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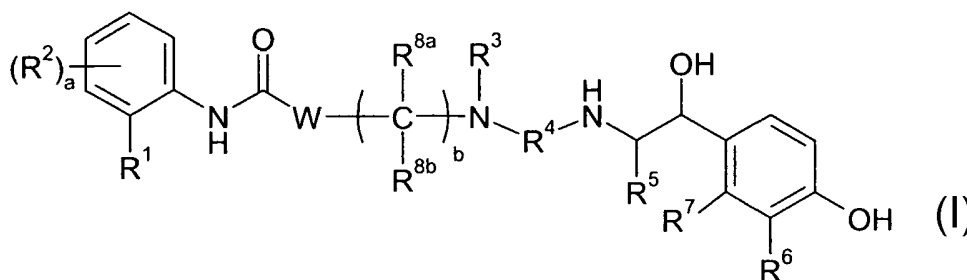
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(54) Title: COMPOUNDS HAVING  $\beta_2$  ADRENERGIC RECEPTOR AGONIST AND MUSCARINIC RECEPTOR ANTAGONIST ACTIVITY



(57) Abstract: This invention provides compounds of formula I wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^{8a}$ ,  $R^{8b}$ , W, a and b are as defined in the specification, or a pharmaceutically acceptable salt or solvate or stereoisomer thereof. The compounds of this invention possess both  $\beta_2$  adrenergic receptor agonist and muscarinic receptor antagonist activity. Accordingly, such compounds are expected to be useful as therapeutic agents for treating pulmonary disorders, such as chronic obstructive pulmonary disease and asthma.

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**COMPOUNDS HAVING  $\beta_2$  ADRENERGIC RECEPTOR AGONIST  
AND MUSCARINIC RECEPTOR ANTAGONIST ACTIVITY**

10 **BACKGROUND OF THE INVENTION**

Field of the Invention

The present invention relates to novel compounds having  $\beta_2$  adrenergic receptor agonist and a muscarinic receptor antagonist activity. This invention also relates to pharmaceutical compositions comprising such compounds, processes and intermediates for preparing such compounds and methods of using such compounds to treat pulmonary disorders.

15

State of the Art

Pulmonary disorders, such as asthma and chronic obstructive pulmonary disease (COPD), are commonly treated with bronchodilators. One class of bronchodilator in widespread use consists of  $\beta_2$  adrenergic receptor (adrenoceptor) agonists, such as albuterol, formoterol and salmeterol. These compounds are generally administered by inhalation. Another class of bronchodilator consists of muscarinic receptor antagonists (anticholinergic compounds), such as ipratropium and tiotropium. These compounds are also typically administered by inhalation.

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Pharmaceutical compositions containing both a  $\beta_2$  adrenergic receptor agonist and a muscarinic receptor antagonist are also known in the art for use in treating pulmonary disorders. For example, U.S. Patent No. 6,433,027 discloses medicament compositions containing a muscarinic receptor antagonist, such as tiotropium bromide, and a  $\beta_2$  adrenergic receptor agonist, such as formoterol fumarate.

30

Although compounds having either  $\beta_2$  adrenergic receptor agonist or muscarinic receptor antagonist activity are known, no compound having both  $\beta_2$  adrenergic receptor agonist and muscarinic receptor antagonist activity has been previously disclosed. Compounds possessing both  $\beta_2$  adrenergic receptor agonist and muscarinic receptor antagonist activity are highly desirable since such bifunctional compounds would provide bronchodilation through two independent modes of action while having single molecule pharmacokinetics. Moreover, a single bifunctional compound would be simpler to formulate for therapeutic uses compared to two separate compounds and would be easier to co-formulate with other therapeutic agents to create triple therapy combinations.

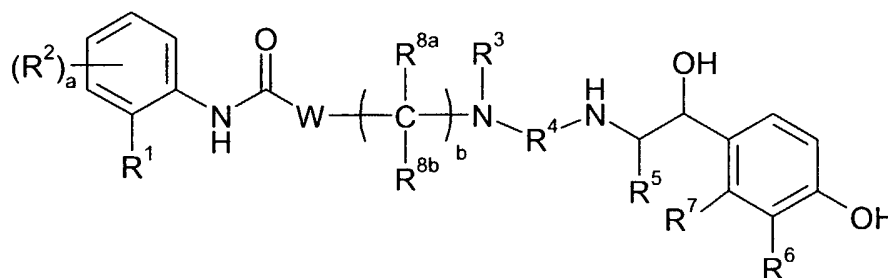
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### SUMMARY OF THE INVENTION

The present invention provides novel compounds that have been found to possess both  $\beta_2$  adrenergic receptor agonist and muscarinic receptor antagonist activity. Such compounds are expected to be useful as therapeutic agents for treating pulmonary disorders.

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Accordingly, in one of its composition aspects, the present invention provides a compound of formula I:



20

I

wherein

W represents O or  $NW^a$ ; where  $W^a$  is hydrogen or (1-4C)alkyl;

$R^1$  is (6-10C)aryl, (2-9C)heteroaryl containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur or (3-7C)cycloalkyl; wherein the aryl, heteroaryl or cycloalkyl group is unsubstituted or substituted with from 1 to 3 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (6-10C)aryl, (2-9C)heteroaryl, (3-5C)heterocyclic, cyano, halo,  $-OR^{1a}$ ,  $-C(O)OR^{1b}$ ,  $-SR^{1c}$ ,  $-S(O)R^{1d}$ ,  $-S(O)_2R^{1e}$ ,  $-NR^{1f}R^{1g}$ ,  $-C(O)R^{1h}$ ,  $-NR^{1i}C(O)OR^{1j}$ ,

25

-OC(O)NR<sup>1k</sup>R<sup>1l</sup>, -NR<sup>1m</sup>C(O)R<sup>1n</sup>, -C(O)NR<sup>1o</sup>R<sup>1p</sup> and -NHS(O)<sub>2</sub>R<sup>1q</sup>; where each of R<sup>1a</sup>, R<sup>1b</sup>, R<sup>1c</sup>, R<sup>1d</sup>, R<sup>1e</sup>, R<sup>1f</sup>, R<sup>1g</sup>, R<sup>1h</sup>, R<sup>1i</sup>, R<sup>1j</sup>, R<sup>1k</sup>, R<sup>1l</sup>, R<sup>1m</sup>, R<sup>1n</sup>, R<sup>1o</sup>, R<sup>1p</sup> and R<sup>1q</sup> is independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and where each (3-6C)cycloalkyl, (6-10C)aryl, (2-9C)heteroaryl and (3-5C)heterocyclic group is

5 unsubstituted or substituted with from 1 to 3 substituents selected from (1-4C)alkyl, halo and -OR<sup>1a</sup>; and where each alkyl group present in R<sup>1</sup> is unsubstituted or substituted with from 1 to 3 fluoro substituents;

each R<sup>2</sup> is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, -OR<sup>2a</sup>, -C(O)OR<sup>2b</sup>, -SR<sup>2c</sup>, -S(O)R<sup>2d</sup>, -S(O)<sub>2</sub>R<sup>2e</sup> and

10 -NR<sup>2f</sup>R<sup>2g</sup>; where each of R<sup>2a</sup>, R<sup>2b</sup>, R<sup>2c</sup>, R<sup>2d</sup>, R<sup>2e</sup>, R<sup>2f</sup> and R<sup>2g</sup> is independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and where each alkyl group present in R<sup>2</sup> is unsubstituted or substituted with from 1 to 3 fluoro substituents;

R<sup>3</sup> is selected from hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, or (3-6C)cycloalkyl, where the alkyl group is unsubstituted or substituted with from 1 to 3

15 fluoro substituents;

R<sup>4</sup> represents a divalent hydrocarbon group containing from 4 to 28 carbon atoms and optionally containing from 1 to 10 heteroatoms selected independently from halo, oxygen, nitrogen and sulfur, provided that the number of contiguous atoms in the shortest chain between the two nitrogen atoms to which R<sup>4</sup> is attached is in the range of from 4 to

20 16;

R<sup>5</sup> represents hydrogen or (1-4C)alkyl;

R<sup>6</sup> is -N(R<sup>6a</sup>)C(O)R<sup>6b</sup> or -CR<sup>6c</sup>R<sup>6d</sup>OR<sup>6e</sup> and R<sup>7</sup> is hydrogen; or R<sup>6</sup> and R<sup>7</sup> together form -N(R<sup>7a</sup>)C(O)C(R<sup>7b</sup>)=C(R<sup>7c</sup>)-, -C(R<sup>7d</sup>)=C(R<sup>7e</sup>)C(O)N(R<sup>7f</sup>)-, -N(R<sup>7g</sup>)C(O)CR<sup>7h</sup>R<sup>7i</sup>-CR<sup>7j</sup>R<sup>7k</sup>- or -CR<sup>7l</sup>R<sup>7m</sup>-CR<sup>7n</sup>R<sup>7o</sup>C(O)-N(R<sup>7p</sup>)-; where each of R<sup>6a</sup>,

25 R<sup>6b</sup>, R<sup>6c</sup>, R<sup>6d</sup> and R<sup>6e</sup> is independently selected from hydrogen and (1-4C)alkyl; and each of R<sup>7a</sup>, R<sup>7b</sup>, R<sup>7c</sup>, R<sup>7d</sup>, R<sup>7e</sup>, R<sup>7f</sup>, R<sup>7g</sup>, R<sup>7h</sup>, R<sup>7i</sup>, R<sup>7j</sup>, R<sup>7k</sup>, R<sup>7l</sup>, R<sup>7m</sup>, R<sup>7n</sup>, R<sup>7o</sup> and R<sup>7p</sup> is independently selected from hydrogen and (1-4C)alkyl;

each R<sup>8a</sup> and R<sup>8b</sup> is independently selected from hydrogen, (1-4C)alkyl, hydroxy and fluoro, or R<sup>8a</sup> and R<sup>8b</sup> are joined together with the atoms to which they are attached to

30 form a (3-6C)cycloalkylene ring or a (2-5C)heterocyclene ring containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, or R<sup>8a</sup> and W<sup>a</sup> are joined together with the atoms to which they are attached to form a (2-6C)azacycloalkylene group;

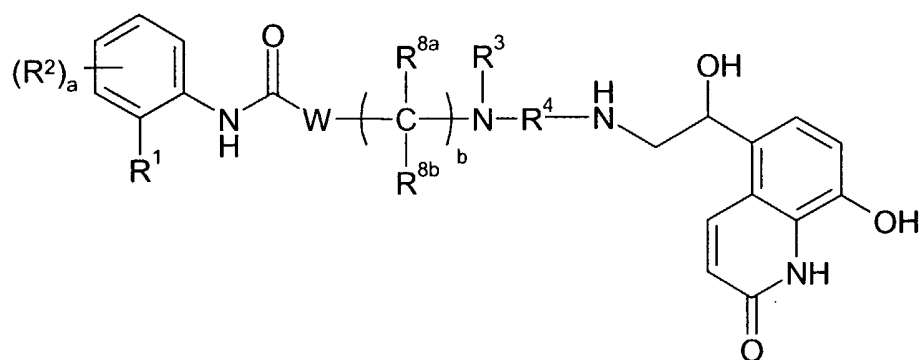
a is 0 or an integer of from 1 to 3;

b is an integer of from 2 to 8;

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

In a particular aspect, this invention provides a compound of formula II:

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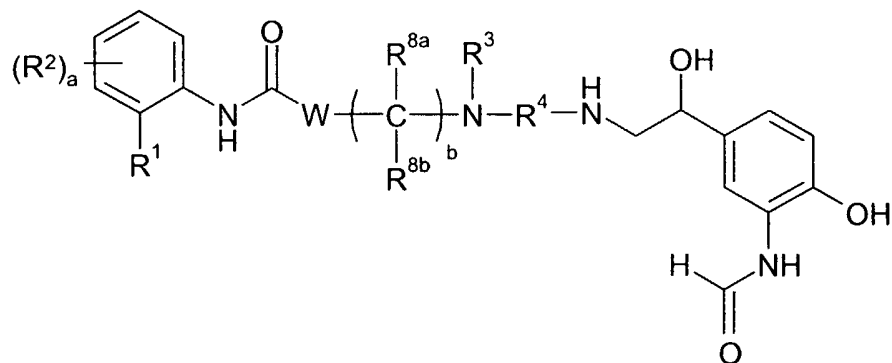


II

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^{8a}$ ,  $R^{8b}$ ,  $W$ ,  $a$  and  $b$  are as defined herein (including any specific or preferred embodiments); or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

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In another particular aspect, this invention provides a compound of formula III:

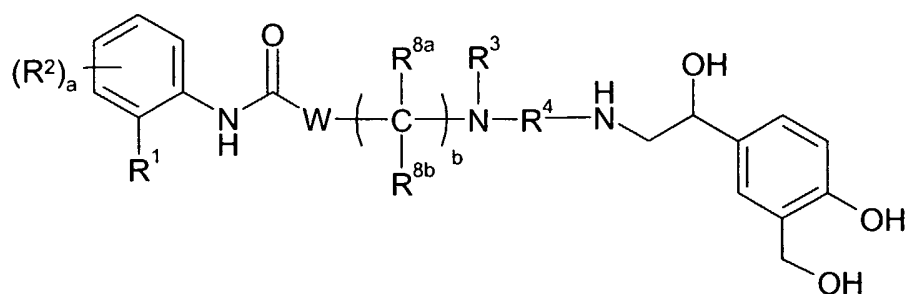


III

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wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^{8a}$ ,  $R^{8b}$ ,  $W$ ,  $a$  and  $b$  are as defined herein (including any specific or preferred embodiments); or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

In yet another particular aspect, this invention provides a compound of formula IV:



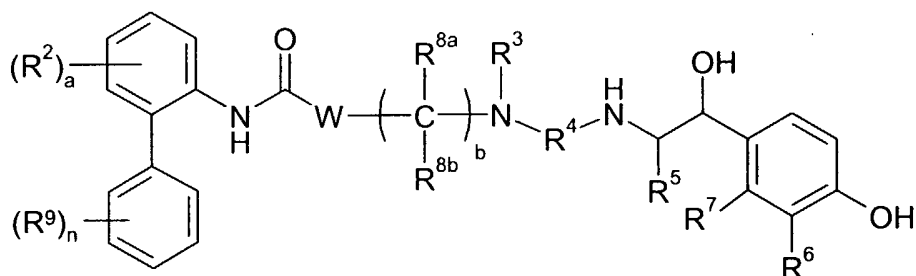
IV

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wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^{8a}$ ,  $R^{8b}$ ,  $W$ ,  $a$  and  $b$  are as defined herein (including any specific or preferred embodiments); or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

In another particular aspect, this invention provides a compound of formula V:

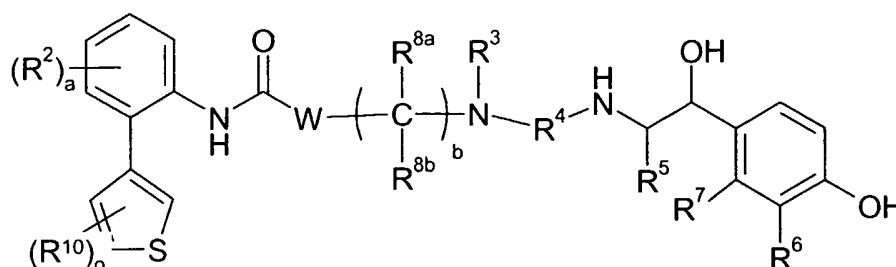
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V

15 wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^{8a}$ ,  $R^{8b}$ ,  $W$ ,  $a$ , and  $b$  are as defined herein (including any specific or preferred embodiments); and each  $R^9$  is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo,  $-OR^{9a}$ ,  $-C(O)OR^{9b}$ ,  $-SR^{9c}$ ,  $-S(O)R^{9d}$ ,  $-S(O)_2R^{9c}$  and  $-NR^{9f}R^{9g}$ ; wherein  $R^{9a}$ ,  $R^{9b}$ ,  $R^{9c}$ ,  $R^{9d}$ ,  $R^{9e}$ ,  $R^{9f}$  and  $R^{9g}$  are independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl;  
 20 and  $n$  is 0, 1, 2 or 3; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

