestine, such as alpha-glucosidase inhibitors (e.g. miglitol and acarbose);
- agents which antagonise the actions of or reduce secretion of glucagon, such as amylin analogues (e.g. pramlintide);
- agents that prevent the reabsorption of glucose by the kidney, such as sodium dependent glucose transporter 2 (SGLT-2) inhibitors (e.g. dapagliflozin);
- 10    • agents designed to treat the complications of prolonged hyperglycaemia, such as aldose reductase inhibitors (e.g. epalrestat and ranirestat); and agents used to treat complications related to micro-angiopathies;
- anti-dyslipidemia agents, such as HMG-CoA reductase inhibitors (statins, e.g. rosuvastatin) and other cholesterol-lowering agents; PPAR $\alpha$  agonists (fibrates, e.g. gemfibrozil and fenofibrate);
- 15    bile acid sequestrants (e.g.cholestyramine); cholesterol absorption inhibitors (e.g. plant sterols (i.e. phytosterols), synthetic inhibitors); cholesteryl ester transfer protein (CETP) inhibitors; inhibitors of the ileal bile acid transport system (IBAT inhibitors); bile acid binding resins; nicotinic acid (niacin) and analogues thereof; anti-oxidants, such as probucol; and omega-3 fatty acids;
- 20    • antihypertensive agents, including adrenergic receptor antagonists, such as beta blockers (e.g. atenolol), alpha blockers (e.g. doxazosin), and mixed alpha/beta blockers (e.g. labetalol); adrenergic receptor agonists, including alpha-2 agonists (e.g. clonidine); angiotensin converting enzyme (ACE) inhibitors (e.g. lisinopril), calcium channel blockers, such as dihydropyridines (e.g. nifedipine), phenylalkylamines (e.g. verapamil), and benzothiazepines (e.g. diltiazem);
- 25    angiotensin II receptor antagonists (e.g. candesartan); aldosterone receptor antagonists (e.g. eplerenone); centrally acting adrenergic drugs, such as central alpha agonists (e.g. clonidine); and diuretic agents (e.g. furosemide);
- haemostasis modulators, including antithrombotics, such as activators of fibrinolysis; thrombin antagonists; factor VIIa inhibitors; anticoagulants, such as vitamin K antagonists (e.g. warfarin),
- 30    heparin and low molecular weight analogues thereof, factor Xa inhibitors, and direct thrombin inhibitors (e.g. argatroban);
- antiplatelet agents, such as cyclooxygenase inhibitors (e.g. aspirin), adenosine diphosphate (ADP) receptor inhibitors (e.g. clopidogrel), phosphodiesterase inhibitors (e.g. cilostazol), glycoprotein IIB/IIA inhibitors (e.g. tirofiban), and adenosine reuptake inhibitors (e.g. dipyridamole);
- 35    • anti-obesity agents, such as appetite suppressant (e.g. ephedrine), including noradrenergic agents (e.g. phentermine) and serotonergic agents (e.g. sibutramine), pancreatic lipase inhibitors (e.g. orlistat), microsomal transfer protein (MTP) modulators, diacyl

glycerolacyltransferase (DGAT) inhibitors, and cannabinoid (CB1) receptor antagonists (e.g. rimonabant);

- feeding behavior modifying agents, such as orexin receptor modulators and melanin-concentrating hormone (MCH) modulators;

5 • glucagon like peptide-1 (GLP-1) receptor modulators;

- neuropeptideY (NPY)/NPY receptor modulators;

- pyruvate dehydrogenase kinase (PDK) modulators;

- serotonin receptor modulators;

- leptin/leptin receptor modulators;

10 • ghrelin/ghrelin receptor modulators;

- monoamine transmission-modulating agents, such as selective serotonin reuptake inhibitors (SSRI), noradrenaline reuptake inhibitors (NARI), noradrenalineserotonin reuptake inhibitors (SNRI), triple monoamine reuptake blockers (e.g. tesofensine), and monoamine oxidase inhibitors (MAOI);

15 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable carrier to a mammal, such as man, in need of such therapeutic treatment.

According to an additional further aspect of this invention there is provided a combination treatment comprising the administration of a pharmacologically pharmacologically effective amount of a  
20 compound of this invention, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable carrier, with the simultaneous, sequential or separate administration of very low calorie diets (VLCD) or low-calorie diets (LCD).

In an additional aspect of the invention, there is provided a method of treating obesity and/or overweight and therewith associated complications in a mammal, such as man, in need of such treatment  
25 which comprises administering to said animal a pharmacologically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable carrier, in simultaneous, sequential or separate administration with a pharmacologically effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug  
30 thereof, optionally together with a pharmaceutically acceptable carrier.

In an additional aspect of the invention, there is provided a method of treating diabetes, in particular type 2 diabetes, in a mammal, such as man, in need of such treatment which comprises administering to said animal a pharmacologically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable carrier,  
35 in simultaneous, sequential or separate administration with a pharmacologically effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of this invention, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable carrier.

According to a further aspect of this invention there is provided a kit comprising a compound of this invention, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

*Combination Therapy with Anti-Inflammatory Agents.* For the treatment of inflammation-related diseases, indications, conditions and syndromes, compounds of this invention may be used in combination therapy, including by means of coadministration, with one or more anti-inflammatory agents. One class of anti-inflammatory agent is glucocorticoids, including but not limited to cortisone, including cortisone acetate, hydrocortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisone acetate, deoxycorticosterone acetate and aldosterone. Other anti-inflammatory agents that may be used in combination therapy, including by means of coadministration, include aspirin, non-steroidal antiinflammatory drugs (NSAIDs) (such as ibuprofen and naproxin), TNF- $\alpha$  inhibitors (such as tenidap and rapamycin or derivatives thereof), or TNF- $\alpha$  antagonists (e.g., infliximab, OR1384), cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as Naproxen® or Celebrex®), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept®), integrin antagonists,  $\alpha$ -4  $\beta$ -7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, prostaglandin synthesis inhibitors, budesonide, clofazimine, p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, therapies for the treatment of irritable bowel syndrome (e.g., Zelmac® and Maxi-K® openers such as those disclosed in U.S. Pat. No. 6,184,231), or other NF- $\kappa$ B inhibitors, such as corticosteroids, calphostin, CSAIDs, 4-substituted imidazo [1,2-A]quinoxalines as disclosed in U.S. Pat. No. 4,200,750; Interleukin-10, salicylates, nitric oxide, and other immunosuppressants; and nuclear translocation inhibitors, such as deoxyspergualin (DSG).

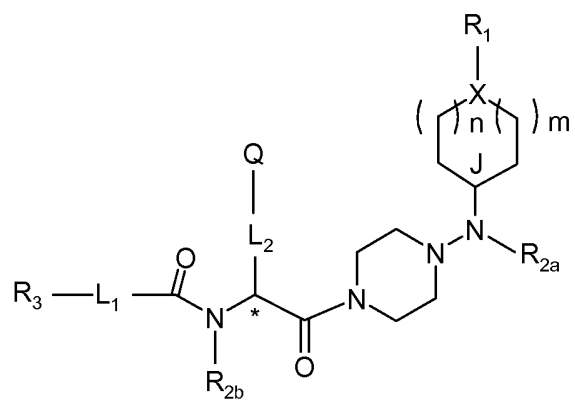
*Combination Therapy with Phosphodiesterase Inhibitors.* For certain applications and indications, it is desirable to increase production of and maintain levels of cyclic adenoise 3',5' monophosphate (cAMP), a nucleotide messenger associated with inflammatory cell activity. Certain compounds of this invention increase intracellular levels of cAMP, and can be coadministered with compounds or substances that inhibit the degradation of cAMP. cAMP is hydrolyzed to an inactive form by phosphodiesterase (PDE); compounds or substances that inhibit PDE may thereby result in maintenance of and/or an increase in available cAMP. A class of compounds known as PDE inhibitors has been extensively studied for use in treatment of inflammatory diseases, such as asthma, COPD and acute respiratory distress syndrome. Preferred are inhibitors of PDE type 1, 2, 3, 4, 7, 8, 10 or 11; in one aspect this includes cAMP-PDE inhibitors that are selective PDE type 4 inhibitors or inhibitors having selectivity for one particular type of PDE 4 isoenzyme, such as, by way of example, rolipram, cilomilast, ibudilast,

and piclamilast. In general, the methods and compositions of this invention may comprise use of one or more cAMP-PDE inhibitors.