In another particular aspect, this invention provides a compound of formula VI:



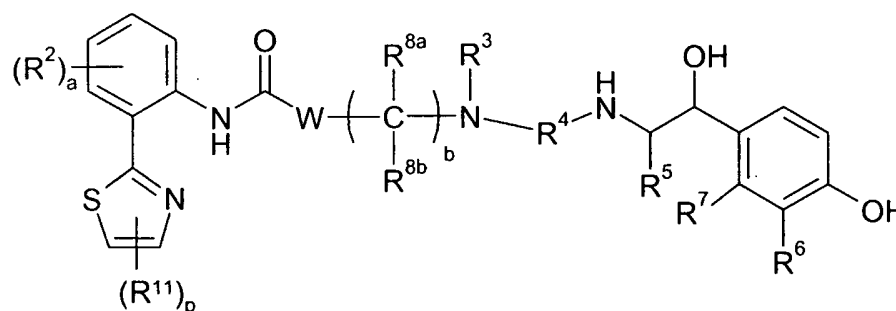
VI

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wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^{8a}$ ,  $R^{8b}$ ,  $W$ ,  $a$  and  $b$  are as defined herein (including any specific or preferred embodiments); and each  $R^{10}$  is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo,  $-OR^{10a}$ ,  $-C(O)OR^{10b}$ ,  $-SR^{10c}$ ,  $-S(O)R^{10d}$ ,  $-S(O)_2R^{10e}$  and  $-NR^{10f}R^{10g}$ ; wherein  $R^{10a}$ ,  $R^{10b}$ ,  $R^{10c}$ ,  $R^{10d}$ ,  $R^{10e}$ ,  $R^{10f}$  and  $R^{10g}$  are independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and  $o$  is 0, 1, 2 or 3; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

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In another particular aspect, this invention provides a compound of formula VII:



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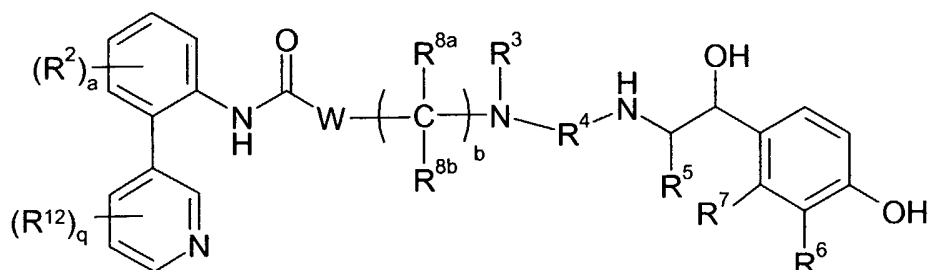
VII

wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^{8a}$ ,  $R^{8b}$ ,  $W$ ,  $a$  and  $b$  are as defined herein (including any specific or preferred embodiments); and each  $R^{11}$  is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo,  $-OR^{11a}$ ,  $-C(O)OR^{11b}$ ,  $-SR^{11c}$ ,  $-S(O)R^{11d}$ ,  $-S(O)_2R^{11e}$  and  $-NR^{11f}R^{11g}$ ; wherein  $R^{11a}$ ,  $R^{11b}$ ,  $R^{11c}$ ,  $R^{11d}$ ,  $R^{11e}$ ,  $R^{11f}$  and  $R^{11g}$  are independently selected from hydrogen, (1-4C)alkyl or

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phenyl-(1-4C)alkyl; and p is 0, 1 or 2; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

In another particular aspect, this invention provides a compound of formula VIII:



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VIII

or the corresponding pyridine N-oxide; wherein  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^{8a}$ ,  $R^{8b}$ ,  $W$ ,  $a$  and  $b$  are as defined herein (including any specific or preferred embodiments); and each  $R^{12}$  is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo,  $-OR^{12a}$ ,  $-C(O)OR^{12b}$ ,  $-SR^{12c}$ ,  $-S(O)R^{12d}$ ,  $-S(O)_2R^{12e}$  and  $-NR^{12f}R^{12g}$ ; wherein  $R^{12a}$ ,  $R^{12b}$ ,  $R^{12c}$ ,  $R^{12d}$ ,  $R^{12e}$ ,  $R^{12f}$  and  $R^{12g}$  are independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and  $q$  is 0, 1 or 2; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

In another of its composition aspects, this invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer thereof. Such pharmaceutical compositions may optionally contain other therapeutic agents. Accordingly, in one embodiment, this invention is directed to such a pharmaceutical composition wherein the composition further comprises a therapeutically effective amount of a steroidal anti-inflammatory agent, such as a corticosteroid.

Compounds of this invention possess both  $\beta_2$  adrenergic receptor agonist activity and muscarinic receptor antagonist activity. Accordingly, the compounds of formula I are expected to be useful as therapeutic agents for treating pulmonary disorders, such as asthma and chronic obstructive pulmonary disease.

Accordingly, in one of its method aspects, this invention provides a method for treating a pulmonary disorder, the method comprising administering to a patient in need of



treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

Additionally, in another of its method aspects, this invention provides a method of producing bronchodilation in a patient, the method comprising administering to a patient  
5 requiring bronchodilation a bronchodilation-producing amount of a compound of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

This invention also provides a method of treating chronic obstructive pulmonary disease or asthma, the method comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically  
10 acceptable salt or solvate or stereoisomer thereof.

Since compounds of this invention possess both  $\beta_2$  adrenergic receptor agonist activity and muscarinic receptor antagonist activity, such compounds are also useful as research tools. Accordingly; in yet another of its method aspects, this invention provides a method for using a compound of formula I or a pharmaceutically acceptable salt or solvate  
15 or stereoisomer thereof as a research tool for studying a biological system or sample, or for discovering new chemical compounds having both  $\beta_2$  adrenergic agonist activity and muscarinic receptor antagonist activity.

This invention also provides processes and novel intermediates useful for preparing compounds of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer  
20 thereof. Accordingly, in another of its method aspects, this invention provides a process of preparing a compound of formula I, the process comprising:

- (a) reacting a compound of formula 1 or a salt thereof, with a compound of formula 2;
- (b) reacting a compound of formula 3 or a salt thereof, with a compound of  
25 formula 4;
- (c) coupling a compound of formula 5 with a compound of formula 6;
- (d) for a compound of formula I wherein  $R^5$  represents a hydrogen atom, reacting a compound of formula 3 with a compound of formula 7 or a hydrate thereof, in the presence of a reducing agent;
- 30 (e) reacting a compound of formula 1 with a compound of formula 8 or a hydrate thereof, in the presence of a reducing agent;
- (f) reacting a compound of formula 9, with a compound of formula 10; or

(g) reacting a compound of formula 11 or a hydrate thereof, with a compound of formula 10, in the presence of a reducing agent;

(h) reacting a compound of formula 12, with a compound of the formula:  $R^1B(OH)_2$  in the presence of a coupling catalyst;

5 and then removing any protecting groups to form a compound of formula I; wherein the compounds of formula 1-12 are as defined therein.

In one embodiment, the above process further comprises the step of forming a pharmaceutically acceptable salt of a compound of formula I. In other embodiments, this invention is directed to the other processes described herein; and to the product prepared  
10 by any of the processes described herein.

In a particular embodiment, this invention is directed to a compound of formula 12, which compound is useful as an intermediate in preparing compounds of formula I.

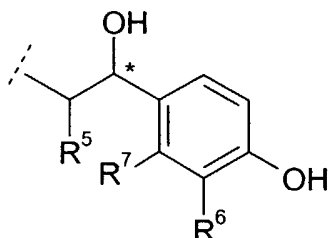
This invention provides a compound of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer thereof, for use in therapy or as a medicament.

15 Additionally, this invention is directed to the use of a compound of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer thereof, for the manufacture of a medicament; especially for the manufacture of a medicament for the treatment of a pulmonary disorder.

## 20 DETAILED DESCRIPTION OF THE INVENTION

In one of its composition aspects, this invention is directed to novel compounds of formula I or pharmaceutically acceptable salts or solvates or stereoisomers thereof. These compounds contain one or more chiral centers and therefore, this invention is directed to racemic mixtures; pure stereoisomers (i.e., enantiomers or diastereomers); stereoisomer-  
25 enriched mixtures and the like unless otherwise indicated. When a particular stereoisomer is shown or named herein, it will be understood by those skilled in the art that minor amounts of other stereoisomers may be present in the compositions of this invention unless otherwise indicated, provided that any utility of the composition as a whole is not eliminated by the presence of such other isomers.

30 In particular, compounds of formula I contain a chiral center at the carbon atom indicated by the symbol \* in the following formula:



5

In one embodiment of this invention, the carbon atom identified by the symbol \* has the (*R*) configuration. In this embodiment, it is preferred for compounds of formula I to have the (*R*) configuration at the carbon atom identified by the symbol \* or to be enriched in a stereoisomeric form having the (*R*) configuration at this carbon atom. In another embodiment of this invention, the carbon atom identified by the symbol \* has the (*S*) configuration. In this embodiment, it is preferred for compounds of formula I to have the (*S*) configuration at the carbon atom identified by the symbol \* or to be enriched in a stereoisomeric form having the (*S*) configuration at this carbon atom. In some cases, in order to optimize the  $\beta_2$  adrenergic agonist activity of the compounds of this invention, it is preferred that the carbon atom identified by the symbol \* has the (*R*) configuration.

The compounds of formula I also contain several basic groups (e.g., amino groups) and therefore, the compounds of formula I can exist as the free base or in various salt forms. All such salt forms are included within the scope of this invention. Furthermore, solvates of compounds of formula I or salts thereof are included within the scope of this invention.

Additionally, where applicable, all *cis-trans* or *E/Z* isomers (geometric isomers), tautomeric forms and topoisomeric forms of the compounds of formula I are included within the scope of this invention unless otherwise specified.

The nomenclature used herein to name the compounds of this invention and intermediates thereof has generally been derived using the commercially-available AutoNom software (MDL, San Leandro, California). Typically, compounds of formula I wherein W is O have been named as ester derivatives of carbamic acid; and compounds of formula I wherein W is NW<sup>a</sup> have been named as urea derivatives.

### Representative Embodiments

The following substituents and values are intended to provide representative  
5 examples of various aspects and embodiments of this invention. These representative  
values are intended to further define and illustrate such aspects and embodiments and are  
not intended to exclude other embodiments or to limit the scope of this invention. In this  
regard, the representation that a particular value or substituent is preferred is not intended  
in any way to exclude other values or substituents from this invention unless specifically  
10 indicated.

In one embodiment of this invention, W is O. In another embodiment, W is NW<sup>a</sup>.  
Generally, it has been found that compounds in which W represents O exhibit particularly  
high affinity for muscarinic and  $\beta_2$  adrenergic receptors. Accordingly, in a particular  
embodiment of this invention, W preferably represents O.

15 When W is NW<sup>a</sup>, W<sup>a</sup> is hydrogen or (1-4C)alkyl; such as hydrogen, methyl, ethyl,  
*n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl and *tert*-butyl. In one embodiment, W<sup>a</sup> is  
hydrogen or (1-3C)alkyl. In another embodiment, W<sup>a</sup> is hydrogen, methyl or ethyl; such as  
hydrogen or methyl. In yet another embodiment, W<sup>a</sup> is hydrogen and NW<sup>a</sup> is NH.

In a particular embodiment, when W is NW<sup>a</sup>, R<sup>6</sup> is -N(R<sup>6a</sup>)C(O)R<sup>6b</sup> (e.g.,  
20 -NHCHO) and R<sup>7</sup> is hydrogen; or R<sup>6</sup> and R<sup>7</sup> together form -N(R<sup>7a</sup>)C(O)C(R<sup>7b</sup>)=C(R<sup>7c</sup>) -  
(e.g., -NHC(O)CH=CH-).

In the compounds of the present invention, R<sup>1</sup> is an optionally substituted (6-  
10C)aryl, (2-9C)heteroaryl or (3-7C)cycloalkyl group. In a particular embodiment, R<sup>1</sup> is  
an optionally substituted (6-10C)aryl group selected from a phenyl and naphthalene ring,  
25 where the point of attachment is at any available carbon ring atom. In another particular  
embodiment, R<sup>1</sup> is an optionally substituted (2-9C)heteroaryl group selected from a  
pyrrole, imidazole, thiazole, oxazole, furan, thiophene, triazole, pyrazole, isoxazole,  
isothiazole, pyridine, pyridine N-oxide, pyrazine, pyridazine, pyrimidine, triazine, indole,  
benzofuran, benzothiophene, benzimidazole, benzthiazole, quinoline, isoquinoline,  
30 quinazoline and quinoxaline ring, where the point of attachment is at any available carbon  
or nitrogen ring atom. In a particular embodiment, R<sup>1</sup> is an optionally substituted phenyl  
ring. In another particular embodiment, R<sup>1</sup> is an optionally substituted naphthalene ring,  
such as a naphth-1-yl or a naphth-2-yl group. In another particular embodiment, R<sup>1</sup> is an

optionally substituted thienyl group, such as thien-2-yl or thien-3-yl group. In another particular embodiment, R<sup>1</sup> is an optionally substituted thiazole group, such as a thiazol-2-yl, thiazol-4-yl or thiazol-5-yl group. In yet another particular embodiment, R<sup>1</sup> is an optionally substituted pyridyl group, such as a pyrid-2-yl, pyrid-3-yl or pyrid-4-yl group, or  
5 the corresponding pyridine N-oxides. In still another particular embodiment, R<sup>1</sup> is an optionally substituted furyl group, such as a fur-2-yl or fur-3-yl group. In another particular embodiment, R<sup>1</sup> is an optionally substituted pyrimidinyl group, such as a pyrimidin-2-yl, pyrimidin-4-yl or pyrimidin-4-yl group. In a particular embodiment, R<sup>1</sup> is an optionally substituted cyclopentyl group, such as cyclopentyl, 2,2-difluorocyclopentyl  
10 or 3,3-difluorocyclopentyl. In another particular embodiment, R<sup>1</sup> is an optionally substituted cyclohexyl group.

In a particular embodiment, the (6-10C)aryl, (2-9C heteroaryl) or (3-7C)cycloalkyl group of R<sup>1</sup> is unsubstituted or substituted with from 1 to 3 substituents selected from (1-4C)alkyl, halo, -OR<sup>1a</sup> and -NR<sup>1f</sup>R<sup>1g</sup>, wherein each alkyl group is unsubstituted or  
15 substituted with from 1 to 3 fluoro substituents. Representative substituents include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, fluoro, chloro, bromo, iodo, hydroxy, methoxy, ethoxy, isopropoxy, amino, methylamino, dimethylamino, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2,-trifluoroethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy  
20 and the like. Particular values for substituents on the R<sup>1</sup> group are fluoro or chloro.

When present, each R<sup>2</sup> may be at the 3, 4, 5 or 6-position on the phenylene ring to which it is attached (where the carbon atom on the phenylene ring attached to the nitrogen atom is position 1). In one embodiment, each R<sup>2</sup> is independently selected from (1-4C)alkyl, halo, -OR<sup>2a</sup> and -NR<sup>2f</sup>R<sup>2g</sup>; wherein each alkyl group is unsubstituted or  
25 substituted with from 1 to 3 fluoro substituents. Representative substituents include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, fluoro, chloro, bromo, iodo, hydroxy, methoxy, ethoxy, isopropoxy, amino, methylamino, dimethylamino, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2,-trifluoroethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy  
30 and the like. Particular values for R<sup>2</sup> are fluoro or chloro.

In a particular embodiment of the compounds of formula I, a is 0, 1 or 2; including 0 or 1. In one embodiment, a is 0.

Each  $R^{1a}$ ,  $R^{1b}$ ,  $R^{1c}$ ,  $R^{1d}$ ,  $R^{1e}$ ,  $R^{1f}$ ,  $R^{1g}$ ,  $R^{1h}$ ,  $R^{1i}$ ,  $R^{1j}$ ,  $R^{1k}$ ,  $R^{1l}$ ,  $R^{1m}$ ,  $R^{1n}$ ,  $R^{1o}$ ,  $R^{1p}$  and  $R^{1q}$ , and  $R^{2a}$ ,  $R^{2b}$ ,  $R^{2c}$ ,  $R^{2d}$ ,  $R^{2e}$ ,  $R^{2f}$  and  $R^{2g}$  as used in  $R^1$  and  $R^2$ , respectively, is independently hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl, where the alkyl group is unsubstituted or substituted with from 1 to 3 fluoro substituents. Representative groups  
 5 include hydrogen, methyl, trifluoromethyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl or benzyl. In one embodiment, these groups are independently hydrogen or (1-3C)alkyl. In another embodiment, these groups are independently hydrogen, methyl or ethyl.

In a particular embodiment of the compounds of formula I,  $b$  is 2, 3, 4, 5 or 6;  
 10 including 2, 3, or 4; such as 2 or 3. In one embodiment,  $b$  is 2. In another embodiment,  $b$  is 3. In yet another embodiment,  $b$  is 4.

In one embodiment, each  $R^{8a}$  and  $R^{8b}$  are independently selected from hydrogen, methyl or ethyl. A particular value for each  $R^{8a}$  and  $R^{8b}$  is hydrogen or methyl. In a particular embodiment,  $R^{8a}$  and  $R^{8b}$  in the  $-CR^{8a}R^{8b}$  unit attached to  $W$  are both methyl,  
 15 while in the remaining  $-CR^{8a}R^{8b}$  unit or units,  $R^{8a}$  and  $R^{8b}$  are both hydrogen. Representative groups in this embodiment include, by way of illustration,  $-C(CH_3)_2CH_2-$ ;  $-C(CH_3)_2CH_2CH_2-$  and  $-C(CH_3)_2CH_2CH_2CH_2-$ .

In another embodiment,  $R^{8a}$  and  $R^{8b}$  in one  $-CR^{8a}R^{8b}$  unit are joined, together with the carbon atom to which they are attached, to form a (3-6C)cycloalkylene group, such as a  
 20 cyclopentadi-1,1-yl or cyclohexadi-1,1-yl. Additionally, in another embodiment,  $R^{8a}$  and  $R^{8b}$  in two  $-CR^{8a}R^{8b}$  units are joined, together with the carbon atom to which they are attached, to form a (3-6C)cycloalkylene group, such as a cyclopentadi-1,2-yl, cyclopentadi-1,3-yl, cyclohexadi-1,2-yl, cyclohexadi-1,3-yl or cyclohexadi-1,4-yl group.

In yet another embodiment,  $R^{8a}$  in the  $-CR^{8a}R^{8b}$  unit attached to  $W$  and  $W^a$  are  
 25 joined, together with the atoms to which they are attached, to form a (4-5C)azacycloalkylene group, i.e., a pyrrolidin-1,2-yl, pyrrolidin-1,3-yl, piperidin-1,2-yl, piperidin-1,3-yl or piperidin-1,4-yl ring.

In a particular embodiment,  $R^3$  is selected from hydrogen or (1-3C)alkyl; such as hydrogen, methyl, ethyl, *n*-propyl or isopropyl. In another aspect,  $R^3$  is methyl or ethyl.

In one embodiment,  $R^5$  is hydrogen or (1-4C)alkyl; such as hydrogen, methyl,  
 30 ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl and *tert*-butyl. In another embodiment, each  $R^5$  is independently hydrogen, methyl or ethyl. In a particular embodiment,  $R^5$  is hydrogen.

In one embodiment,  $R^6$  is  $-N(R^{6a})C(O)R^{6b}$  and  $R^7$  is hydrogen, where each of  $R^{6a}$  and  $R^{6b}$  is independently hydrogen or (1-4C)alkyl, such as hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl and *tert*-butyl. In one embodiment, these groups are independently hydrogen or (1-3C)alkyl. In another embodiment, these groups are independently hydrogen, methyl or ethyl. A particular value for  $R^6$  in this embodiment is -NHCHO.

In another embodiment,  $R^6$  and  $R^7$  together form  $-N(R^{7a})C(O)-CR^{7b}=CR^{7c}-$ ,  $-CR^{7d}=CR^{7e}-C(O)N(R^{7f})-$ ,  $-N(R^{7g})C(O)CR^{7h}R^{7i}-CR^{7j}R^{7k}-$  or  $-CR^{7l}R^{7m}-CR^{7n}R^{7o}-C(O)N(R^{7p})-$ ; where each of  $R^{7a}$ ,  $R^{7b}$ ,  $R^{7c}$ ,  $R^{7d}$ ,  $R^{7e}$ ,  $R^{7f}$ ,  $R^{7g}$ ,  $R^{7h}$ ,  $R^{7i}$ ,  $R^{7j}$ ,  $R^{7k}$ ,  $R^{7l}$ ,  $R^{7m}$ ,  $R^{7n}$ ,  $R^{7o}$  and  $R^{7p}$  is independently hydrogen or (1-4C)alkyl; such as hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl and *tert*-butyl. In one embodiment, these groups are independently hydrogen or (1-3C)alkyl. In another embodiment, these groups are independently hydrogen, methyl or ethyl. Particular values for  $R^6$  and  $R^7$  in this embodiment are  $R^6$  and  $R^7$  together form -NHC(O)-CH=CH-, -CH=CH-C(O)-NH-, -CH<sub>2</sub>-CH<sub>2</sub>-C(O)NH- or -NHC(O)-CH<sub>2</sub>-CH<sub>2</sub>-; including where  $R^6$  and  $R^7$  together form -NHC(O)-CH=CH- or -CH=CH-C(O)-NH-; and in particular, where  $R^6$  and  $R^7$  together form -NHC(O)-CH=CH- (i.e., the nitrogen atom is attached at  $R^6$  and the carbon atom is attached at  $R^7$  to form, together with the hydroxyphenyl ring to which  $R^6$  and  $R^7$  are attached, a 8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl group).

In a particular embodiment,  $R^6$  is -NHCHO or -CH<sub>2</sub>OH and  $R^7$  is hydrogen; or  $R^6$  and  $R^7$  together form -NHC(O)CH=CH-, -CH=CHC(O)NH-, -CH<sub>2</sub>CH<sub>2</sub>C(O)NH- or -NHC(O)CH<sub>2</sub>CH<sub>2</sub>-.

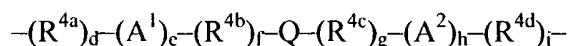
The divalent hydrocarbon group of this invention (e.g.,  $R^4$  in formula 1) contains from 4 to 28 carbon atoms and optionally containing from 1 to 10 heteroatoms selected independently from halo, oxygen, nitrogen and sulfur. In one embodiment, this group contains from 4 to 24 carbon atoms, including from 6 to 20 carbon atoms, such as from 8 to 18 carbon atoms; and optionally contains from 1 to 8 heteroatoms, including from 1 to 6 heteroatoms.

The divalent hydrocarbon may contain any arrangement of atoms including alkylene, alkenylene, alkynylene, cycloalkylene, arylene, heteroarylene and heterocyclene groups or combinations thereof. The hydrocarbon group may be interrupted by one or more heteroatoms or combinations of heteroatoms and carbon atoms to form various

functional groups, such as ethers, thioethers, amines, amides, esters, carbamates, ureas, sulfones, sulfoxides, sulfonamides and the like.

In a particular aspect of this invention, the divalent hydrocarbon group of the compounds of this invention (e.g., R<sup>4</sup> in formula I) is a divalent group of the formula:

5



wherein

d, e, f, g, h and i are each independently selected from 0 and 1;

10

R<sup>4a</sup>, R<sup>4b</sup>, R<sup>4c</sup> and R<sup>4d</sup> are each independently selected from (1-10C)alkylene, (2-10C)alkenylene and (2-10C)alkynylene, wherein each alkylene, alkenylene or alkynylene group is unsubstituted or substituted with from 1 to 5 substituents independently selected from (1-4C)alkyl, fluoro, hydroxy, phenyl and phenyl-(1-4C)alkyl; or R<sup>4d</sup> represents (1-6C)alkylene-NHC(O)-(1-6C)alkylene;

15

A<sup>1</sup> and A<sup>2</sup> are each independently selected from (3-7C)cycloalkylene, (6-10C)arylene, -O-(6-10C)arylene, (6-10C)arylene-O-, (2-9C)heteroarylene, -O-(2-9C)heteroarylene, (2-9C)heteroarylene-O- and (3-6C)heterocyclene, wherein each cycloalkylene is unsubstituted or substituted with from 1 to 4 substituents selected independently from (1-4C)alkyl, and each arylene, heteroarylene or heterocyclene group is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, -S-(1-4C)alkyl, -S(O)-(1-4C)alkyl, -S(O)<sub>2</sub>-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy;

20

Q is selected from a bond, -O-, -C(O)O-, -OC(O)-, -S-, -S(O)-, -S(O)<sub>2</sub>-, -N(Q<sup>a</sup>)C(O)-, -C(O)N(Q<sup>b</sup>)-, -N(Q<sup>c</sup>)S(O)<sub>2</sub>-, -S(O)<sub>2</sub>N(Q<sup>d</sup>)-, -N(Q<sup>e</sup>)C(O)N(Q<sup>f</sup>)-, -N(Q<sup>g</sup>)S(O)<sub>2</sub>N(Q<sup>h</sup>)-, -OC(O)N(Q<sup>i</sup>)-, -N(Q<sup>j</sup>)C(O)O- and -N(Q<sup>k</sup>); where Q<sup>a</sup>, Q<sup>b</sup>, Q<sup>c</sup>, Q<sup>d</sup>, Q<sup>e</sup>, Q<sup>f</sup>, Q<sup>g</sup>, Q<sup>h</sup>, Q<sup>i</sup>, Q<sup>j</sup> and Q<sup>k</sup> are each independently selected from hydrogen, (1-6C)alkyl, A<sup>3</sup> and (1-4C)alkylene-A<sup>4</sup>, wherein the alkyl group is unsubstituted or substituted with from 1 to 3 substituents independently selected from fluoro, hydroxy and (1-4C)alkoxy; or together with the nitrogen atom and the group R<sup>4b</sup> or R<sup>4c</sup> to which they are attached, form a 4 to 6 membered azacycloalkylene group; and

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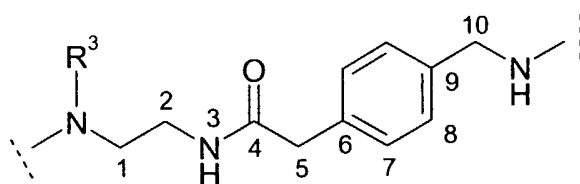
A<sup>3</sup> and A<sup>4</sup> are each independently selected from (3-6C)cycloalkyl, (6-10C)aryl, (2-9C)heteroaryl and (3-6C)heterocyclyl, wherein each cycloalkyl is unsubstituted or substituted with from 1 to 4 substituents selected independently from (1-4C)alkyl and each



aryl, heteroaryl or heterocyclyl group is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl and (1-4C)alkoxy.

In the compound of this invention, the values of each of the components  $R^{4a}$ ,  $A^1$ ,  $R^{4b}$ ,  $Q$ ,  $R^{4c}$ ,  $A^2$  and  $R^{4d}$  are selected such that the number of contiguous atoms in the shortest chain between the two nitrogen atoms to which  $R^4$  is attached is in the range of from 4 to 16, (specifically, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16); including 8, 9, 10, 11, 12, 13 or 14; such as 8, 9, 10 or 11; or 9 or 10. When selecting values for each variable in  $R^4$ , it will be appreciated by those skilled in the art that values should be selected such that a chemically stable group is formed.

When determining the number of contiguous atoms in the shortest chain between the two nitrogen atoms to which  $R^4$  is attached, each contiguous atom of the chain is counted consecutively starting from the first atom in the  $R^4$  group adjacent to the nitrogen to which  $R^3$  is attached and ending with the last atom in the  $R^4$  group adjacent to the nitrogen of the aminohydroxyethyl group. Where two or more chains are possible, the shortest chain is used to determine the number of contiguous atoms. As shown below, for example, when  $R^4$  is  $-(CH_2)_2-NHC(O)-CH_2-(phen-1,4-ylene)-CH_2-$ , there are 10 contiguous atoms in the shortest chain counted consecutively starting from the first atom in the  $R^4$  group adjacent to the nitrogen to which  $R^3$  is attached and ending with the last atom in the  $R^4$  group adjacent to the nitrogen of the aminohydroxyethyl group as shown below:



20

In one embodiment of  $R^4$ ,  $R^{4a}$  is selected from (1-10C)alkylene, (2-10C)alkenylene and (2-10C)alkynylene wherein the alkylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy and phenyl.

Representative examples of particular values for  $R^{4a}$  are  $-CH_2-$ ,  $-(CH_2)_2-$ ,  $-(CH_2)_3-$ ,  $-(CH_2)_4-$ ,  $-(CH_2)_5-$ ,  $-(CH_2)_6-$ ,  $-(CH_2)_7-$ ,  $-(CH_2)_8-$ ,  $-(CH_2)_9-$ ,  $-(CH_2)_{10}-$ ,  $-(CH_2)CH(CH_3)-$ ,  $-(CH_2)C(CH_3)_2-$ , and  $-(CH_2)_2C(phenyl)_2-$ . In another aspect,  $R^{4a}$  is  $-(CH_2)C(=CH_2)-$ .

In one embodiment, d is 1.

30

In one embodiment, A<sup>1</sup> is an optionally substituted (3-7C)cycloalkylene group; including a cyclohexylene group, such as cyclohex-1,4-ylyene and cyclohex-1,3-ylyene; and a cyclopentylene group, such as cyclopent-1,3-ylyene.

In another embodiment, A<sup>1</sup> is an optionally substituted (6-10C)arylene group, including a phenylene group, such as phen-1,4-ylyene, phen-1,3-ylyene and phen-1,2-ylyene; and a naphthylene group, such as naphth-1,4-ylyene and naphth-1,5-ylyene.

In yet another embodiment, A<sup>1</sup> is an optionally substituted (2-9C)heteroarylene group, including a pyridylene group, such as pyrid-1,4-ylyene; a furylene group, such as fur-2,5-ylyene and fur-2,4-ylyene; a thienylene group, such as thien-2,5-ylyene and thien-2,4-ylyene; and a pyrrolylene, such as pyrrol-2,5-ylyene and pyrrol-2,4-ylyene.

In still another embodiment, A<sup>1</sup> is an optionally substituted (3-6C)heterocyclene group, including a piperidinylene group, such as piperidin-1,4-ylyene; and a pyrrolidinylene group, such as pyrrolidin-2,5-ylyene.

In a particular embodiment, A<sup>1</sup> is an optionally substituted phenylene, thienylene, cyclopentylene, cyclohexylene or piperidinylene.

In one embodiment, e is 0.

In a particular embodiment, R<sup>4b</sup> is (1-5C)alkylene. Representative examples of particular values for R<sup>4b</sup> are -CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>-, -(CH<sub>2</sub>)<sub>4</sub>-, -(CH<sub>2</sub>)<sub>5</sub>-; including methylene, ethylene and propylene.

In one embodiment, f is 0.

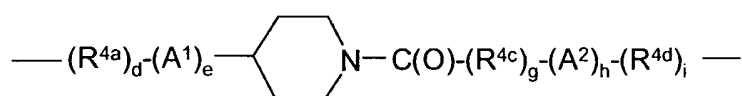
In a particular embodiment, Q is selected from a bond, -O-, -N(Q<sup>a</sup>)C(O)-, -C(O)N(Q<sup>b</sup>)-, -N(Q<sup>c</sup>)S(O)<sub>2</sub>-, -S(O)<sub>2</sub>N(Q<sup>d</sup>)-, -N(Q<sup>e</sup>)C(O)N(Q<sup>f</sup>)-, -OC(O)N(Q<sup>g</sup>)-, -N(Q<sup>j</sup>)C(O)O- or -N(Q<sup>k</sup>); such as where Q is a bond, -N(Q<sup>a</sup>)C(O)- or -C(O)N(Q<sup>b</sup>)-. Representative examples of particular values for Q are a bond, O, NH-, -C(O)NH-, -C(O)N(CH<sub>3</sub>)-, -NHC(O)-, -N(CH<sub>3</sub>)C(O)-, -S(O)<sub>2</sub>NH-, -S(O)<sub>2</sub>N(CH<sub>3</sub>)-, -NHS(O)<sub>2</sub>-, -N(CH<sub>3</sub>)S(O)<sub>2</sub>- and -NHC(O)NH-. Another example of a value for Q, together with R<sup>4c</sup>, is -C(O)(piperidin-1,4-ylyene).