*Combination Therapy in Ocular Indications.* For ocular indications, an ophthalmic dosage form may include one or more active ingredients in addition to one or more of the compounds of this invention, such as for example artificial tear components, topical corticosteroids, non-steroidal anti-inflammatory drugs, or calcineurin inhibitors such as cyclosporine-A (Restasis® - Allergan). It is also possible that coadministration includes administration of one or more additional compounds given separately from a compound of this invention, such as separate administration of an ophthalmic dosage form including an artificial tear component, a topical corticosteroid, a non-steroidal anti-inflammatory drugs, a calcineurin inhibitor such a cyclosporine-A, or a combination of any of the foregoing. Combination ophthalmic solutions may be employed, including specifically solutions including more than one active pharmaceutical ingredient. In one aspect, a non-steroidal anti-inflammatory drug (NSAID) is employed in combination with a compound of this invention. NSAIDs suitable for use in combination ophthalmic solutions include agents, their esters and pharmaceutically acceptable salts thereof that inhibit the cyclooxygenase (COX)-1 and/or -2 enzyme, including but not limited to propionic acid compounds such as naproxen, flurbiprofen, oxaprozin, ibuprofen, ketoprofen, fenoprofen; ketorolac tromethamine; acetic acid derivatives such as sulindac, indomethacin, and etodolac; phenylacetic acids such as diclofenac, bromfenac, and suprofen; arylacetic prodrugs such as nepafenac, and amfenac; salicylic acids, such as aspirin, salsalate, diflunisal, choline magnesium trisalicylate; para-aminophenol derivatives such as acetaminophen; naphthylalkanones such as nabumetone; enolic acid derivatives such as piroxicam and meloxicam; femanates such as mefenamic acid, meclofenamate and flufenamic acid; pyrroleacetic acids such as tolmetin; and pyrazolones such as phenylbutazone; and COX-2 selective inhibitors such as celecoxib, valdecoxib, parecoxib, etoricoxib, and lumaricoxib. The ophthalmic solutions may additionally comprise other active ingredients, including, but not limited to, vasoconstrictors, anti-allergenic agents, anti-infectives, steroids, anesthetics, anti-inflammatories, analgesics, dry eye treatment agents (e.g. secretagogues, mucomimetics, polymers, lipids, antioxidants), and the like, or be administered in conjunction (simultaneously or sequentially) with pharmaceutical compositions comprising other active ingredients, including, but not limited to, vasoconstrictors, anti-allergenic agents, anti-infectives, steroids, anesthetics, anti-inflammatories, analgesics, dry eye treatment agents (e.g. secretagogues, mucomimetics, polymers, lipids, antioxidants), and the like.

#### 8. ILLUSTRATIVE COMPOUNDS OF THE INVENTION

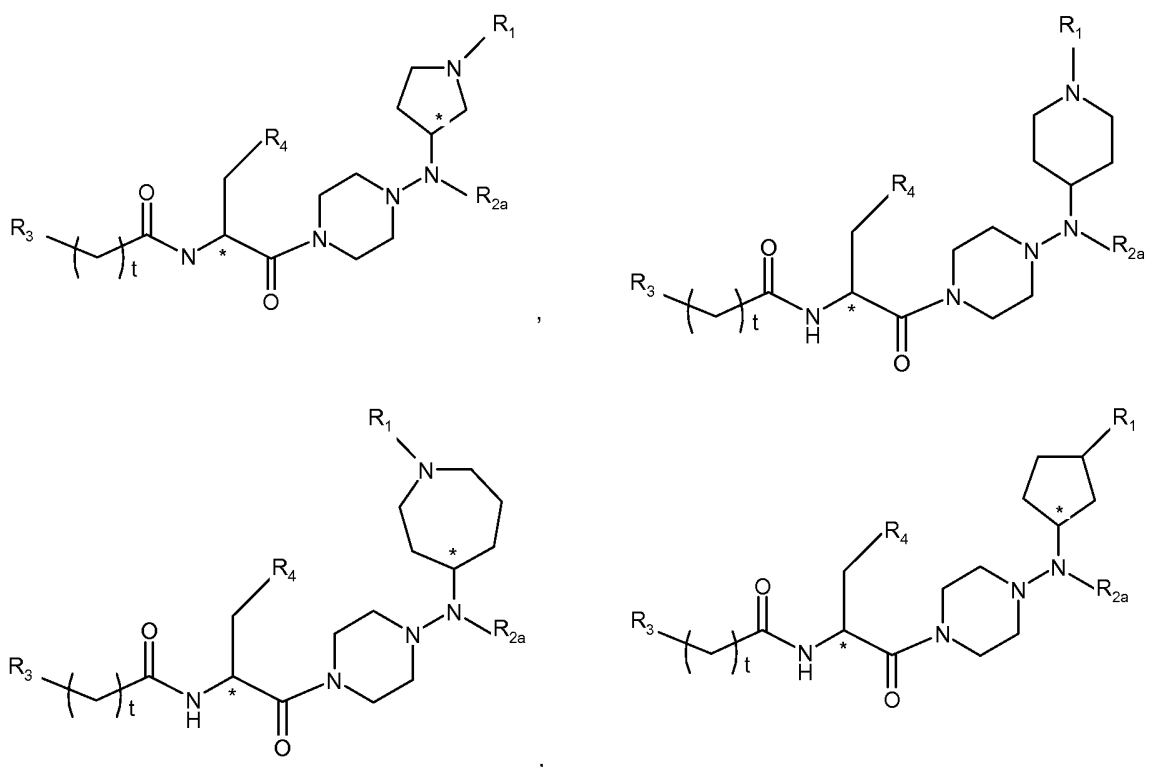
In one broad aspect, the invention provides a compound of the formula I:

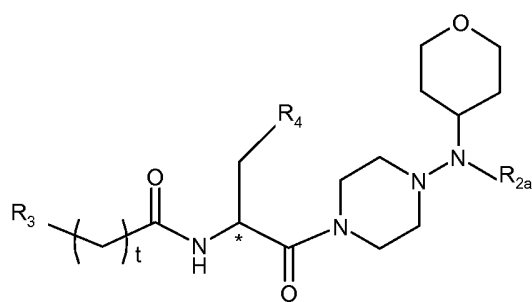
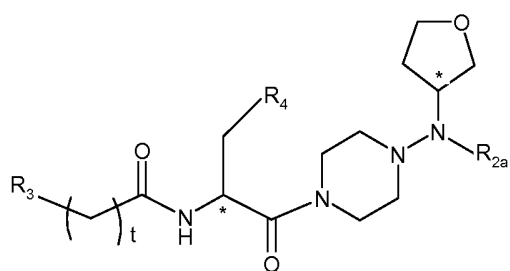
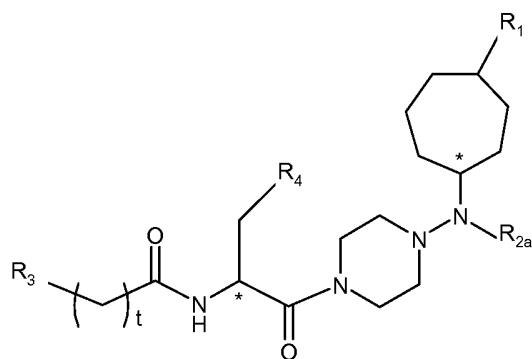
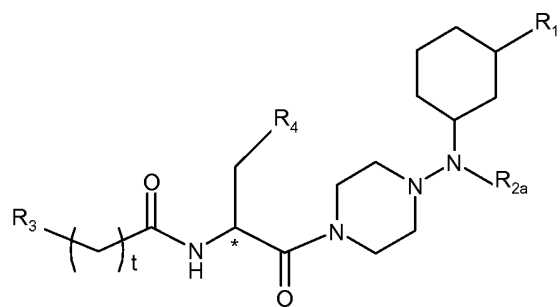
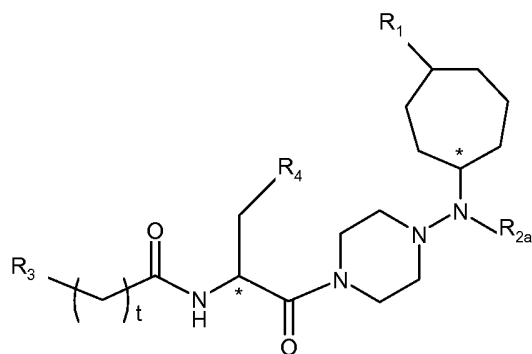
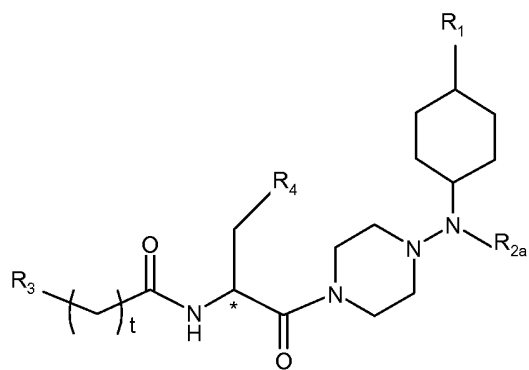
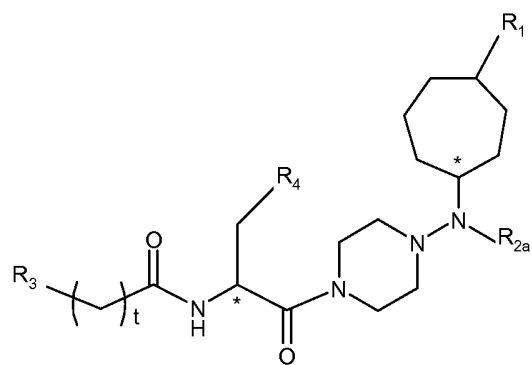
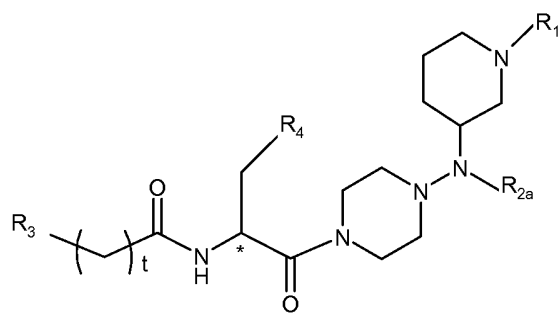