In one embodiment, Q<sup>a</sup>, Q<sup>b</sup>, Q<sup>c</sup>, Q<sup>d</sup>, Q<sup>e</sup>, Q<sup>f</sup>, Q<sup>g</sup>, Q<sup>h</sup>, Q<sup>i</sup>, Q<sup>j</sup> and Q<sup>k</sup> are each independently selected from hydrogen and (1-6C)alkyl, wherein the alkyl group is unsubstituted or substituted with from 1 to 3 substituents independently selected from fluoro, hydroxy and (1-4C)alkoxy. For example, Q<sup>a</sup>, Q<sup>b</sup>, Q<sup>c</sup>, Q<sup>d</sup>, Q<sup>e</sup>, Q<sup>f</sup>, Q<sup>g</sup>, Q<sup>h</sup>, Q<sup>i</sup>, Q<sup>j</sup> and Q<sup>k</sup> are each independently selected from hydrogen, and (1-3C)alkyl, including hydrogen,

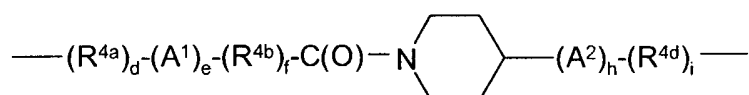
methyl, ethyl, *n*-propyl and isopropyl. An example of a value for each of Q<sup>a</sup>, Q<sup>b</sup>, Q<sup>c</sup>, Q<sup>d</sup>, Q<sup>e</sup>, Q<sup>f</sup>, Q<sup>g</sup>, Q<sup>h</sup>, Q<sup>i</sup>, Q<sup>j</sup> and Q<sup>k</sup> is hydrogen.

In another embodiment, Q<sup>a</sup>, Q<sup>b</sup>, Q<sup>c</sup>, Q<sup>d</sup>, Q<sup>e</sup>, Q<sup>f</sup>, Q<sup>g</sup>, Q<sup>h</sup>, Q<sup>i</sup>, Q<sup>j</sup> and Q<sup>k</sup> together with the nitrogen atom and the group R<sup>4b</sup> or R<sup>4c</sup> to which they are attached, form a 4-6  
 5 membered azacycloalkylene group. For example, Q<sup>a</sup> and Q<sup>b</sup> together with the nitrogen atom and the group R<sup>4b</sup> or R<sup>4c</sup> to which they are attached, form a piperidin-4-ylene group. By way of illustration, when Q represents -N(Q<sup>a</sup>)C(O)- and Q<sup>a</sup> together with the nitrogen atom and the group R<sup>4b</sup> to which it is attached, forms a piperidin-4-ylene group, R<sup>4</sup> is a group of formula:

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Similarly, when Q represents -C(O)N(Q<sup>b</sup>)- and Q<sup>b</sup> together with the nitrogen atom and the group R<sup>4c</sup> to which it is attached, forms a piperidin-4-ylene group, R<sup>4</sup> is a group of  
 15 formula:



In a particular embodiment, R<sup>4c</sup> is (1-5C)alkylene. Representative examples of  
 20 particular values for R<sup>4c</sup> are -CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>-, -(CH<sub>2</sub>)<sub>4</sub>-, -(CH<sub>2</sub>)<sub>5</sub>-; including methylene, ethylene and propylene.

In one embodiment, A<sup>2</sup> is an optionally substituted (3-7C)cycloalkylene group; including a cyclohexylene group, such as cyclohex-1,4-ylene and cyclohex-1,3-ylene; and a cyclopentylene group, such as cyclopent-1,3-ylene.

In another embodiment, A<sup>2</sup> is an optionally substituted (6-10C)arylene group,  
 25 including a phenylene group, such as phen-1,4-ylene, phen-1,3-ylene and phen-1,2-ylene; and a naphthylene group, such as naphth-1,4-ylene and naphth-1,5-ylene.

In yet another embodiment, A<sup>2</sup> is an optionally substituted (2-9C)heteroarylene group, including a pyridylene group, such as pyrid-1,4-ylene; a furylene group, such as fur-

2,5-ylene and fur-2,4-ylene; a thienylene group, such as thien-2,5-ylene and thien-2,4-ylene; and a pyrrolylene, such as pyrrol-2,5-ylene and pyrrol-2,4-ylene.

In still another embodiment, A<sup>2</sup> is an optionally substituted (3-6C)heterocyclene group, including a piperidinylene group, such as piperidin-1,4-ylene; and a pyrrolidinylene group, such as pyrrolidin-2,5-ylene.

In a particular embodiment, A<sup>2</sup> is optionally substituted phenylene, thienylene, cyclopentylene, cyclohexylene or piperidinylene.

By way of illustration, either A<sup>1</sup> or A<sup>2</sup> or both can be phenylene, such as phen-1,4-ylene or phen-1,3-ylene, where the phenylene group is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, -S-(1-4C)alkyl, -S(O)-(1-4C)alkyl, -S(O)<sub>2</sub>-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy. Representative examples include phen-1,3-ylene, phen-1,4-ylene, 4-chlorophen-1,3-ylene, 6-chlorophen-1,3-ylene, 4-methylphen-1,3-ylene, 2-fluorophen-1,4-ylene, 2-chlorophen-1,4-ylene, 2-bromophen-1,4-ylene, 2-iodophen-1,4-ylene, 2-methylphen-1,4-ylene, 2-methoxyphen-1,4-ylene, 2-trifluoromethoxyphen-1,4-ylene, 3-nitrophen-1,4-ylene, 3-chlorophen-1,4-ylene, 2,5-difluorophen-1,4-ylene, 2,6-dichlorophen-1,4-ylene, 2,6-diiodophen-1,4-ylene, 2-chloro-6-methylphen-1,4-ylene, 2-chloro-5-methoxyphen-1,4-ylene, 2,3,5,6-tetrafluorophen-1,4-ylene.

Alternatively, A<sup>1</sup> or A<sup>2</sup> or both can be cyclopentylene or cyclohexylene; wherein the cyclopentylene or cyclohexylene group is unsubstituted or substituted with (1-4C)alkyl. Representative examples include *cis*-cyclopent-1,3-ylene, *trans*-cyclopent-1,3-ylene, *cis*-cyclohex-1,4-ylene and *trans*-cyclohex-1,4-ylene. A<sup>1</sup> or A<sup>2</sup> or both can also be optionally substituted thienylene or piperidinylene, for example, thien-2,5-ylene or piperidin-1,4-ylene.

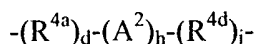
In one embodiment, R<sup>4d</sup> is selected from (1-10C)alkylene, (2-10C)alkenylene and (2-10C)alkynylene wherein the alkylene is unsubstituted or substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy and phenyl. Representative examples of particular values for R<sup>4d</sup> are -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>-, -(CH<sub>2</sub>)<sub>4</sub>-, -(CH<sub>2</sub>)<sub>5</sub>-, -(CH<sub>2</sub>)<sub>6</sub>-, -(CH<sub>2</sub>)<sub>7</sub>-, -(CH<sub>2</sub>)<sub>8</sub>-, -(CH<sub>2</sub>)<sub>9</sub>-, -(CH<sub>2</sub>)<sub>10</sub>-, -(CH<sub>2</sub>)CH(CH<sub>3</sub>)-, -(CH<sub>2</sub>)C(CH<sub>3</sub>)<sub>2</sub>- and -(CH<sub>2</sub>)<sub>2</sub>C(phenyl)<sub>2</sub>-.

In a particular embodiment, R<sup>4</sup> is a divalent group of the formula: -(R<sup>4a</sup>)<sub>d</sub>- where R<sup>4a</sup> is (4-10C)alkylene. In one aspect of this embodiment, R<sup>4</sup> is a divalent group of the

formula:  $-(\text{CH}_2)_j-$  where  $j$  is 8, 9 or 10. Examples of particular values for  $R^4$  in this embodiment are  $-(\text{CH}_2)_4-$ ,  $-(\text{CH}_2)_5-$ ,  $-(\text{CH}_2)_6-$ ,  $-(\text{CH}_2)_7-$ ,  $-(\text{CH}_2)_8-$ ,  $-(\text{CH}_2)_9-$ , and  $-(\text{CH}_2)_{10}-$ ; including  $-(\text{CH}_2)_8-$ ,  $-(\text{CH}_2)_9-$  and  $-(\text{CH}_2)_{10}-$ .

In another particular embodiment,  $R^4$  is a divalent group of the formula:

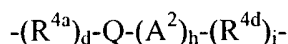
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where  $R^{4a}$  is (1-10C)alkylene, such as  $-(\text{CH}_2)-$ ,  $-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_3-$ ;  $A^2$  is (6-10C)arylene, such as phen-1,4-ylene or phen-1,3-ylene, or (2-9C)heteroarylene, such as thien-2,5-ylene or thien-2,4-ylene; and  $R^{4d}$  is (1-10C)alkylene, such as  $-(\text{CH}_2)-$ ,  $-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_3-$ . Examples of particular values for  $R^4$  in this embodiment are  $-(\text{CH}_2)-(\text{phen-1,4-ylene})-(\text{CH}_2)-$ ;  $-(\text{CH}_2)-(\text{phen-1,4-ylene})-(\text{CH}_2)_2-$ ;  $-(\text{CH}_2)-(\text{phen-1,4-ylene})-(\text{CH}_2)_3-$ ;  $-(\text{CH}_2)_2-(\text{phen-1,4-ylene})-(\text{CH}_2)-$ ;  $-(\text{CH}_2)_2-(\text{phen-1,4-ylene})-(\text{CH}_2)_2-$ ;  $-(\text{CH}_2)_2-(\text{phen-1,4-ylene})-(\text{CH}_2)_3-$ ;  $-(\text{CH}_2)_3-(\text{phen-1,4-ylene})-(\text{CH}_2)-$ ;  $-(\text{CH}_2)_3-(\text{phen-1,4-ylene})-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_3-(\text{phen-1,4-ylene})-(\text{CH}_2)_3-$ ,  $-(\text{CH}_2)_4-(\text{phen-1,4-ylene})-(\text{CH}_2)-$ ;  $-(\text{CH}_2)_4-(\text{phen-1,4-ylene})-(\text{CH}_2)_2-$  and  $-(\text{CH}_2)_4-(\text{phen-1,4-ylene})-(\text{CH}_2)_3-$ .

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In yet another particular embodiment,  $R^4$  is a divalent group of the formula:



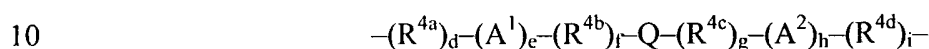
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where  $Q$  is  $-\text{O}-$  or  $-\text{N}(\text{Q}^k)-$ ;  $\text{Q}^k$  is hydrogen or (1-3C)alkyl, such as methyl or ethyl;  $R^{4a}$  is (1-10C)alkylene, such as  $-(\text{CH}_2)-$ ,  $-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_3-$ ;  $A^2$  is (6-10C)arylene, such as phen-1,4-ylene or phen-1,3-ylene, or (2-9C)heteroarylene, such as thien-2,5-ylene or thien-2,4-ylene; and  $R^{4d}$  is (1-10C)alkylene, such as  $-(\text{CH}_2)-$ ,  $-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_3-$ . In this embodiment, the (6-10C)arylene or (2-9C)heteroarylene group is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy,  $-\text{S}-(1-4\text{C})\text{alkyl}$ ,  $-\text{S}(\text{O})-(1-4\text{C})\text{alkyl}$ ,  $-\text{S}(\text{O})_2-(1-4\text{C})\text{alkyl}$ ,  $-\text{C}(\text{O})\text{O}(1-4\text{C})\text{alkyl}$ , carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy; such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, fluoro, chloro, bromo, iodo, hydroxy, methoxy, ethoxy, isopropoxy, trifluoromethyl and trifluoromethoxy, and the like. Examples of particular values for  $R^4$  in this embodiment are  $-(\text{CH}_2)_2-\text{O}-(\text{phen-1,4-ylene})-(\text{CH}_2)-$ ;  $-(\text{CH}_2)_2-\text{O}-(\text{phen-1,4-ylene})-(\text{CH}_2)_2-$ ;  $-(\text{CH}_2)_2-\text{O}-(\text{phen-1,4-ylene})-(\text{CH}_2)_3-$ ;  $-(\text{CH}_2)_3-\text{O}-(\text{phen-1,4-ylene})-(\text{CH}_2)-$ ;  $-(\text{CH}_2)_3-\text{O}-(\text{phen-1,4-ylene})-(\text{CH}_2)_2-$  and  $-(\text{CH}_2)_3-\text{O}-(\text{phen-1,4-ylene})-(\text{CH}_2)_3-$ .

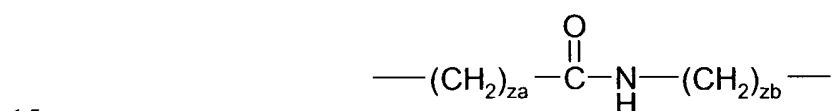
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ylene)-(CH<sub>2</sub>)<sub>2</sub>-; -(CH<sub>2</sub>)<sub>3</sub>-O-(phen-1,4-ylene)-(CH<sub>2</sub>)<sub>3</sub>-; -(CH<sub>2</sub>)<sub>2</sub>-NH-(phen-1,4-ylene)-  
 (CH<sub>2</sub>)<sub>2</sub>-; -(CH<sub>2</sub>)<sub>2</sub>-NH-(phen-1,4-ylene)-(CH<sub>2</sub>)<sub>2</sub>-; -(CH<sub>2</sub>)<sub>2</sub>-NH-(phen-1,4-ylene)-(CH<sub>2</sub>)<sub>3</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>-NH-(phen-1,4-ylene)-(CH<sub>2</sub>)<sub>2</sub>-; -(CH<sub>2</sub>)<sub>3</sub>-NH-(phen-1,4-ylene)-(CH<sub>2</sub>)<sub>2</sub>-; -(CH<sub>2</sub>)<sub>3</sub>-  
 NH-(phen-1,4-ylene)-(CH<sub>2</sub>)<sub>3</sub>-; -(CH<sub>2</sub>)<sub>2</sub>-NH-(2-fluorophen-1,4-ylene)-(CH<sub>2</sub>)<sub>2</sub>-; -(CH<sub>2</sub>)<sub>2</sub>-NH-  
 5 (2-chlorophen-1,4-ylene)-(CH<sub>2</sub>)<sub>2</sub>-; -(CH<sub>2</sub>)<sub>2</sub>-NH-(5-methoxyphen-1,4-ylene)-(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>-NH-(2-chloro-5-methoxyphen-1,4-ylene)-(CH<sub>2</sub>)<sub>2</sub>-; and -(CH<sub>2</sub>)<sub>2</sub>-NH-(2-chloro-5-  
 ethoxyphen-1,4-ylene)-(CH<sub>2</sub>)<sub>2</sub>-.

In yet another particular embodiment, R<sup>4</sup> is a divalent group of the formula:

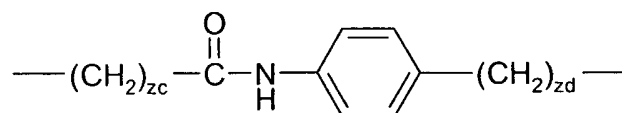


where Q is -N(Q<sup>a</sup>)C(O)- or -C(O)N(Q<sup>b</sup>)-. A particular value for R<sup>4</sup> in this  
 embodiment is the formula:



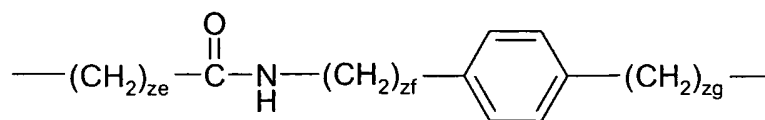
where *za* is an integer from 2 to 10; and *zb* is an integer from 2 to 10; provided that  
*za* + *zb* is an integer from 4 to 12. In this formula for R<sup>4</sup>, *d* and *g* are 1 and *e*, *f*, *h* and *i* are  
 0; and R<sup>4a</sup> is -(CH<sub>2</sub>)<sub>za</sub>-, R<sup>4c</sup> is -(CH<sub>2</sub>)<sub>zb</sub>- and Q is -C(O)NH-. Particular values for *za* are 2  
 20 or 3; and for *zb*, 4, 5 or 6.

Another particular value for R<sup>4</sup> is the formula:



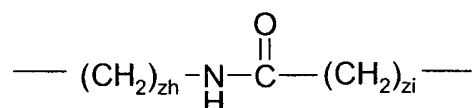
where *zc* is an integer from 2 to 7; and *zd* is an integer from 1 to 6; provided that *zc*  
 + *zd* is an integer from 3 to 8. In this formula for R<sup>4</sup>, *d*, *h* and *i* are 1 and *e*, *f* and *g* are 0;  
 and R<sup>4a</sup> is -(CH<sub>2</sub>)<sub>zc</sub>-, A<sup>2</sup> is phen-1,4-ylene, R<sup>4d</sup> is -(CH<sub>2</sub>)<sub>zd</sub>- and Q is -C(O)NH-. Particular  
 values for *zc* are 2 or 3; and for *zd*, 1 or 2. In this embodiment, the phen-1,4-ylene group  
 may be optionally substituted as defined herein for A<sup>2</sup>.

Another particular value for R<sup>4</sup> is the formula:



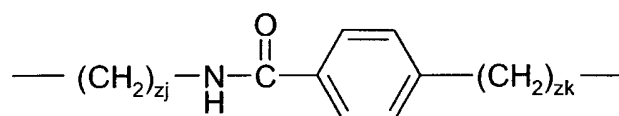
where  $ze$  is an integer from 2 to 6;  $zf$  is an integer from 1 to 5; and  $zg$  is an integer from 1 to 5; provided that  $ze + zf + zg$  is an integer from 4 to 8. In this formula for  $R^4$ ,  $d$ ,  $g$ ,  $h$  and  $i$  are 1 and  $e$  and  $f$  are 0; and  $R^{4a}$  is  $-(\text{CH}_2)_{ze}$ ,  $R^{4c}$  is  $-(\text{CH}_2)_{zf}$ ,  $A^2$  is 1,4-phenylene,  $R^{4d}$  is  $-(\text{CH}_2)_{zg}$  and  $Q$  is  $-\text{C}(\text{O})\text{NH}-$ . Particular values for  $ze$  are 2 or 3; for  $zf$ , 1 or 2; and for  $zg$ , 1 or 2. In this embodiment, the phen-1,4-ylene group may be optionally substituted as defined herein for  $A^2$ .

10 Another particular value for  $R^4$  is the formula:



where  $zh$  is an integer from 2 to 10; and  $zi$  is an integer from 2 to 10; provided that  $zh + zi$  is an integer from 4 to 12. In this formula for  $R^4$ ,  $d$  and  $g$  are 1 and  $e$ ,  $f$ ,  $h$  and  $i$  are 0; and  $R^{4a}$  is  $-(\text{CH}_2)_{zh}$ ,  $R^{4c}$  is  $-(\text{CH}_2)_{zi}$  and  $Q$  is  $-\text{NHC}(\text{O})-$ . Particular values for  $zh$  are 2 or 3; and for  $zi$ , 4, 5 or 6.

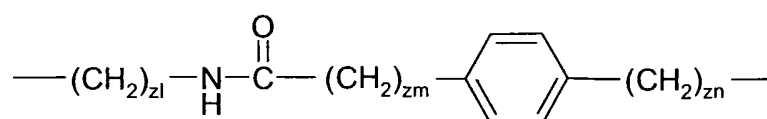
Another particular value for  $R^4$  is the formula:



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where  $zj$  is an integer from 2 to 7; and  $zk$  is an integer from 1 to 6; provided that  $zj + zk$  is an integer from 3 to 8. In this formula for  $R^4$ ,  $d$ ,  $h$  and  $i$  are 1 and  $e$ ,  $f$  and  $g$  are 0; and  $R^{4a}$  is  $-(\text{CH}_2)_{zj}$ ,  $A^2$  is 1,4-phenylene,  $R^{4d}$  is  $-(\text{CH}_2)_{zk}$  and  $Q$  is  $-\text{NHC}(\text{O})-$ . Particular values for  $zj$  are 2 or 3; and for  $zk$ , 1 or 2. In this embodiment, the phen-1,4-ylene group may be optionally substituted as defined herein for  $A^2$ .

Another particular value for  $R^4$  is the formula:



where  $z1$  is an integer from 2 to 6;  $z2$  is an integer from 1 to 5; and  $z3$  is an integer from 1 to 5; provided that  $z1 + z2 + z3$  is an integer from 4 to 8. In this formula for  $R^4$ ,  $d$ ,  $g$ ,  $h$  and  $i$  are 1 and  $e$  and  $f$  are 0; and  $R^{4a}$  is  $-(\text{CH}_2)_{z1}$ ,  $R^{4c}$  is  $-(\text{CH}_2)_{z2}$ ,  $A^2$  is 1,4-phenylene,  $R^{4d}$  is  $-(\text{CH}_2)_{z3}$  and  $Q$  is  $-\text{NHC}(\text{O})-$ . Particular values for  $z1$  are 2 or 3; for  $z2$ , 1 or 2; and for  $z3$ , 1 or 2. In this embodiment, the phen-1,4-ylene group may be optionally substituted as defined herein for  $A^2$ .

By way of further illustration,  $R^4$  can be selected from:

- 10  $-(\text{CH}_2)_{7-}$ ;  
 $-(\text{CH}_2)_{8-}$ ;  
 $-(\text{CH}_2)_{9-}$ ;  
 $-(\text{CH}_2)_{10-}$ ;  
 $-(\text{CH}_2)_{11-}$ ;
- 15  $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{CH}_2)_5-$ ;  
 $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(\text{CH}_2)_5-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})\text{NH}(\text{CH}_2)_5-$ ;
- 20  $-(\text{CH}_2)_3\text{NHC}(\text{O})\text{NH}(\text{CH}_2)_5-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NHCH}_2(\text{cyclohex-1,3-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{cyclopent-1,3-ylene})-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $1-[-(\text{CH}_2)_2\text{C}(\text{O})](\text{piperidin-4-yl})(\text{CH}_2)_2-$ ;
- 25  $-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{trans-cyclohex-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{cis-cyclopent-1,3-ylene})-$ ;  
 $-(\text{CH}_2)_2\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $1-[-(\text{CH}_2)_2\text{NHC}(\text{O})](\text{piperidin-4-yl})(\text{CH}_2)_2-$ ;  
 $-\text{CH}_2(\text{phen-1,4-ylene})\text{NH}(\text{phen-1,4-ylene})\text{CH}_2-$ ;
- 30  $-(\text{CH}_2)_2\text{C}(\text{O})\text{NHCH}_2(\text{phen-1,3-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NHCH}_2(\text{pyrid-2,6-ylene})\text{CH}_2-$ ;



- $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{cis-cyclohex-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{trans-cyclohex-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{cis-cyclopent-1,3-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(\text{phen-1,3-ylene})\text{CH}_2-$ ;  
5  $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(\text{trans-cyclohex-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{phen-1,4-ylene})\text{C}^*\text{H}(\text{CH}_3)-$  ((*S*)-isomer);  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{phen-1,4-ylene})\text{C}^*\text{H}(\text{CH}_3)-$  ((*R*)-isomer);  
 $2-[(\text{S})-(\text{-CH}_2-)](\text{pyrrolidin-1-yl})\text{C}(\text{O})(\text{CH}_2)_4-$ ;  
 $2-[(\text{S})-(\text{-CH}_2-)](\text{pyrrolidin-1-yl})\text{C}(\text{O})(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
10  $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(4\text{-chlorophen-1,3-ylene})\text{CH}_2-$ ;  
 $-\text{CH}_2(2\text{-fluorophen-1,3-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(4\text{-methylphen-1,3-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(6\text{-chlorophen-1,3-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2\text{-chlorophen-1,4-ylene})\text{CH}_2-$ ;  
15  $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2,6\text{-dichlorophen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})\text{NHCH}_2(\text{phen-1,3-ylene})\text{CH}_2-$ ;  
 $4-[-\text{CH}_2-](\text{piperidin-1-yl})\text{C}(\text{O})(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{N}(\text{CH}_2\text{CH}_3)(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
 $1-[-(\text{CH}_2)_2\text{NHC}(\text{O})](\text{piperidin-4-yl})-$ ;  
20  $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{thien-2,5-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(3\text{-nitrophen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(\text{trans-cyclohex-1,4-ylene})-$ ;  
 $1-[-\text{CH}_2(2\text{-fluorophen-1,3-ylene})\text{CH}_2](\text{piperidin-4-yl})-$ ;  
25  $5-[-(\text{CH}_2)_2\text{NHC}(\text{O})](\text{pyrid-2-yl})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_3(\text{thien-2,5-ylene})(\text{CH}_2)_3-$ ;  
 $-(\text{CH}_2)_2(\text{phen-1,4-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-\text{CH}_2(\text{phen-1,2-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
30  $1-[-\text{CH}_2(2\text{-fluorophen-1,3-ylene})\text{CH}_2](\text{piperidin-4-yl})(\text{CH}_2)_2-$ ;  
 $1-[-\text{CH}_2(2\text{-fluorophen-1,3-ylene})\text{CH}_2](\text{piperidin-4-yl})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(3\text{-chlorophen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2\text{-}(\text{CF}_3\text{O-})\text{phen-1,4-ylene})\text{CH}_2-$

- $-(\text{CH}_2)_3(\text{phen-1,3-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_2\text{S}(\text{O})_2\text{NH}(\text{CH}_2)_5-$ ;  
 $-\text{CH}_2(\text{phen-1,3-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2\text{-iodophen-1,4-ylene})\text{CH}_2-$ ;  
 5  $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2\text{-chloro-5-methoxyphen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2\text{-chloro-6-methylphen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{S}(\text{O})_2(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2\text{-bromophen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_3(\text{phen-1,4-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 10  $-(\text{CH}_2)_3(\text{phen-1,2-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $1-[-\text{CH}_2(2\text{-fluorophen-1,3-ylene})\text{CH}_2](\text{piperidin-4-yl})(\text{CH}_2)_3-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2\text{-methoxyphen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_5\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $4-[-(\text{CH}_2)_2](\text{piperidin-1-yl})(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 15  $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{phen-1,4-ylene})\text{CH}(\text{CH}_3)\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2(\text{trans-cyclohex-1,4-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2\text{-fluorophen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2(\text{phen-1,3-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2,5\text{-difluorophen-1,4-ylene})\text{CH}_2-$ ;  
 20  $-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $1-[-\text{CH}_2(\text{pyrid-2,6-ylene})\text{CH}_2](\text{piperidin-4-yl})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_3\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_2\text{NH}(\text{naphth-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_3\text{O}(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
 25  $1-[-(\text{CH}_2)_3](\text{piperidin-4-yl})\text{CH}_2-$ ;  
 $4-[-(\text{CH}_2)_2](\text{piperidin-1-yl})\text{C}(\text{O})(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_3(\text{phen-1,4-ylene})\text{NHC}(\text{O})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_3\text{O}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $2-[-(\text{CH}_2)_2](\text{benzimidazol-5-yl})\text{CH}_2-$ ;  
 30  $-(\text{CH}_2)_2(\text{trans-cyclohex-1,4-ylene})\text{NHC}(\text{O})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_2(\text{trans-cyclohex-1,4-ylene})\text{NHC}(\text{O})(\text{CH}_2)_4-$ ;  
 $-(\text{CH}_2)_2(\text{trans-cyclohex-1,4-ylene})\text{NHC}(\text{O})(\text{CH}_2)_5-$ ;  
 $4-[-(\text{CH}_2)_2](\text{piperidin-1-yl})\text{C}(\text{O})(\text{CH}_2)_2-$ ;

- (CH<sub>2</sub>)<sub>2</sub>NHC(O)NH(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>)<sub>2</sub>(*cis*-cyclohex-1,4-ylene)-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2,3,5,6-tetrafluorophen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2,6-diiodophen-1,4-ylene)CH<sub>2</sub>-;  
 5 4[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(CH<sub>2</sub>)<sub>3</sub>-;  
 4[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(CH<sub>2</sub>)<sub>4</sub>-;  
 4[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(CH<sub>2</sub>)<sub>5</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NHCH<sub>2</sub>(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>NHC(O)NHCH<sub>2</sub>(phen-1,4-ylene)CH<sub>2</sub>-;  
 10 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2-methylphen-1,4-ylene)CH<sub>2</sub>-;  
 1[-(CH<sub>2</sub>)<sub>3</sub>O(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>](piperidin-4-yl)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NHCH<sub>2</sub>(phen-1,3-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)CH<sub>2</sub>O(phen-1,4-ylene)CH<sub>2</sub>-;  
 15 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)CH<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)(fur-2,5-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)(thien-2,5-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,4-ylene)O(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)(phen-1,4-ylene)CH<sub>2</sub>-;  
 20 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,2-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)(fur-2,5-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)(thien-2,5-ylene)CH<sub>2</sub>-;  
 25 4[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)CH<sub>2</sub>O(phen-1,2-ylene)CH<sub>2</sub>-;  
 4[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)CH<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 4[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)CH<sub>2</sub>O(phen-1,4-ylene)CH<sub>2</sub>-;  
 4[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(fur-2,5-ylene)CH<sub>2</sub>-;  
 4[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(thien-2,5-ylene)CH<sub>2</sub>-;  
 30 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)(phen-1,3-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,2-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;

- (CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)(fur-2,5-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)(thien-2,5-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)(phen-1,3-ylene)CH<sub>2</sub>-;  
 5 -(CH<sub>2</sub>)<sub>3</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 -CH<sub>2</sub>CH(OH)CH<sub>2</sub>NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>4</sub>NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(phen-1,4-ylene)CH<sub>2</sub>NHC(O)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>NHC(O)CH<sub>2</sub>-;  
 10 -(CH<sub>2</sub>)<sub>2</sub>C(O)NHCH<sub>2</sub>(*trans*-cyclohex-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>NHC(O)(CH<sub>2</sub>)<sub>5</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,3-ylene)O(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,2-ylene)O(CH<sub>2</sub>)<sub>2</sub>-;  
 -CH<sub>2</sub>(phen-1,2-ylene)O(phen-1,2-ylene)CH<sub>2</sub>-;  
 15 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(CH<sub>2</sub>)<sub>6</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,4-ylene)(CH<sub>2</sub>)<sub>3</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>4</sub>(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(furan-2,5-ylene)(CH<sub>2</sub>)<sub>3</sub>-;  
 20 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,3-ylene)(CH<sub>2</sub>)<sub>3</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(tetrahydrofuran-2,5-ylene)(CH<sub>2</sub>)<sub>3</sub>-; and  
 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,4-ylene)C(O)(CH<sub>2</sub>)<sub>2</sub>-

25

#### Representative Subgeneric Groupings

The following subgeneric formulae and groupings are intended to provide representative examples of various aspects and embodiments of this invention and as such, they are not intended to exclude other embodiments or to limit the scope of this invention unless otherwise indicated.