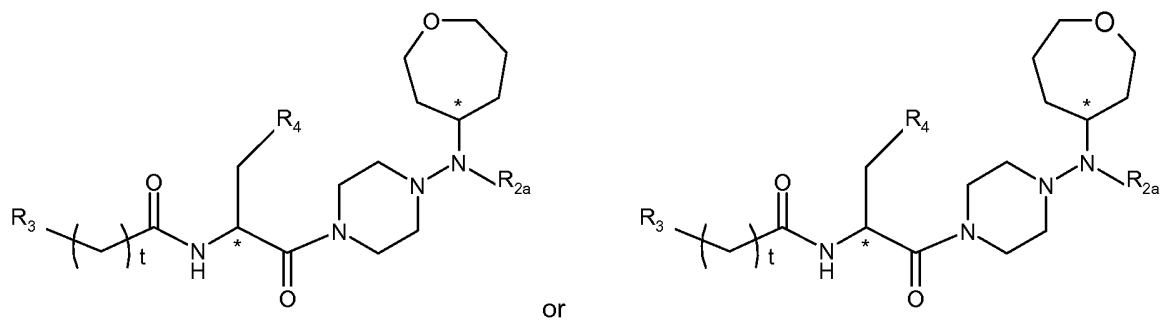
or an enantiomer, stereoisomer or diastereoisomer thereof, or a pharmaceutically acceptable salt thereof, where the variables are as defined in the Summary of the Invention and Claims.

In the compound of formula I, X may be N, O, C or CH, n may be 1 or 2 and m may be 0, 1 or 2.

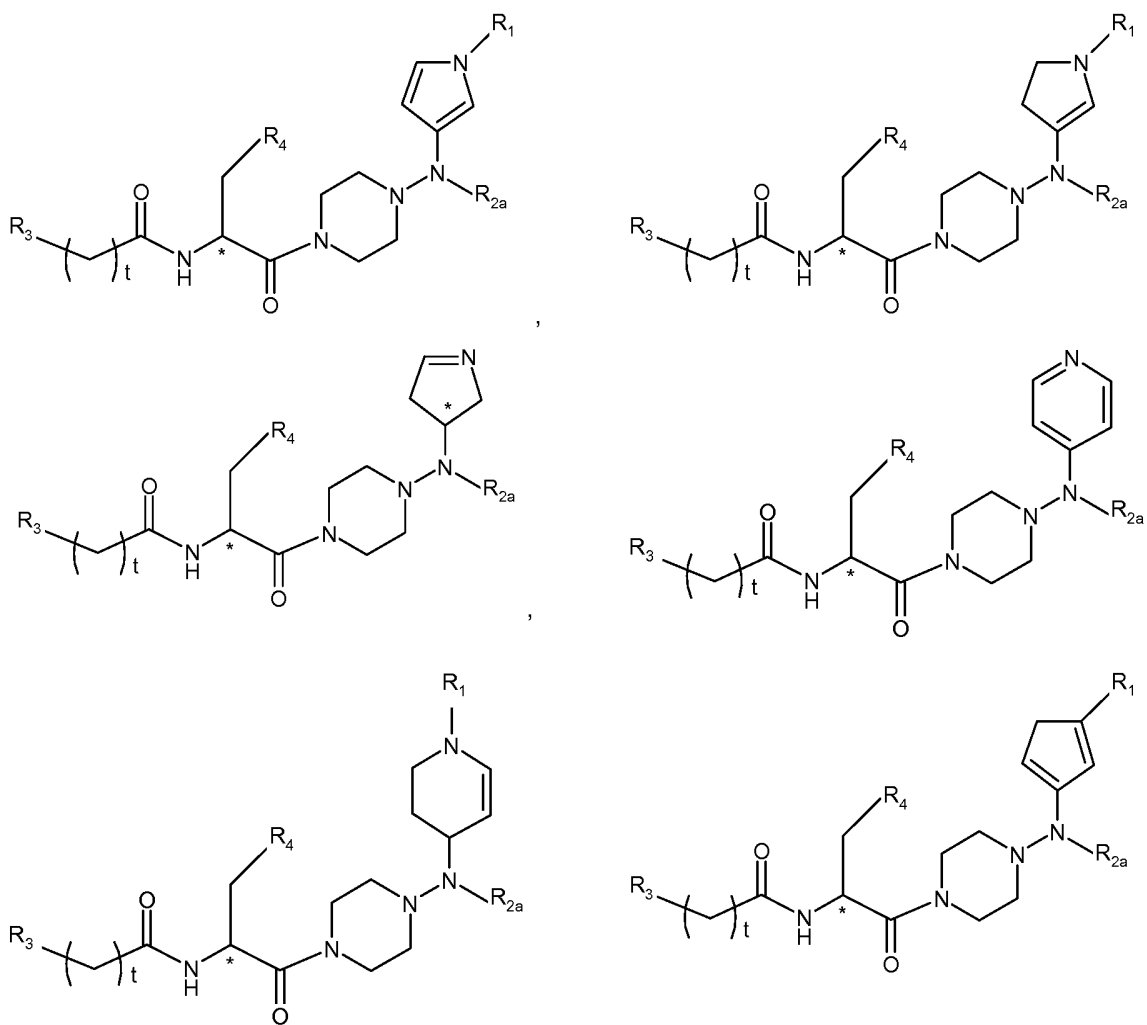
- 5 Thus in one aspect compounds of the following formulas are encompassed by the invention, it being understood that the following formulas are intended to exemplify only certain of the formulas encompassed by the specification and claims, and that the following are not to be construed as limiting the invention:

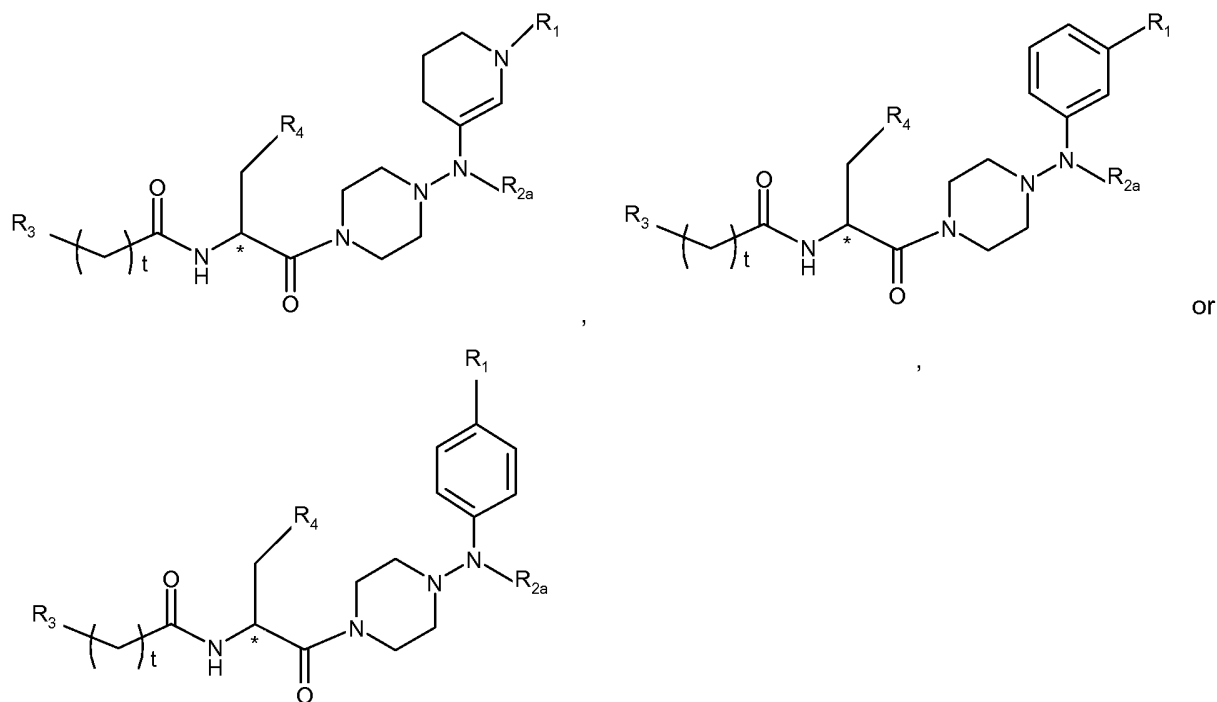






and to further include any number of compounds wherein the ring marked J in formula I includes one or more double bonds, including without limitation and only by way of example the following:





In the compounds of the invention, if present  $R_1$  may be H, a  $C_1$  to  $C_{17}$  linear or branched alkyl, cycloalkyl, or alkylcycloalkyl, or a  $C_1$  to  $C_7$  acyl group, in each instance optionally substituted with a terminal amide, amino, monosubstituted amino, disubstituted amino, or nitrile, or  $R_1$  may be an amide, amino, monosubstituted amino, or disubstituted amino. Thus in one aspect  $R_1$  may be:

- H,
- CH<sub>3</sub>,
- CH<sub>2</sub>-CH<sub>3</sub>,
- CH-(CH<sub>3</sub>)<sub>2</sub>,
- C(=O)-CH<sub>3</sub>, or
- C(=O)-CH-(CH<sub>3</sub>)<sub>2</sub>.

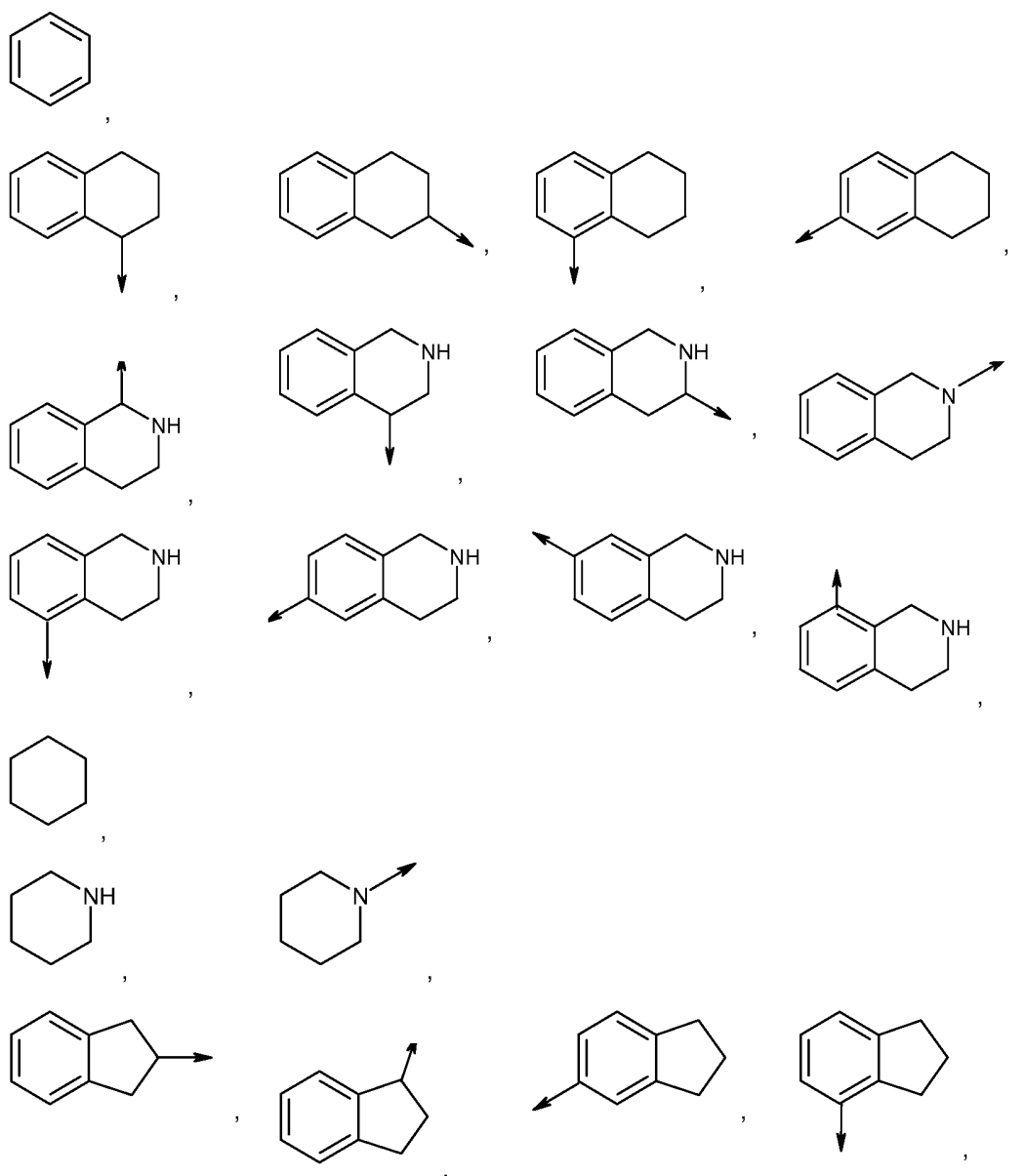
In the compounds of the invention,  $R_{2a}$  is H, a  $C_1$  to  $C_{17}$  linear or branched alkyl, cycloalkyl, or alkylcycloalkyl, or a  $C_1$  to  $C_7$  acyl group, in each instance optionally substituted with one or more substituents, and when one or more substituents are present, such substituents are the same or different and independently halo, amino, monosubstituted amino, disubstituted amino, hydroxy, or carboxy. Thus in one aspect  $R_{2a}$  may be:

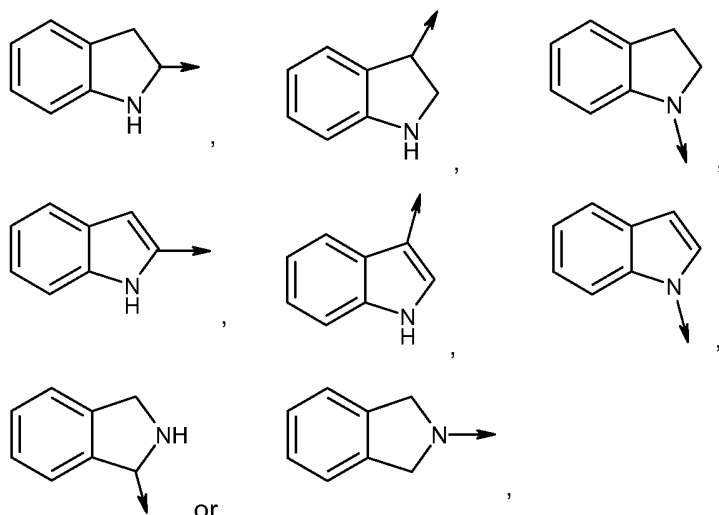
- H,
- CH<sub>3</sub>,
- CH<sub>2</sub>-CH<sub>3</sub>,
- CH-(CH<sub>3</sub>)<sub>2</sub>,
- C(=O)-CH<sub>3</sub>,
- C(=O)-O-CH<sub>2</sub>-CH<sub>3</sub>,
- C(=O)-NH-CH<sub>2</sub>-CH<sub>3</sub>,



-C(=O)-CH-(CH<sub>3</sub>)<sub>2</sub>, or  
-methyl-cyclopropane.

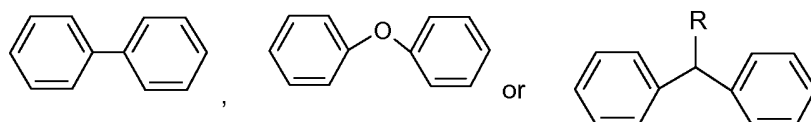
In the compounds of the invention, R<sub>3</sub> is one or two cyclic radicals, and if two cyclic radicals, may in one aspect be fused cyclic radicals, optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl. In general, the cyclic radicals comprising R<sub>3</sub> may be have a covalent bond attachment to the remainder of the compound of the invention at any chemically permissible position. Thus in one aspect, R<sub>3</sub> may be:





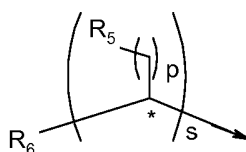
it being understood that the foregoing is merely illustrative, is not intended to be limiting, and that numerous other groups for  $R_3$ , together with substitutions as permitted, are contemplated and within the scope of the invention.

In an alternative aspect,  $R_3$  may be two cyclic radicals joined by a bond or linking group, such as  $L_3$ , including, by way of example and not limitation, the following where the two cyclic radicals are phenyl:



where R is a suitable substituent, including but not limited to oxo. Where  $R_3$  is two cyclic radicals joined by a bond or linking group, one or both of the cyclic radicals may optionally be substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl.