30

A particular group of compounds of formula I are those where: a is 0; b is 2, 3 or 4; W is O; R<sup>1</sup> is phenyl; R<sup>5</sup> is hydrogen; and R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8a</sup> and R<sup>8b</sup> are as defined herein; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

Yet another particular group of compounds of formula I are those wherein: a is 0; b is 2, 3 or 4; W is O; R<sup>1</sup> is phenyl; R<sup>4</sup> is -(CH<sub>2</sub>)<sub>j</sub>- where j is 8, 9 or 10; R<sup>5</sup> is hydrogen; and R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8a</sup> and R<sup>8b</sup> are as defined herein; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

5 Another particular group of compounds of formula I are those of formula II as defined herein; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

Another particular group of compounds of formula I are those of formula III as defined herein; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

10 Another particular group of compounds of formula I are those of formula IV as defined herein; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

Another particular group of compounds of formula I are those of formula V as defined herein; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

Another particular group of compounds of formula I are those of formula VI as defined herein; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

15 Another particular group of compounds of formula I are those of formula VII as defined herein; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

Another particular group of compounds of formula I are those of formula VIII as defined herein; or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

Another particular group of compounds of formula I are those selected from:

20 biphenyl-2-ylcarbamic acid 3-({9-[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}methylamino)-1,1-dimethylpropyl ester;

(2-thien-3-ylphenyl)carbamic acid 3-({9-[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}methylamino)-1,1-dimethylpropyl ester;

25 biphenyl-2-ylcarbamic acid 3-{{2-(4-{{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}benzoylamino)ethyl]methylamino}-1,1-dimethylpropyl ester;

biphenyl-2-ylcarbamic acid 3-{{4-(4-{2-[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenyl)butyl}methylamino}-1,1-dimethyl-propyl ester; and

30 biphenyl-2-ylcarbamic acid 3-{{2-(2-chloro-4-{{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbonyl)ethyl]-methylamino}-1,1-dimethylpropyl ester.

### Definitions

When describing the compounds, compositions, methods and processes of this invention, the following terms have the following meanings unless otherwise indicated.

The term "alkyl" means a monovalent saturated hydrocarbon group which may be linear or branched. Unless otherwise defined, such alkyl groups typically contain from 1 to 10 carbon atoms. Representative alkyl groups include, by way of example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

The term "alkylene" means a divalent saturated hydrocarbon group which may be linear or branched. Unless otherwise defined, such alkylene groups typically contain from 1 to 10 carbon atoms. Representative alkylene groups include, by way of example, methylene, ethane-1,2-diyl ("ethylene"), propane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl and the like.

The term "alkoxy" means a monovalent group of the formula (alkyl)-O-, where alkyl is as defined herein. Representative alkoxy groups include, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy and the like.

The term "alkenyl" means a monovalent unsaturated hydrocarbon group which may be linear or branched and which has at least one, and typically 1, 2 or 3, carbon-carbon double bonds. Unless otherwise defined, such alkenyl groups typically contain from 2 to 10 carbon atoms. Representative alkenyl groups include, by way of example, ethenyl, *n*-propenyl, isopropenyl, *n*-but-2-enyl, *n*-hex-3-enyl and the like. The term "alkenylene" means a divalent alkenyl group.

The term "alkynyl" means a monovalent unsaturated hydrocarbon group which may be linear or branched and which has at least one, and typically 1, 2 or 3, carbon-carbon triple bonds. Unless otherwise defined, such alkynyl groups typically contain from 2 to 10 carbon atoms. Representative alkynyl groups include, by way of example, ethynyl, *n*-propynyl, *n*-but-2-ynyl, *n*-hex-3-ynyl and the like. The term "alkynylene" means a divalent alkynyl group.

The term "aryl" means a monovalent aromatic hydrocarbon having a single ring (i.e., phenyl) or fused rings (i.e., naphthalene). Unless otherwise defined, such aryl groups typically contain from 6 to 10 carbon ring atoms. Representative aryl groups include, by

way of example, phenyl and naphthalene-1-yl, naphthalene-2-yl, and the like. The term "arylene" means a divalent aryl group.

The term "azacycloalkyl" means a monovalent heterocyclic ring containing one nitrogen atom, i.e., a cycloalkyl group in which one carbon atom has been replaced with a nitrogen atom. Unless otherwise defined, such azacycloalkyl groups typically contain from 2 to 9 carbon atoms. Representative examples of an azacycloalkyl group are pyrrolidinyl and piperidinyl groups. The term "azacycloalkylene" means a divalent azacycloalkyl group. Representative examples of an azacycloalkylene group are pyrrolidinylene and piperidinylene groups.

10 The term "cycloalkyl" means a monovalent saturated carbocyclic hydrocarbon group. Unless otherwise defined, such cycloalkyl groups typically contain from 3 to 10 carbon atoms. Representative cycloalkyl groups include, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The term "cycloalkylene" means a divalent cycloalkyl group.

15 The term "halo" means fluoro, chloro, bromo and iodo.

The term "heteroaryl" means a monovalent aromatic group having a single ring or two fused rings and containing in the ring at least one heteroatom (typically 1 to 3 heteroatoms) selected from nitrogen, oxygen or sulfur. Unless otherwise defined, such heteroaryl groups typically contain from 5 to 10 total ring atoms. Representative heteroaryl groups include, by way of example, monovalent species of pyrrole, imidazole, thiazole, oxazole, furan, thiophene, triazole, pyrazole, isoxazole, isothiazole, pyridine, pyrazine, pyridazine, pyrimidine, triazine, indole, benzofuran, benzothiophene, benzimidazole, benzthiazole, quinoline, isoquinoline, quinazoline, quinoxaline and the like, where the point of attachment is at any available carbon or nitrogen ring atom. The term "heteroarylene" means a divalent heteroaryl group.

25 The term "heterocyclyl" or "heterocyclic" means a monovalent saturated or unsaturated (non-aromatic) group having a single ring or multiple condensed rings and containing in the ring at least one heteroatom (typically 1 to 3 heteroatoms) selected from nitrogen, oxygen or sulfur. Unless otherwise defined, such heterocyclic groups typically contain from 2 to 9 total ring carbon atoms. Representative heterocyclic groups include, by way of example, monovalent species of pyrrolidine, imidazolidine, pyrazolidine, piperidine, 1,4-dioxane, morpholine, thiomorpholine, piperazine, 3-pyrroline and the like,

where the point of attachment is at any available carbon or nitrogen ring atom. The term "heterocyclene" means a divalent heterocyclyl or heterocyclic group.

When a specific number of carbon atoms is intended for a particular term used herein, the number of carbon atoms is shown in parentheses preceding the term. For  
5 example, the term "(1-4C)alkyl" means an alkyl group having from 1 to 4 carbon atoms.

The term "pharmaceutically acceptable salt" means a salt which is acceptable for administration to a patient, such as a mammal (e.g., salts having acceptable mammalian safety for a given dosage regime). Such salts can be derived from pharmaceutically acceptable inorganic or organic bases and from pharmaceutically acceptable inorganic or  
10 organic acids. Salts derived from pharmaceutically acceptable inorganic bases include ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine,  
15 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, piperadine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.  
20 Salts derived from pharmaceutically acceptable acids include acetic, ascorbic, benzenesulfonic, benzoic, camphosulfonic, citric, ethanesulfonic, edisyllic, fumaric, gentisic, gluconic, glucuronic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, lactobionic, maleic, malic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, naphthalene-1,5-disulfonic, naphthalene-2,6-disulfonic, nicotinic, nitric, orotic, pamoic,  
25 pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, xinafoic and the like.

The term "salt thereof" means a compound formed when the hydrogen of an acid is replaced by a cation, such as a metal cation or an organic cation and the like. Preferably, the salt is a pharmaceutically acceptable salt, although this is not required for salts of  
30 intermediate compounds that are not intended for administration to a patient.

The term "solvate" means a complex or aggregate formed by one or more molecules of a solute, i.e. a compound of formula I or a pharmaceutically acceptable salt thereof, and one or more molecules of a solvent. Such solvates are typically crystalline



solids having a substantially fixed molar ratio of solute and solvent. Representative solvents include, by way of example, water, methanol, ethanol, isopropanol, acetic acid and the like. When the solvent is water, the solvate formed is a hydrate.

It will be appreciated that the term “or a pharmaceutically acceptable salt or solvate or stereoisomer thereof” is intended to include all permutations of salts, solvates and stereoisomers, such as a solvate of a pharmaceutically acceptable salt of a stereoisomer of a compound of formula I.

The term “therapeutically effective amount” means an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term “treating” or “treatment” as used herein means the treating or treatment of a disease or medical condition (such as COPD) in a patient, such as a mammal (particularly a human) that includes:

- (a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;
- (b) ameliorating the disease or medical condition, i.e., eliminating or causing regression of the disease or medical condition in a patient;
- (c) suppressing the disease or medical condition, i.e., slowing or arresting the development of the disease or medical condition in a patient; or
- (d) alleviating the symptoms of the disease or medical condition in a patient.

The term “leaving group” means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

The term “protected derivatives thereof” means a derivative of the specified compound in which one or more functional groups of the compound are protected from undesired reactions with a protecting or blocking group. Functional groups which may be protected include, by way of example, carboxylic acid groups, amino groups, hydroxyl groups, thiol groups, carbonyl groups and the like. Representative protecting groups for carboxylic acids include esters (such as a *p*-methoxybenzyl ester), amides and hydrazides; for amino groups, carbamates (such as *tert*-butoxycarbonyl) and amides; for hydroxyl groups, ethers and esters; for thiol groups, thioethers and thioesters; for carbonyl groups, acetals and ketals; and the like. Such protecting groups are well-known to those skilled in

the art and are described, for example, in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

The term "amino-protecting group" means a protecting group suitable for preventing undesired reactions at an amino group. Representative amino-protecting groups include, but are not limited to, *tert*-butoxycarbonyl (BOC), trityl (Tr), benzyloxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), formyl, trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBS), and the like.

The term "carboxy-protecting group" means a protecting group suitable for preventing undesired reactions at a carboxy group. Representative carboxy-protecting groups include, but are not limited to, esters, such as methyl, ethyl, *tert*-butyl, benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBS), diphenylmethyl (benzhydryl, DPM) and the like.

The term "hydroxyl-protecting group" means a protecting group suitable for preventing undesirable reactions at a hydroxyl group. Representative hydroxyl-protecting groups include, but are not limited to, silyl groups including tri(1-6C)alkylsilyl groups, such as trimethylsilyl (TMS), triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS) and the like; esters (acyl groups) including (1-6C)alkanoyl groups, such as formyl, acetyl and the like; arylmethyl groups, such as benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), diphenylmethyl (benzhydryl, DPM) and the like. Additionally, two hydroxyl groups can also be protected as an alkylidene group, such as prop-2-ylidene, formed, for example, by reaction with a ketone, such as acetone.

#### General Synthetic Procedures

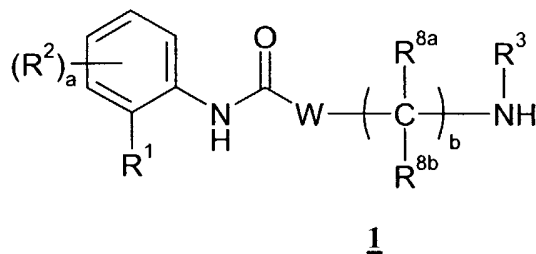
The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures or by using other information readily available to those of ordinary skill in the art. Although a particular embodiment of the present invention may be shown or described herein, those skilled in the art will recognize that all embodiments or aspects of the present invention can be prepared using the methods described herein or by using other methods, reagents and starting materials known to those skilled in the art. It will also be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used

unless otherwise stated. While the optimum reaction conditions may vary depending on the particular reactants or solvent used, such conditions can be readily determined by one skilled in the art by routine optimization procedures.

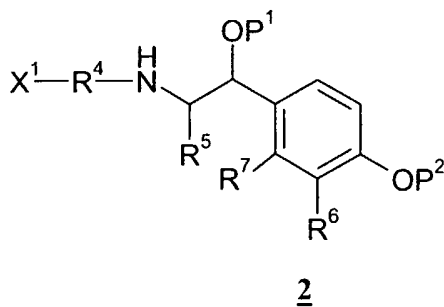
Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary or desired to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection of such functional groups are well-known in the art. Protecting groups other than those illustrated in the procedures described herein may be used, if desired. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

By way of illustration, the compounds of this invention can be prepared by a process comprising:

15 (a) reacting a compound of formula 1:



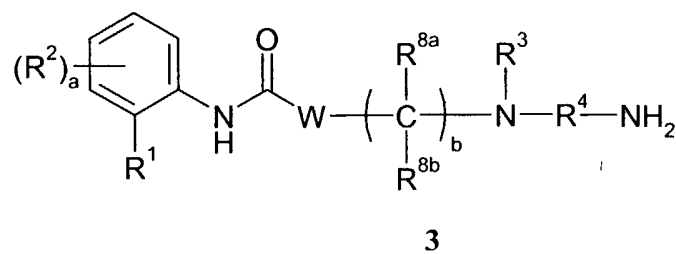
20 or a salt thereof; with a compound of formula 2:



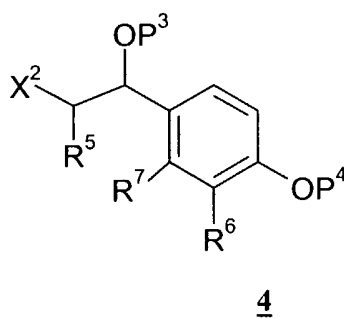
25

wherein  $X^1$  represents a leaving group, and  $P^1$  and  $P^2$  each independently represent a hydrogen atom or a hydroxyl-protecting group;

(b) reacting a compound of formula 3:

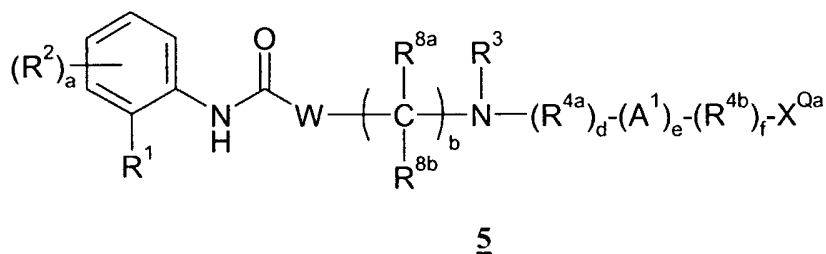


or salt thereof; with a compound of formula 4:

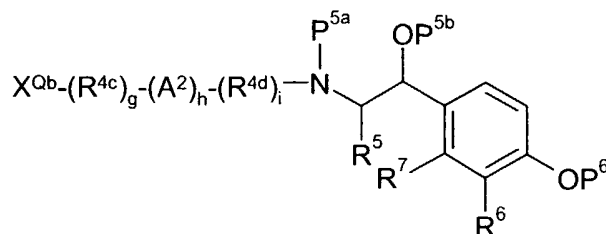


wherein  $X^2$  represents a leaving group, and  $P^3$  and  $P^4$  each independently represent a hydrogen atom or a hydroxyl-protecting group;

15 (c) coupling a compound of formula 5:



with a compound of formula 6:

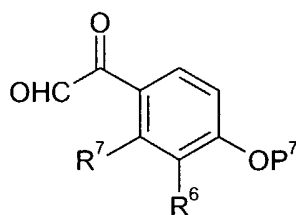


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wherein  $X^{Qa}$  and  $X^{Qb}$  each independently represent functional groups that couple to form a group Q,  $P^{5a}$  represents a hydrogen atom or an amino-protecting group; and  $P^{5b}$  and  $P^6$  each independently represent a hydrogen atom or a hydroxyl-protecting group;

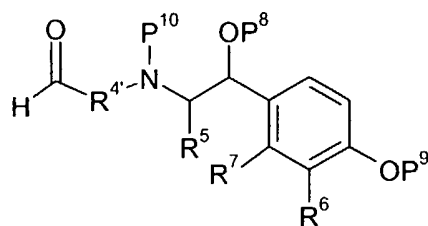
10 (d) for a compound of formula I wherein  $R^5$  represents a hydrogen atom, reacting a compound of formula 3 with a compound of formula 7:

7

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or a hydrate thereof (e.g., a glyoxal), in the presence of a reducing agent, wherein  $P^7$  represents a hydrogen atom or a hydroxyl-protecting group;

(e) reacting a compound of formula 1 with a compound of formula 8:

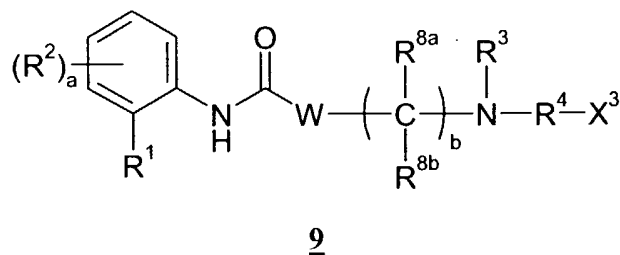


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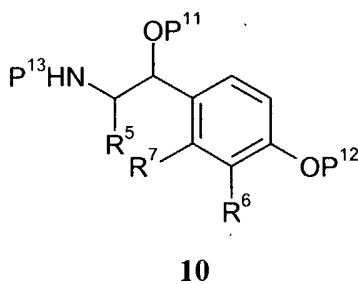
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or a hydrate thereof, in the presence of a reducing agent, wherein P<sup>8</sup> and P<sup>9</sup> each independently represent a hydrogen atom or a hydroxyl-protecting group, P<sup>10</sup> represents a hydrogen atom or an amino-protecting group, and R<sup>4'</sup> represents a residue that, together with the carbon to which it is attached, affords a group R<sup>4</sup> upon completion of the reaction;

5 (f) reacting a compound of formula 9:

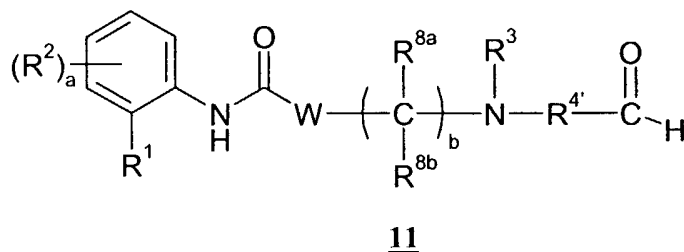


10 wherein X<sup>3</sup> represents a leaving group, with a compound of formula 10:



15 wherein P<sup>11</sup> and P<sup>12</sup> each independently represent a hydrogen atom or a hydroxyl-protecting group, and P<sup>13</sup> represents a hydrogen atom or an amino-protecting group; or

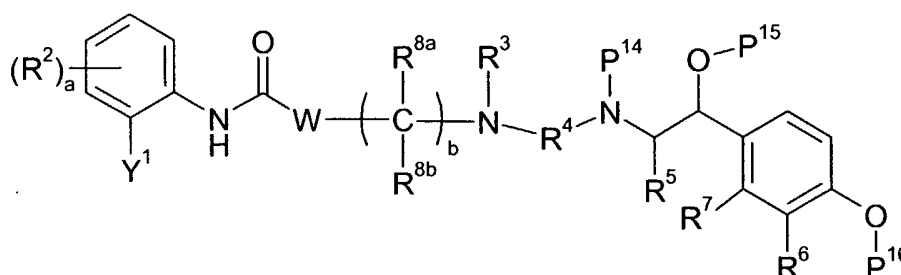
(g) reacting a compound of formula 11:



20

or a hydrate thereof; wherein R<sup>4'</sup> represents a residue that, together with the carbon to which it is attached, affords a group R<sup>4</sup> upon completion of the reaction; with a compound of formula 10 in the presence of a reducing agent;

(h) reacting a compound of formula 12:



12

5

wherein  $Y^1$  represents chloro, bromo, iodo or  $CF_3SO_2O-$ ,  $P^{14}$  represents a hydrogen atom or an amino-protecting group; and  $P^{15}$  and  $P^{16}$  each independently represent a hydrogen atom or a hydroxyl-protecting group; with a compound of the formula:  $R^1-B(OH)_2$  in the presence of a coupling catalyst; and then

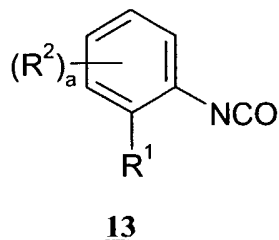
10 removing any protecting group  $P^1, P^2, P^3, P^4, P^{5a}, P^{5b}, P^6, P^7, P^8, P^9, P^{10}, P^{11}, P^{12}, P^{13}, P^{14}, P^{15}$  and  $P^{16}$  to provide a compound of formula I; and optionally, forming a pharmaceutically acceptable salt thereof.

Generally, if a salt of one of the starting materials is used in the processes described above, such as an acid addition salt, the salt is typically neutralized before or during the  
15 reaction process. This neutralization reaction is typically accomplished by contacting the salt with one molar equivalent of a base for each molar equivalent of acid addition salt.

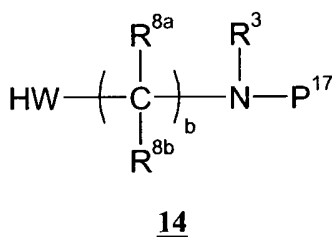
In process (a), i.e., the reaction between the compounds of formula 1 and 2, the leaving group represented by  $X^1$  can be, for example, halo, such as chloro, bromo or iodo, or a sulfonic ester group, such as mesylate or tosylate. The groups  $P^1$  and  $P^2$  can be, for  
20 example, trimethylsilyl and benzyl, respectively. This reaction is typically conducted in an inert diluent, such as acetonitrile, in the presence of a base. For example, this reaction can be conducted in the presence of a tertiary amine, such as diisopropylethylamine.

Generally, this reaction is conducted at a temperature in the range of from  $0\text{ }^\circ\text{C}$  to  $100\text{ }^\circ\text{C}$  until the reaction is substantially complete. The reaction product is then isolated using  
25 conventional procedures, such as extraction, recrystallization, chromatography and the like.

Compounds of formula 1 are generally known in the art or can be prepared from commercially available starting materials and reagents using well-known procedures. For example, compounds of formula 1 can be prepared by reacting an isocyanate compound of formula 13:



with a compound of formula 14:



wherein P<sup>17</sup> represents an amino-protecting group, such as a benzyl group; followed by removal of the protecting group P<sup>17</sup> to afford a compound of formula 1. For example, when P<sup>17</sup> is a benzyl group, the benzyl group is removed by hydrogenolysis, for example, using hydrogen and a group VIII metal catalyst, such as palladium on carbon. When W represents NW<sup>a</sup>, the hydrogenolysis reaction is conveniently performed using Pearlman's catalyst (i.e., Pd(OH)<sub>2</sub>).

Compounds of formula 2 can be prepared by various procedures described herein or by procedures that are well-known to those skilled in the art. For example, the hydroxyl group of a compound of formula 22 below, can be readily converted into a leaving group using well-known reagents and procedures. By way of illustration, a hydroxyl group can be converted into a halo group using an inorganic acid halide, such as thionyl chloride, phosphorous trichloride, phosphorous tribromide, phosphorous oxychloride and the like, or a halogen acid, such a hydrogen bromide.

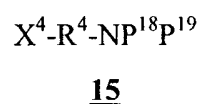
In process (b), i.e., the reaction of a compound of formula 3 with a compound of formula 4, the leaving represented by X<sup>2</sup> can be, for example, halo, such as chloro, bromo



or iodo, or a sulfonic ester group, such as mesylate or tosylate. The groups P<sup>3</sup> and P<sup>4</sup> can be, for example, *tert*-butyldimethylsilyl and benzyl, respectively. This reaction is typically conducted in the presence of a base, such as sodium bicarbonate, and an alkali metal iodide, such as sodium iodide. Generally, this reaction is conducted in an inert diluent, such as tetrahydrofuran, at a temperature ranging from 25 °C to 100 °C until the reaction is substantially complete. The reaction product is then isolated using conventional procedures, such as extraction, recrystallization, chromatography and the like.

Compounds of formula 3 can be prepared by reacting a compound of formula 1 with a compound of formula 15:

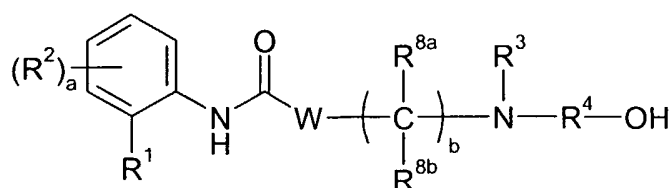
10



wherein X<sup>4</sup> represents a leaving group such as halo, such as chloro, bromo or iodo, or sulfonic ester group, such as mesylate or tosylate. This reaction is typically conducted by contacting a compound of formula 1 with a compound of formula 15 in an inert diluent, such as acetonitrile, DMF or mixtures thereof, at a temperature ranging from about 0 °C to about 100 °C until the reaction is substantially complete. Subsequent removal of the protecting groups, P<sup>18</sup> and P<sup>19</sup>, affords a compound of formula 3. For example, when P<sup>18</sup> is a *tert*-butoxycarbonyl group and P<sup>19</sup> is hydrogen, the *tert*-butoxycarbonyl group can be removed by treating the protected compound with trifluoroacetic acid.

Alternatively, compounds of formula 3 can be obtained by reductive amination of a compound of formula 11. The reductive amination can be performed by reacting the compound of formula 11 with, for example, benzylamine and hydrogen in the presence of palladium on carbon.

Compounds of formula 11 may be prepared by oxidizing the corresponding alcohol of formula 16:



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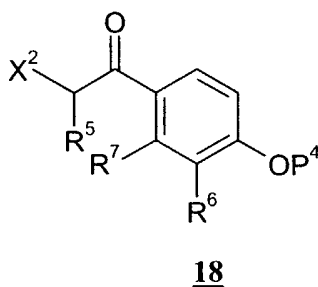
using a suitable oxidizing agent, such as sulfur trioxide pyridine complex and dimethyl sulfoxide. This oxidation reaction is typically conducted in an inert diluent, such as dichloromethane, the presence of a tertiary amine, such as diisopropylethylamine, at a  
 5 temperature ranging from about  $-20\text{ }^{\circ}\text{C}$  to about  $25\text{ }^{\circ}\text{C}$ .

Compounds of formula **16** can be prepared by reacting a compound of formula **1** with a compound of formula **17**:



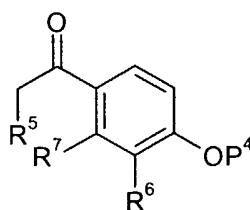
wherein  $\text{X}^5$  represents a leaving group such as halo, such as chloro, bromo or iodo, or a sulfonic ester group, such as mesylate or tosylate.

Compounds of formula **4** can be prepared by reacting a compound of formula **18**:  
 15



with a reducing agent, such as borane. If desired, such a reduction can be performed in the  
 20 presence of a chiral catalyst to provide compounds of formula **4** in chiral form. For example, compounds of formula **18** can be reduced in the presence of a chiral catalyst formed from (*R*)-(+)- $\alpha,\alpha$ -diphenyl-2-pyrrolidinemethanol and trimethylboroxine; or alternatively, from (*S*)-(-)- $\alpha,\alpha$ -diphenyl-2-pyrrolidinemethanol and trimethylboroxine. The resulting hydroxyl group can then be protected with a hydroxyl-protecting group,  $\text{P}^3$ ,  
 25 by reaction with, for example, *tert*-butyldimethylsilyl trifluoromethanesulfonate.

Compounds of formula **18** in which  $\text{X}^2$  represents a bromine atom can be prepared by reacting a compound of formula **19**:

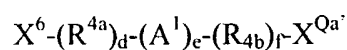
19

with bromine in the presence of a Lewis acid, such as boron trifluoride diethyl etherate.

- 5 Compounds of formula 19 are well-known in the art or can be prepared by well-known procedures using commercially available starting materials and reagents.

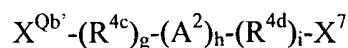
Referring to process (c), i.e., the reaction of a compound of formula 5 with a compound of formula 6, it will be appreciated that the groups  $X^{Qa}$  and  $X^{Qb}$  should be selected so as to afford the desired group Q upon completion of the reaction. For example, 10 when the desired group Q is an amide group, i.e.,  $-N(Q^a)C(O)-$  or  $-C(O)N(Q^b)$ , one of  $X^{Qa}$  and  $X^{Qb}$  can be an amine group (i.e.,  $-NHQ^a$  or  $-NHQ^b$ ) and the other can be a carboxyl group (i.e.,  $-COOH$ ) or a reactive derivative thereof (such as acyl halide, such as an acyl chloride or acyl bromide). The groups  $P^{5a}$ ,  $P^{5b}$  and  $P^6$  can be, for example, benzyl, trimethylsilyl and benzyl, respectively. When Q is an amide group, the reaction can be 15 performed under conventional amide coupling conditions. Similarly, when the desired group Q is a sulfonamide, i.e.,  $-N(Q^c)S(O)_2-$  or  $-S(O)_2N(Q^d)-$ , one of  $X^{Qa}$  and  $X^{Qb}$  can be an amine group,  $-NHQ^c$  or  $-NHQ^d$  and the other can be a sulfonyl halide group (such as sulfonyl chloride or sulfonyl bromide).

Compounds of formula 5 can be prepared by reacting a compound of formula 1 20 with a compound of formula 20:

20

25 wherein  $X^6$  represents a leaving group including halo, such as chloro, bromo or iodo, and a sulfonic ester group, such as mesylate or tosylate; and  $X^{Qa'}$  represents  $X^{Qa}$ , such as a carboxyl group or an amino group  $NHQ^a$ , or a protected derivative thereof, such as a (1-6C)alkoxycarbonylamino group or a *tert*-butoxycarbonylamino group. This reaction is typically conducted by a method analogous to that used to prepare compounds of formula 30 3, followed by removing any protecting group in  $X^{Qa'}$ .

Compounds of formula 6 can be prepared by reacting a compound of formula 10 with a compound of formula 21:



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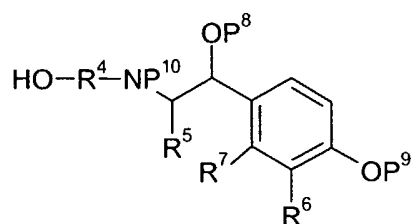
wherein  $X^7$  represents a leaving group including halo, such as chloro, bromo or iodo, and a sulfonic ester group, such as mesylate or tosylate; and  $X^{Qb'}$  represents  $X^{Qb}$ , such as a carboxyl group or an amino group  $NH^{Qb}$ , or a protected derivative thereof, such as a (1-  
10 6C)alkoxycarbonyl group or a *tert*-butoxycarbonylamino group. This reaction is typically conducted by a method analogous to that used to prepare compounds of formula 3, followed by removing any protecting group in  $X^{Qb'}$ .

Referring to process (d), i.e., the reaction of a compound of formula 3 with a compound of formula 7, any suitable reducing agent may be used in this reaction. For  
15 example, the reducing agent can be hydrogen in the presence of a Group VIII metal catalyst, such as palladium on carbon; or a metal hydride reagent, such as sodium triacetoxyborohydride. The group  $P^7$  can be, for example, benzyl. This reaction is typically conducted in an inert diluent and a protic solvent, such as a mixture of dichloroethane and methanol, at a temperature in the range of from 0 °C to 100 °C until the  
20 reaction is substantially complete.

Compounds of formula 7 in the form of a hydrate can be prepared by conventional procedures, for example, by dibrominating a compound of formula 19, and then hydrolyzing the resulting dibromide to form a glyoxal or a hydrate thereof. For example, a compound of formula 19 can be reacted with hydrogen bromide and then hydrolyzed with  
25 water to form the corresponding glyoxal hydrate.

Referring to process (e), i.e., the reaction of a compound of formula 1 with a compound of formula 8, any suitable reducing agent may be used in this reaction. For example, the reducing agent may be hydrogen in the presence of a Group VIII metal catalyst, such as palladium on carbon; or a metal hydride reagent, such as sodium  
30 triacetoxyborohydride. The groups  $P^8$ ,  $P^9$  and  $P^{10}$  can be, for example, trimethylsilyl, benzyl and benzyl, respectively. Typically, this reduction reaction is conducted in an inert diluent and a protic solvent, such as dichloroethane and methanol, at a temperature in the range of from 0 °C to 100 °C until the reaction is substantially complete.

Compounds of formula 8 may be prepared by oxidizing a compound of formula 22:

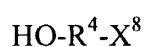


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using any suitable oxidizing agent, such as sulfur trioxide pyridine complex and dimethyl sulfoxide. This reaction is typically conducted in the presence of a tertiary amine, such as diisopropylethylamine, at a temperature in the range of from about  $-20\text{ }^{\circ}\text{C}$  to about  $25\text{ }^{\circ}\text{C}$  until the oxidation is substantially complete.