Alternatively,  $R_3$  may be a group of the structure



where  $R_5$  is H or one or two cyclic radicals, and if two cyclic radicals, fused cyclic radicals or cyclic radicals joined by  $L_3$ , the one or two cyclic radicals optionally substituted with one or more ring substituents, where  $R_6$  is

an amine,

an amine substituted with one or two linear or branched  $C_1$  to  $C_{17}$  alkyl, cycloalkyl, aryl, heteroaryl, alkylaryl, alkene, alkenyl, or aralkyl chains,

a  $C_1$  to  $C_7$  acyl group,

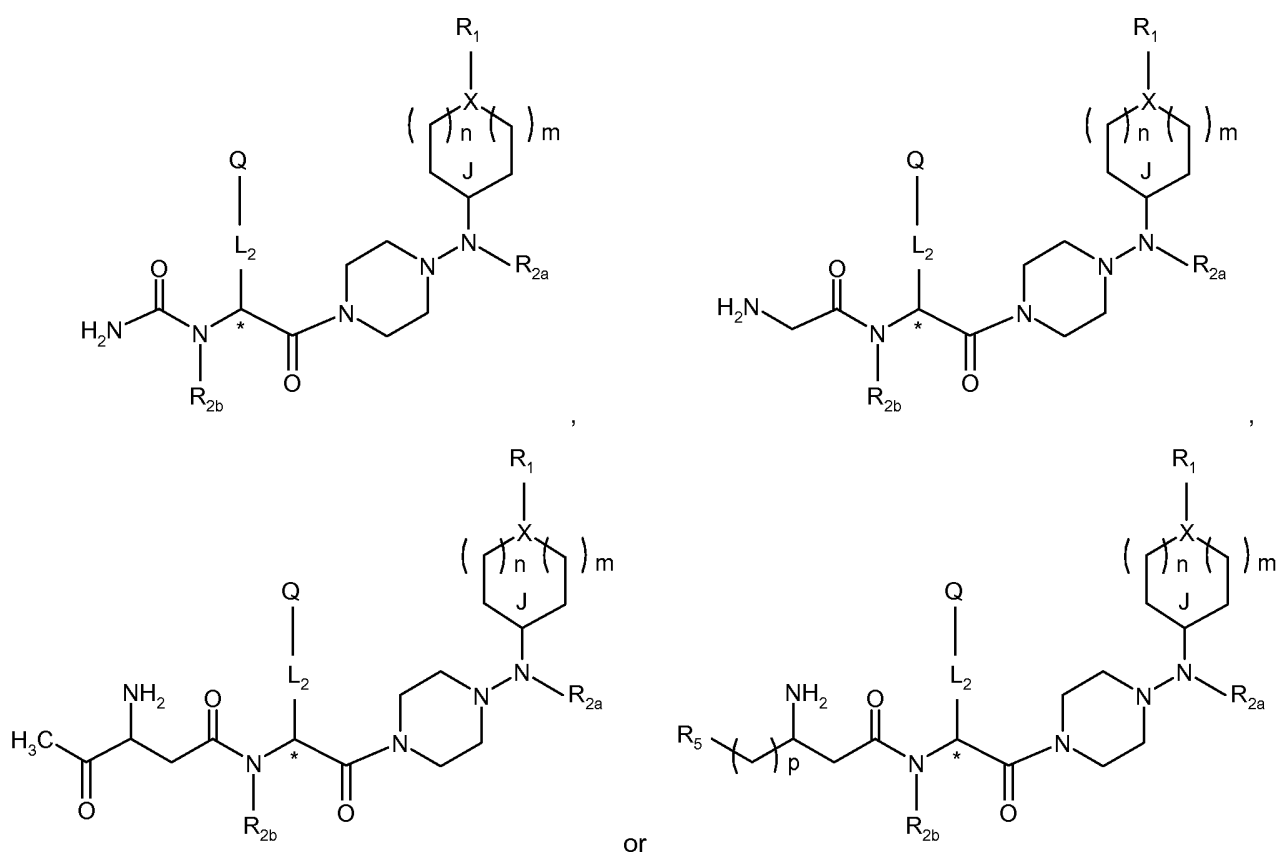
a C<sub>1</sub> to C<sub>7</sub> alkylamine group, wherein the alkyl is linear, branched or cyclic and the amine is optionally substituted with one or two C<sub>1</sub> to C<sub>17</sub> linear or branched alkyl, cycloalkyl, aryl, heteroaryl, alkylaryl, alkene, alkenyl, or aralkyl chains, or

an N-acylated linear or branched C<sub>1</sub> to C<sub>17</sub> alkyl, aryl, heteroaryl, alkene, alkenyl, or aralkyl chain,

wherein any cyclic radical in R<sub>6</sub> is optionally substituted with one or more ring substituents,

and where L<sub>3</sub> is a bond or -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-, -CH<sub>2</sub>-S-, -S-CH<sub>2</sub>-, -C(=O)-NH-, -NH-C(=O)-, -C(=O)-O-, or -O-C(=O)-, s is 1 or 0, and if 0, then the bracketed group is absent, and p is

from 0 to 3. Thus in one aspect compounds of the following formulas are encompassed by the invention, it being understood that the following formulas are intended to exemplify only a very limited number of the formulas encompassed by the specification and claims, and that the following are not to be construed as limiting the invention:



In the foregoing, R<sub>5</sub> may be one or two cyclic radicals, and if two cyclic radicals, then fused cyclic radicals or cyclic radicals joined by L<sub>3</sub>. Thus, by way of example and not limitation, R<sub>5</sub> may include an aryl group, a cycloalkyl group, a heterocycloalkyl group, a heteroaryl group or a combination of two or more thereof, optionally with L<sub>3</sub> where R<sub>5</sub> includes two cyclic radicals.

It is to be understood that all references to compounds of the invention, including a specific chemical formula or name, are intended to include all pharmaceutically acceptable salts, solvates, hydrates, polymorphs, prodrugs, metabolites, stereoisomers, and tautomeric isomers thereof. Throughout

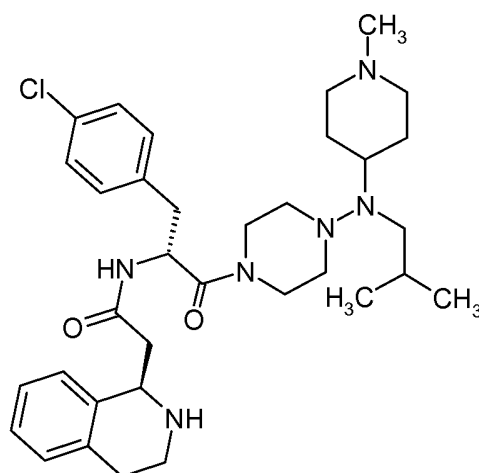
the specification and the appended claims, a given chemical formula or name shall encompass, where possible, all stereoisomers and tautomeric isomers thereof, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof.

## 9. EXAMPLES

5 The invention is further illustrated by the following non-limiting examples.

1 N-((R)-1-(4-Chloro-benzyl)-2-{4-[isobutyl-(1-methyl-piperidin-4-yl)-amino]-piperazin-1-yl}-2-oxo-ethyl)-2-(R)-1,2,3,4-tetrahydro-isoquinolin-1-yl-acetamide

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:

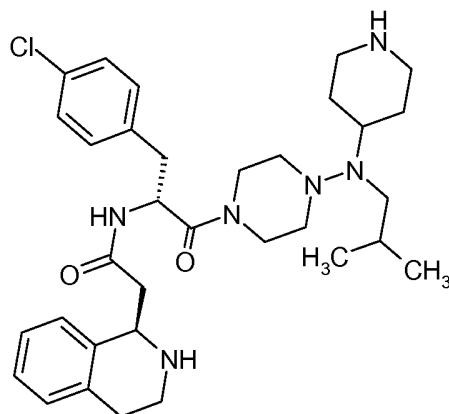


10 and a molecular formula of  $C_{34}H_{49}ClN_6O_2$ . The compound was prepared as the TFA salt, and had a molecular weight of 609.24 without salt, and 951.30 with TFA salt.

In binding studies, the compound had a  $K_i$  of 1 nM at MCR-4 and 220 nM at MCR-1. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 78%, with an  $EC_{50}$  value of 2 nM.

15 2 N-((R)-1-(4-Chloro-benzyl)-2-[4-(isobutyl-piperidin-4-yl-amino)-piperazin-1-yl]-2-oxo-ethyl)-2-(R)-1,2,3,4-tetrahydro-isoquinolin-1-yl-acetamide

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:

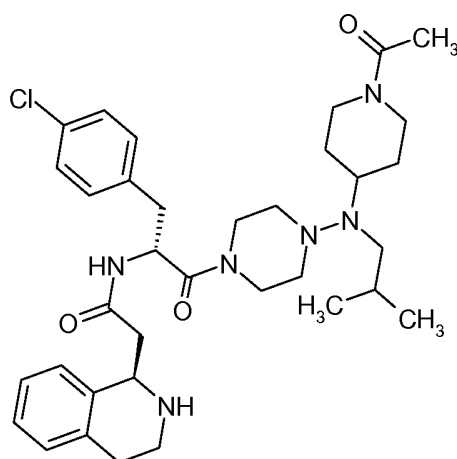


and a molecular formula of  $C_{33}H_{47}ClN_6O_2$ . The compound was prepared as the TFA salt, and had a molecular weight of 595.22 without salt, and 937.28 with TFA salt.

In binding studies, the compound had a  $K_i$  of 1 nM at MCR-4 and 40 nM at MCR-1. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 80%, with an  $EC_{50}$  value of 0.85 nM.

3 N-[(R)-2-{4-[(1-Acetyl-piperidin-4-yl)-isobutyl-amino]-piperazin-1-yl}-1-(4-chloro-benzyl)-2-oxo-ethyl]-2-(R)-1,2,3,4-tetrahydro-isoquinolin-1-yl-acetamide

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:

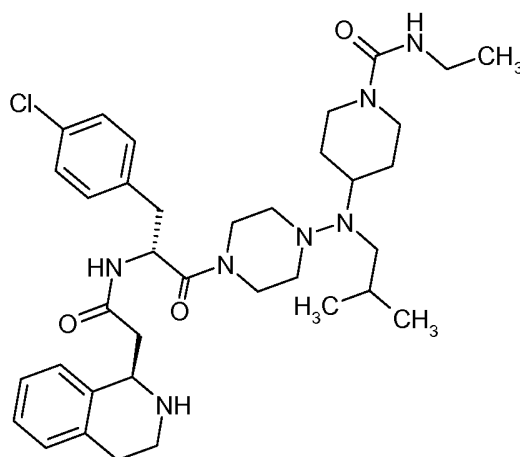


and a molecular formula of  $C_{35}H_{49}ClN_6O_3$ . The compound was prepared as the TFA salt, and had a molecular weight of 637.25 without salt, and 865.29 with TFA salt.

In binding studies, the compound had a  $K_i$  of 0.5 nM at MCR-4 and 85 nM at MCR-1. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 62%, with an  $EC_{50}$  value of 0.15 nM.

4 4-({4-[(R)-3-(4-Chloro-phenyl)-2-((R)-2-1,2,3,4-tetrahydro-isoquinolin-1-yl-acetylamino)-propionyl]-piperazin-1-yl}-isobutyl-amino)-piperidine-1-carboxylic acid ethylamide

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:

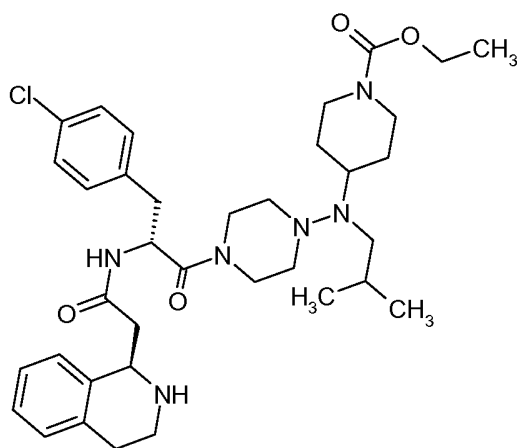


and a molecular formula of  $C_{36}H_{52}ClN_7O_3$ . The compound was prepared as the TFA salt, and had a molecular weight of 660.30 without salt, and 894.34 with TFA salt.

In binding studies, the compound had a  $K_i$  of 1 nM at MCR-4 and 210 nM at MCR-1. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 94%, with an  $EC_{50}$  value of 1 nM.

5 4-({4-[(R)-3-(4-Chloro-phenyl)-2-((R)-2-1,2,3,4-tetrahydro-isoquinolin-1-yl-acetyl-amino)-propionyl]-piperazin-1-yl}-isobutyl-amino)-piperidine-1-carboxylic acid ethyl ester

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:

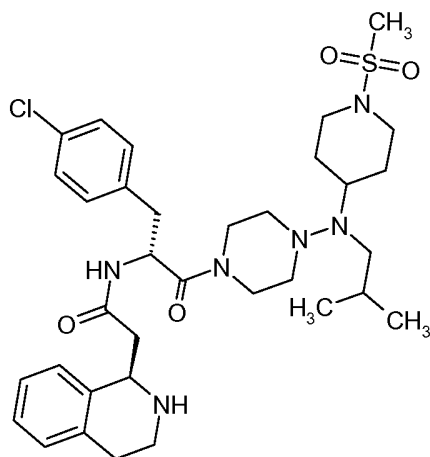


and a molecular formula of  $C_{36}H_{51}ClN_6O_4$ . The compound was prepared as the TFA salt, and had a molecular weight of 667.28 without salt, and 895.32 with TFA salt.

In binding studies, the compound had a  $K_i$  of 3 nM at MCR-4. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 92%, with an  $EC_{50}$  value of 25 nM.

6 N-((R)-1-(4-Chloro-benzyl)-2-{4-[isobutyl-(1-methanesulfonyl-piperidin-4-yl)-amino]-piperazin-1-yl}-2-oxo-ethyl)-2-(R)-1,2,3,4-tetrahydro-isoquinolin-1-yl-acetamide

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:

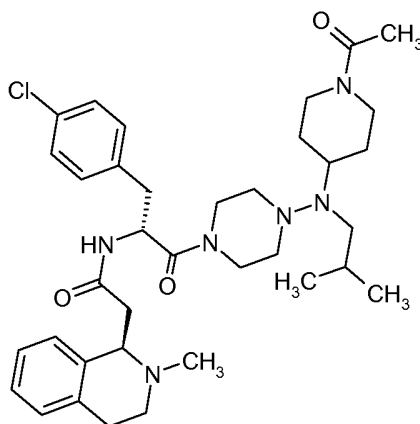


and a molecular formula of  $C_{34}H_{44}ClN_6O_4S$ . The compound was prepared as the TFA salt, and had a molecular weight of 673.31 without salt, and 901.35 with TFA salt.

In binding studies, the compound had a  $K_i$  of 6 nM at MCR-4. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 94%, with an  $EC_{50}$  value of 12 nM.

7 N-[(R)-2-{4-[(1-Acetyl-piperidin-4-yl)-isobutyl-amino]-piperazin-1-yl}-1-(4-chloro-benzyl)-2-oxo-ethyl]-2-((R)-2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-acetamide

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:

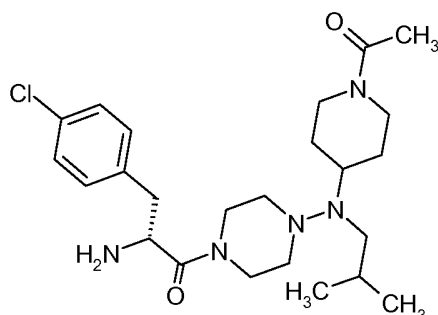


and a molecular formula of  $C_{36}H_{51}ClN_6O_3$ . The compound was prepared as the TFA salt, and had a molecular weight of 651.28 without salt, and 879.32 with TFA salt.

In binding studies, the compound had a  $K_i$  of 3 nM at MCR-4. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 26%, with an  $EC_{50}$  value of 0.3 nM.

8. (R)-1-{4-[(1-Acetyl-piperidin-4-yl)-isobutyl-amino]-piperazin-1-yl}-2-amino-3-(4-chloro-phenyl)-propan-1-one

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:

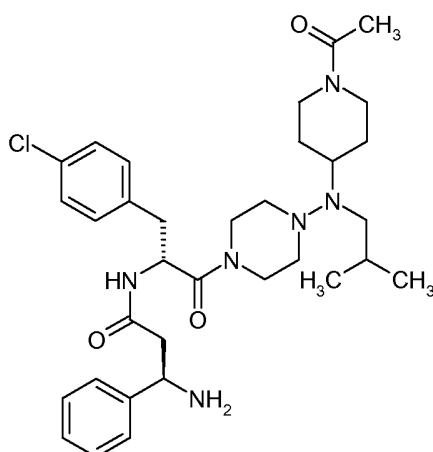


and a molecular formula of  $C_{24}H_{38}ClN_5O_2$ . The compound was prepared as the TFA salt, and had a molecular weight of 464.04 without salt, and 692.08 with TFA salt.

In binding studies, the compound had a  $K_i$  of 23 nM at MCR-4. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 21%, with an  $EC_{50}$  value of 71 nM.

9 (R)-N-[(R)-2-{4-[(1-Acetyl-piperidin-4-yl)-isobutyl-amino]-piperazin-1-yl}-1-(4-chloro-benzyl)-2-oxo-ethyl]-3-amino-3-phenyl-propionamide

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:



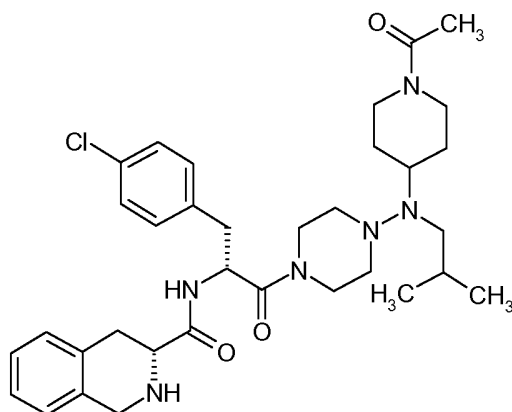
and a molecular formula of  $C_{33}H_{47}ClN_6O_3$ . The compound was prepared as the TFA salt, and had a molecular weight of 611.22 without salt, and 839.26 with TFA salt.

In binding studies, the compound had a  $K_i$  of 3 nM at MCR-4. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 45%, with an  $EC_{50}$  value of 8 nM.

10 (R)-1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid [(R)-2-{4-[(1-acetyl-piperidin-4-yl)-isobutyl-amino]-piperazin-1-yl}-1-(4-chloro-benzyl)-2-oxo-ethyl]-amide

The compound was synthesized using the methods of the foregoing synthetic schemes. The compound had the structural formula:





and a molecular formula of C<sub>34</sub>H<sub>47</sub>ClN<sub>6</sub>O<sub>3</sub>. The compound was prepared as the TFA salt, and had a molecular weight of 623.23 without salt, and 851.27 with TFA salt.

In binding studies, the compound had a K<sub>i</sub> of 1 nM at MCR-4. In functional studies in a human MCR-4 expression system approximating maximal physiologic receptor densities, the compound had a relative efficacy, compared to NDP- $\alpha$ -MSH, of 26%, with an EC<sub>50</sub> value of 0.95 nM.

Each of the foregoing is merely illustrative, and other equivalent embodiments are possible and contemplated.

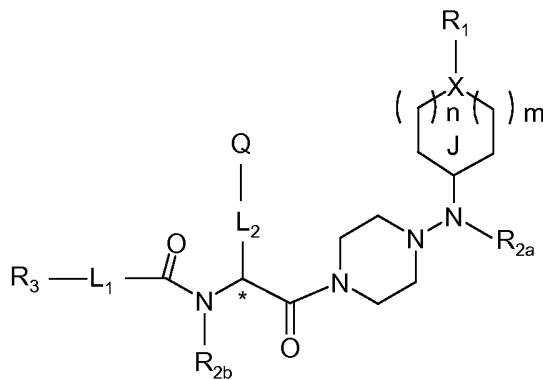
Although this invention has been described with reference to these preferred embodiments, other embodiments can achieve the same results. Variations and modifications of this invention will be obvious to those skilled in the art and it is intended to cover in the appended claims all such modifications and equivalents. The entire disclosures of all applications, patents, and publications cited above are hereby incorporated by reference.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

## CLAIMS

What is claimed is:

1. A compound of formula I:



or an enantiomer, stereoisomer or diastereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

$R_1$  is not present if X is O or N forming a double bond with another ring atom, and otherwise  $R_1$  is

H,

a  $C_1$  to  $C_{17}$  linear or branched alkyl, cycloalkyl, or alkylcycloalkyl, optionally substituted with a terminal amide, amino, monosubstituted amino, disubstituted amino, or nitrile,

a  $C_1$  to  $C_7$  acyl group, optionally substituted with a terminal amide, amino, monosubstituted amino, disubstituted amino, or nitrile,

an amide,

an amino,

a monosubstituted amino,

a disubstituted amino or

nitrile;

$R_{2a}$  and  $R_{2b}$  are each independently

H,

a  $C_1$  to  $C_{17}$  linear or branched alkyl, cycloalkyl, or alkylcycloalkyl,

a  $C_1$  to  $C_7$  acyl group,

sulfonyl,

carbamoyl or

urea,

in each instance optionally substituted with one or more substituents, and when one or more substituents are present, such substituents are the same or different and independently halo, amino, monosubstituted amino, disubstituted amino, hydroxy, or carboxy;

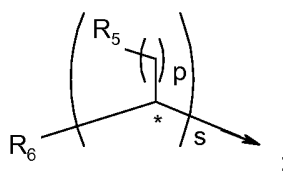
$L_1$  and  $L_2$  are each independently

a bond or

a  $C_1$  to  $C_6$  aliphatic chain,

and if a C<sub>1</sub> to C<sub>6</sub> aliphatic chain, optionally wherein one or more carbon atoms in the C<sub>1</sub> to C<sub>6</sub> aliphatic chain are replaced by oxygen or nitrogen atoms, and further optionally wherein the C<sub>1</sub> to C<sub>6</sub> aliphatic chain is substituted with one or more substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl;

R<sub>3</sub> is one or two cyclic radicals, and if two cyclic radicals, fused cyclic radicals or cyclic radicals joined by L<sub>3</sub>, the one or two cyclic radicals optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl, or R<sub>3</sub> is a group of the structure



Q is a monocyclic or polycyclic aryl or heteroaryl group, optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, oxo, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl;

L<sub>3</sub> is a bond or -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-, -CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-, -CH<sub>2</sub>-S-, -S-CH<sub>2</sub>-, -C(=O)-NH-, -NH-C(=O)-, -C(=O)-O-, or -O-C(=O)-;

R<sub>5</sub> is H or one or two cyclic radicals, and if two cyclic radicals, fused cyclic radicals or cyclic radicals joined by L<sub>3</sub>, the one or two cyclic radicals optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkythio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl;

R<sub>6</sub> is

an amine,

an amine substituted with one or two linear or branched C<sub>1</sub> to C<sub>17</sub> alkyl, cycloalkyl, aryl, heteroaryl, alkylaryl, alkene, alkenyl, or aralkyl chains,

a C<sub>1</sub> to C<sub>7</sub> acyl group,

a C<sub>1</sub> to C<sub>7</sub> alkylamine group, wherein the alkyl is linear, branched or cyclic and the amine is optionally substituted with one or two C<sub>1</sub> to C<sub>17</sub> linear or branched alkyl, cycloalkyl, aryl, heteroaryl, alkylaryl, alkene, alkenyl, or aralkyl chains, or

an N-acylated linear or branched C<sub>1</sub> to C<sub>17</sub> alkyl, aryl, heteroaryl, alkene, alkenyl, or aralkyl chain,

wherein any cyclic radical in  $R_6$  is optionally substituted with one or more ring substituents, and when one or more substituents are present, such substituents are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl;

5 X is N, O, C or CH;

m is from 0 to 2;

n is 1 or 2;

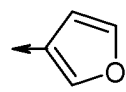
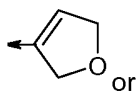
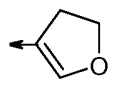
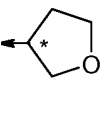
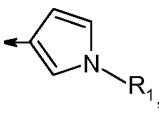
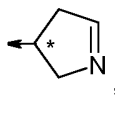
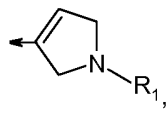
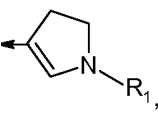
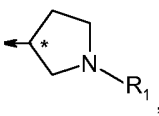
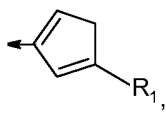
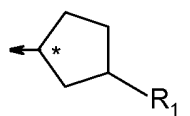
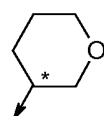
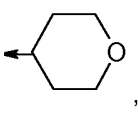
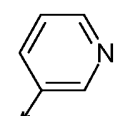
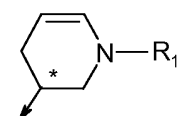
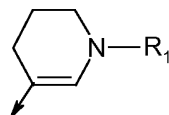
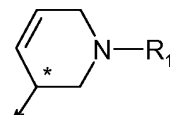
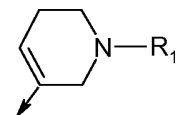
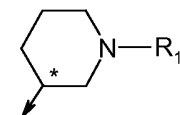
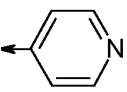
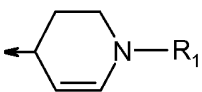
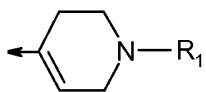
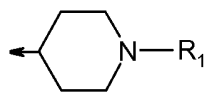
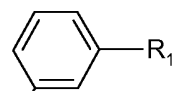
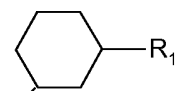
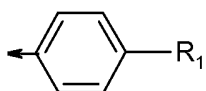
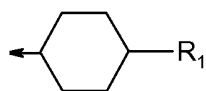
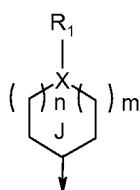
p is from 0 to 3; and

s is 0 or 1, and if 0, then the bracketed group is absent;

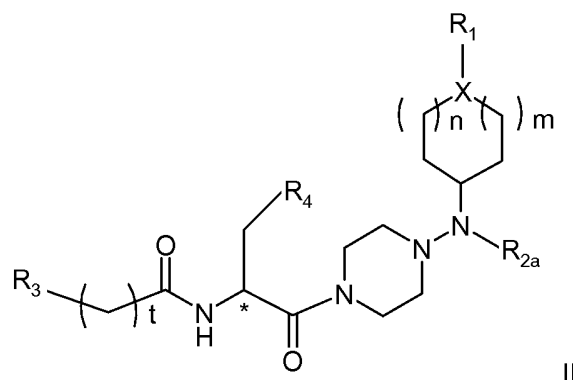
10 wherein the ring atoms of the ring marked J comprise from 0 to 3 double bonds; and

wherein the carbon atoms marked with an asterisk can have any stereochemical configuration.

15 2. The compound of claim 1 wherein



3. The compound of claim 1 of formula II:

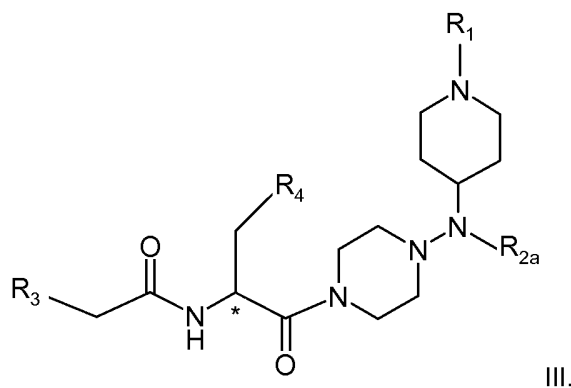


or an enantiomer, stereoisomer or diastereoisomer thereof, or a pharmaceutically acceptable salt thereof,  
 5 wherein:

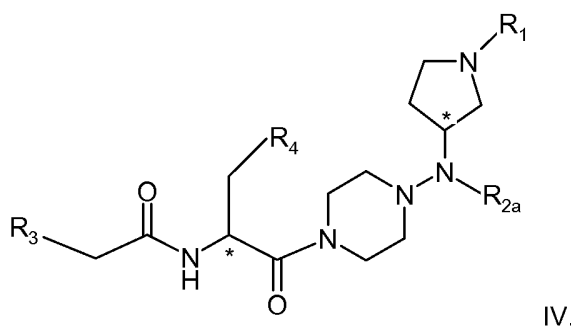
R<sub>4</sub> is heteroaryl, phenyl or naphthyl, optionally substituted with one or more ring substituents, and  
 when one or more substituents are present, such substituents are the same or different and  
 independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, oxo, halo, nitro, acyl, cyano, aryl, alkylaryl,  
 aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-  
 10 carbonyl; and

t is from 0 to 4.

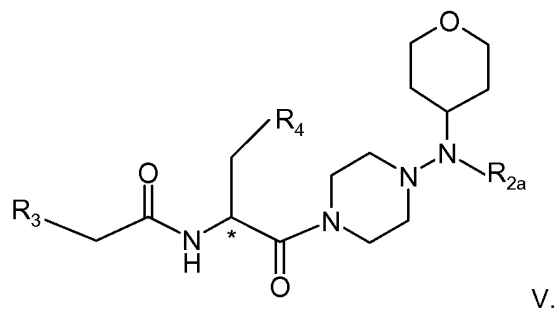
4. The compound of claim 3 of formula III:



5. The compound of claim 3 of formula IV:



6. The compound of claim 3 of formula V:



- 5 7. The compound of any one of claims 1, 3, 4 or 5 in which R<sub>1</sub> is:

-H,  
 -CH<sub>3</sub>,  
 -CH<sub>2</sub>-CH<sub>3</sub>,  
 -CH-(CH<sub>3</sub>)<sub>2</sub>,  
 -C(=O)-CH<sub>3</sub>, or  
 -C(=O)-CH-(CH<sub>3</sub>)<sub>2</sub>.

10

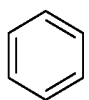
8. The compound of any one of claims 1, 3, 4, 5 or 6, in which R<sub>2a</sub> is:

-H,  
 -CH<sub>3</sub>,  
 -CH<sub>2</sub>-CH<sub>3</sub>,  
 -CH-(CH<sub>3</sub>)<sub>2</sub>,  
 -C(=O)-CH<sub>3</sub>,  
 -C(=O)-O-CH<sub>2</sub>-CH<sub>3</sub>,  
 -C(=O)-NH-CH<sub>2</sub>-CH<sub>3</sub>,  
 -C(=O)-CH-(CH<sub>3</sub>)<sub>2</sub>, or  
 -methyl-cyclopropane.

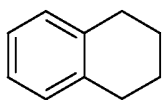
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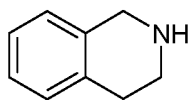
9. The compound of any one of claims 1, 3, 4, 5 or 6, in which R<sub>3</sub> is:



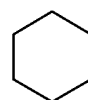
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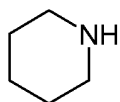
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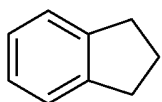
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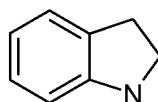
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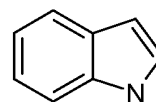
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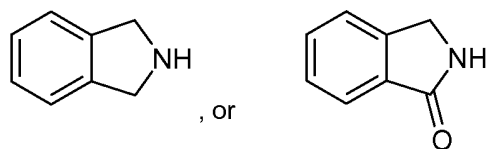
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,



,



10. The compound of any one of claims 1, 3, 4, 5 or 6, in which  $R_4$  is phenyl, optionally substituted with one or more ring substituents, and when one or more substituents are present, are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, halo, nitro, acyl, cyano, aryl,

5 alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl.

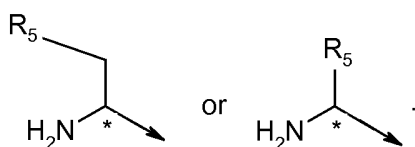
11. The compound of any one of claims 1, 3, 4, 5 or 6, in which  $R_4$  is naphthyl, optionally substituted with one or more ring substituents, and when one or more substituents are present, are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, halo, nitro, acyl, cyano, aryl,

10 alkylaryl, aryloxy, amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl.

12. The compound of any one of claims 1, 3, 4, 5 or 6, in which  $R_4$  is heteroaryl which is pyridine, pyrimidine, thiophene, thiazole, oxazole or imidazole, optionally substituted with one or more ring substituents, and when one or more substituents are present, are the same or different and independently alkyl, haloalkyl, cycloalkyl, alkoxy, alkylthio, halo, nitro, acyl, cyano, aryl, alkylaryl, aryloxy,

15 amino, monosubstituted amino, disubstituted amino, sulfonamide, hydroxy, carboxy, or alkoxy-carbonyl.

13. The compound of any one of claims 1, 3, 4, 5 or 6, in which  $R_3$  is a group of the structure:



14. A pharmaceutical composition comprising a compound of any one of claims 1, 3, 4, 5, or 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14, further comprising at least one additional active pharmaceutical agent.

16. A method of treating a patient with a disease, disorder, condition or syndrome responsive to modulation of a melanocortin receptor, comprising administration to the patient of a pharmaceutically effective amount of a pharmaceutical composition of claim 14.

17. The method of claim 14, wherein the disease, disorder, condition or syndrome responsive to modulation of a melanocortin receptor comprises obesity.

18. The method of claim 14, wherein the disease, disorder, condition or syndrome responsive to  
5 modulation of a melanocortin receptor comprises metabolic syndrome.

19. The method of claim 14, wherein the disease, disorder, condition or syndrome responsive to modulation of a melanocortin receptor comprises erectile dysfunction in a male patient or female sexual dysfunction in a female patient.

10



# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/066671

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D211/58 C07D295/12 C07D401/12 A61K31/495 A61K31/496  
A61P15/00 A61P25/00

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, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/232807 A1 (POINDEXTER GRAHAM S [US] ET AL) 18 December 2003 (2003-12-18) paragraph [0073] - paragraph [0120]; claims; examples 288,344; table 11	1-19
A	US 2004/224957 A1 (SHARMA SHUBH D [US] ET AL SHARMA SHUBH D [US] ET AL) 11 November 2004 (2004-11-11) paragraph [0436] - paragraph [0446]; claims; examples 14,15,39,40	1-19
A	WO 02/062766 A (MILLENNIUM PHARM INC [US]; MAGUIRE MARTIN P [US]; DAI MINGSHI [US]; VO) 15 August 2002 (2002-08-15) page 46, line 3 - page 60, line 30; claims; examples 3-5	1-19

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

☒ See patent family annex.

\* Special categories of cited documents :

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"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.

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Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/066671

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