10 Compounds of formula 22 can be prepared by reacting a compound of formula 10 with a compound of formula 23:



23

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wherein  $X^8$  represents a leaving group including halo, such as chloro, bromo or iodo, and a sulfonic ester group, such as mesylate or tosylate.

Referring to process (f), i.e., the reaction of a compound of formula 9 with a compound of formula 10, the leaving group represented by  $X^3$  can be, for example, halo, such as chloro, bromo or iodo, or a sulfonic ester group, such as mesylate or tosylate. The groups  $P^{11}$ ,  $P^{12}$  and  $P^{13}$  can be, for example, trimethylsilyl, benzyl and benzyl, respectively. This reaction is typically conducted in an inert diluent, such as acetonitrile, in the presence of a suitable base. For example, this reaction can be conducted in the presence of a tertiary amine, such as diisopropylethylamine. Generally, this reaction is conducted at a temperature in the range of from  $0\text{ }^{\circ}\text{C}$  to  $100\text{ }^{\circ}\text{C}$  until the reaction is substantially complete.

25

Compounds of formula 9 can be prepared by steps analogous to those of methods (a) to (e) herein, starting from a compound of formula 1. Additionally, compounds of formula 10 can be prepared from compounds of formula 4 by reaction with an amine of formula  $P^{13}\text{NH}_2$ .

Referring to process (g), i.e., the reaction of a compound of formula **11** with a compound of formula **10**, any suitable reducing agent may be used in this reaction. For example, the reducing agent may be hydrogen in the presence of a Group VIII metal catalyst, such as palladium on carbon; or a metal hydride reagent, such as sodium triacetoxyborohydride. The groups P<sup>11</sup>, P<sup>12</sup> and P<sup>13</sup> can be, for example, *tert*-butyldimethylsilyl, benzyl and benzyl, respectively. Typically, this reduction reaction is conducted in an inert diluent and a protic solvent, such as dichloroethane and methanol, at a temperature in the range of from 0 °C to 100 °C until the reaction is substantially complete.

10 Compounds of formula **11** are readily prepared by oxidation of the corresponding alcohol or by hydrolysis of the corresponding acetal. Any suitable oxidizing agent may be employed in this reaction to provide the aldehyde, such as sulfur trioxide pyridine complex and dimethyl sulfoxide. The acetal may be hydrolyzed under conventional conditions using aqueous acid to provide the aldehyde.

15 Referring to process (h), i.e., the reaction of a compound of formula **12** with a boronic acid compound of formula R<sup>1</sup>-B(OH)<sub>2</sub>, any suitable coupling catalyst can be used to couple **12** with the boronic acid derivative using Suzuki coupling reaction conditions. For example, representative catalysts include palladium and nickel catalysts, such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), bis[1,2-  
20 bis(diphenylphosphino)propane]palladium(0), palladium(II) acetate, [1,1'-bis(diphenylphosphino)ferrocene]dichloronickel(II) and the like. Optionally, a base is employed in this reaction, such as sodium carbonate, sodium bicarbonate, potassium phosphate, triethylamine and the like. Generally, compounds of formula **12** in which Y<sup>1</sup> represents bromo, iodo or CF<sub>3</sub>SO<sub>2</sub>O<sup>-</sup> (i.e., triflate) are more reactive in the coupling  
25 reaction and therefore, such compounds are typically preferred. Particularly useful compounds of formula **12** are those in which Y<sup>1</sup> is bromo. In the compounds of formula **12**, P<sup>14</sup>, P<sup>15</sup> and P<sup>16</sup> can be any suitable amino- and hydroxyl-protecting groups, such as benzyl, *tert*-butyldimethylsilyl and benzyl, respectively.

The boronic acid compounds employed in process (h) are either commercially  
30 available or can be prepared from commercially available starting materials and reagents using procedures well known to those skilled in the art. For example, boronic acid derivatives can be prepared by reacting the corresponding lithium derivative with a trialkyl

borate, such as triisopropyl borate, and then hydrolyzing the resulting product to provide the boronic acid derivative.

Those skilled in the art will appreciate that the Suzuki coupling reaction can be conducted at any suitable step of the synthetic process. For example, the Suzuki coupling reaction can be conducted as the final step of the synthetic process after the remaining portions of the compound have been prepared. Alternatively, the Suzuki coupling reaction can be conducted earlier in the synthetic process to prepare intermediates having the desired biaryl ring system. Additionally, the boronic acid moiety may be present on the compound of formula **12**, i.e., where  $Y^1$  in **12** is  $-B(OH)_2$ ; and this compound may be coupled to a compound of the formula:  $R^1-Y^2$ , where  $Y^2$  represents chloro, bromo, iodo or  $CF_3SO_2O-$ .

Compounds of formula I in which  $R^6$  and  $R^7$  together form  $-NR^{7g}C(O)-CR^{7h}R^{7i}-CR^{7j}R^{7k}-$  or  $-CR^{7l}R^{7m}-CR^{7n}R^{7o}-C(O)-NR^{7p}-$  may be prepared by reducing a corresponding compound of formula I in which  $R^6$  and  $R^7$  together form  $-NR^{7a}C(O)-CR^{7b}=CR^{7c}-$  or  $-CR^{7d}=CR^{7e}-C(O)-NR^{7f}-$ . For example, such compounds can be reduced by catalytic hydrogenation in the presence of a suitable hydrogenation catalyst.

Further details regarding specific reaction conditions and other procedures for preparing representative compounds of this invention or intermediates thereof are described in the Examples set forth below.

#### Pharmaceutical Compositions and Formulations

The compounds of this invention are typically administered to a patient in the form of a pharmaceutical composition or formulation. Such pharmaceutical compositions may be administered to the patient by any acceptable route of administration including, but not limited to, inhaled, oral, nasal, topical (including transdermal) and parenteral modes of administration. It will be understood that any form of the compounds of this invention, (i.e., free base, pharmaceutically acceptable salt, solvate, etc.) that is suitable for the particular mode of administration can be used in the pharmaceutical compositions discussed herein.

Accordingly, in one of its compositions aspects, this invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and a therapeutically effective amount of a compound of formula I, or a pharmaceutically

acceptable salt thereof. Optionally, such pharmaceutical compositions may contain other therapeutic and/or formulating agents if desired.

The pharmaceutical compositions of this invention typically contain a therapeutically effective amount of a compound of the present invention or a  
5 pharmaceutically acceptable salt thereof. Typically, such pharmaceutical compositions will contain from about 0.01 to about 95% by weight of the active agent; including, from about 0.01 to about 30% by weight; such as from about 0.01 to about 10% by weight of the active agent.

Any conventional carrier or excipient may be used in the pharmaceutical  
10 compositions of this invention. The choice of a particular carrier or excipient, or combinations of carriers or excipients, will depend on the mode of administration being used to treat a particular patient or type of medical condition or disease state. In this regard, the preparation of a suitable pharmaceutical composition for a particular mode of administration is well within the scope of those skilled in the pharmaceutical arts.  
15 Additionally, the ingredients for such compositions are commercially available from, for example, Sigma, P.O. Box 14508, St. Louis, MO 63178. By way of further illustration, conventional formulation techniques are described in *Remington: The Science and Practice of Pharmacy*, 20<sup>th</sup> Edition, Lippincott Williams & White, Baltimore, Maryland (2000); and H.C. Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7<sup>th</sup> Edition,  
20 Lippincott Williams & White, Baltimore, Maryland (1999).

Representative examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, the following: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose  
25 acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium  
30 hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; (21) compressed propellant gases, such as chlorofluorocarbons and hydrofluorocarbons; and (22) other non-toxic compatible substances employed in pharmaceutical compositions.



The pharmaceutical compositions of this invention are typically prepared by thoroughly and intimately mixing or blending a compound of the invention with a pharmaceutically acceptable carrier and one or more optional ingredients. If necessary or desired, the resulting uniformly blended mixture can then be shaped or loaded into tablets, capsules, pills, canisters, cartridges, dispensers and the like using conventional procedures and equipment.

In one embodiment, the pharmaceutical compositions of this invention are suitable for inhaled administration. Suitable pharmaceutical compositions for inhaled administration will typically be in the form of an aerosol or a powder. Such compositions are generally administered using well-known delivery devices, such as a nebulizer inhaler, a metered-dose inhaler (MDI), a dry powder inhaler (DPI) or a similar delivery device.

In a specific embodiment of this invention, the pharmaceutical composition comprising the active agent is administered by inhalation using a nebulizer inhaler. Such nebulizer devices typically produce a stream of high velocity air that causes the pharmaceutical composition comprising the active agent to spray as a mist that is carried into the patient's respiratory tract. Accordingly, when formulated for use in a nebulizer inhaler, the active agent is typically dissolved in a suitable carrier to form a solution. Alternatively, the active agent can be micronized and combined with a suitable carrier to form a suspension of micronized particles of respirable size, where micronized is typically defined as having about 90% or more of the particles with a diameter of less than about 10  $\mu\text{m}$ . Suitable nebulizer devices are provided commercially, for example, by PARI GmbH (Starnberg, German). Other nebulizer devices include Respimat (Boehringer Ingelheim) and those disclosed, for example, in U.S. Patent No. 6,123,068 and WO 97/12687.

A representative pharmaceutical composition for use in a nebulizer inhaler comprises an isotonic aqueous solution comprising from about 0.05  $\mu\text{g/mL}$  to about 10  $\text{mg/mL}$  of a compound of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

In another specific embodiment of this invention, the pharmaceutical composition comprising the active agent is administered by inhalation using a dry powder inhaler. Such dry powder inhalers typically administer the active agent as a free-flowing powder that is dispersed in a patient's air-stream during inspiration. In order to achieve a free-flowing powder, the active agent is typically formulated with a suitable excipient such as lactose or starch.

A representative pharmaceutical composition for use in a dry powder inhaler comprises dry lactose having a particle size between about 1  $\mu\text{m}$  and about 100  $\mu\text{m}$  and micronized particles of a compound of formula I, or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

5           Such a dry powder formulation can be made, for example, by combining the lactose with the active agent and then dry blending the components. Alternatively, if desired, the active agent can be formulated without an excipient. The pharmaceutical composition is then typically loaded into a dry powder dispenser, or into inhalation cartridges or capsules for use with a dry powder delivery device.

10           Examples of dry powder inhaler delivery devices include Diskhaler (GlaxoSmithKline, Research Triangle Park, NC) (see, e.g., U.S. Patent No. 5,035,237); Diskus (GlaxoSmithKline) (see, e.g., U.S. Patent No. 6,378,519; Turbuhaler (AstraZeneca, Wilmington, DE) (see, e.g., U.S. Patent No. 4,524,769); Rotahaler (GlaxoSmithKline) (see, e.g., U.S. Patent No. 4,353,365) and Handihaler (Boehringer Ingelheim). Further examples  
15 of suitable DPI devices are described in U.S. Patent Nos. 5,415,162, 5,239,993, and 5,715,810 and references cited therein.

In yet another specific embodiment of this invention, the pharmaceutical composition comprising the active agent is administered by inhalation using a metered-dose inhaler. Such metered-dose inhalers typically discharge a measured amount of the  
20 active agent or a pharmaceutically acceptable salt thereof using compressed propellant gas. Accordingly, pharmaceutical compositions administered using a metered-dose inhaler typically comprise a solution or suspension of the active agent in a liquefied propellant. Any suitable liquefied propellant may be employed including chlorofluorocarbons, such as  $\text{CCl}_3\text{F}$ , and hydrofluoroalkanes (HFAs), such as 1,1,1,2-tetrafluoroethane (HFA 134a) and  
25 1,1,1,2,3,3,3-heptafluoro-*n*-propane, (HFA 227). Due to concerns about chlorofluorocarbons affecting the ozone layer, formulations containing HFAs are generally preferred. Additional optional components of HFA formulations include co-solvents, such as ethanol or pentane, and surfactants, such as sorbitan trioleate, oleic acid, lecithin, and glycerin. See, for example, U.S. Patent No. 5,225,183, EP 0717987 A2, and WO  
30 92/22286.

A representative pharmaceutical composition for use in a metered-dose inhaler comprises from about 0.01 % to about 5 % by weight of a compound of formula I, or a pharmaceutically acceptable salt or solvate or stereoisomer thereof; from about 0 % to

about 20 % by weight ethanol; and from about 0 % to about 5 % by weight surfactant; with the remainder being an HFA propellant.

Such compositions are typically prepared by adding chilled or pressurized hydrofluoroalkane to a suitable container containing the active agent, ethanol (if present) and the surfactant (if present). To prepare a suspension, the active agent is micronized and then combined with the propellant. The formulation is then loaded into an aerosol canister, which forms a portion of a metered-dose inhaler device. Examples of metered-dose inhaler devices developed specifically for use with HFA propellants are provided in U.S. Patent Nos. 6,006,745 and 6,143,277. Alternatively, a suspension formulation can be prepared by spray drying a coating of surfactant on micronized particles of the active agent. See, for example, WO 99/53901 and WO 00/61108.

For additional examples of processes of preparing respirable particles, and formulations and devices suitable for inhalation dosing see U.S. Patent Nos. 6,268,533, 5,983,956, 5,874,063, and 6,221,398, and WO 99/55319 and WO 00/30614.

In another embodiment, the pharmaceutical compositions of this invention are suitable for oral administration. Suitable pharmaceutical compositions for oral administration may be in the form of capsules, tablets, pills, lozenges, cachets, dragees, powders, granules; or as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil liquid emulsion; or as an elixir or syrup; and the like; each containing a predetermined amount of a compound of the present invention as an active ingredient.

When intended for oral administration in a solid dosage form (i.e., as capsules, tablets, pills and the like), the pharmaceutical compositions of this invention will typically comprise a compound of the present invention as the active ingredient and one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate. Optionally or alternatively, such solid dosage forms may also comprise: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and/or sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as cetyl alcohol and/or glycerol monostearate; (8) absorbents, such as kaolin and/or bentonite clay;

(9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and/or mixtures thereof; (10) coloring agents; and (11) buffering agents.

Release agents, wetting agents, coating agents, sweetening, flavoring and  
5 perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of this invention. Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfate sodium sulfite and the like; (2) oil-soluble  
10 antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like. Coating agents for tablets, capsules, pills and like, include those used for enteric coatings, such as cellulose acetate phthalate  
(CAP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose phthalate,  
15 methacrylic acid-methacrylic acid ester copolymers, cellulose acetate trimellitate (CAT), carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), and the like.

If desired, the pharmaceutical compositions of the present invention may also be formulated to provide slow or controlled release of the active ingredient using, by way of  
20 example, hydroxypropyl methyl cellulose in varying proportions; or other polymer matrices, liposomes and/or microspheres.

In addition, the pharmaceutical compositions of the present invention may optionally contain opacifying agents and may be formulated so that they release the active ingredient only, or preferentially, in a certain portion of the gastrointestinal tract,  
25 optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Suitable liquid dosage forms for oral administration include, by way of illustration, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups  
30 and elixirs. Such liquid dosage forms typically comprise the active ingredient and an inert diluent, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (esp., cottonseed, groundnut,

corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Suspensions, in addition to the active ingredient, may contain suspending agents such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, 5 aluminium metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

When intended for oral administration, the pharmaceutical compositions of this invention are preferably packaged in a unit dosage form. The term "unit dosage form" means a physically discrete unit suitable for dosing a patient, i.e., each unit containing a predetermined quantity of active agent calculated to produce the desired therapeutic effect 10 either alone or in combination with one or more additional units. For example, such unit dosage forms may be capsules, tablets, pills, and the like.

The compounds of this invention can also be administered transdermally using known transdermal delivery systems and excipients. For example, a compound of this invention can be admixed with permeation enhancers, such as propylene glycol, 15 polyethylene glycol monolaurate, azacycloalkan-2-ones and the like, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers and buffers, may be used in such transdermal compositions if desired.

The pharmaceutical compositions of this invention may also contain other therapeutic agents that are co-administered with a compound of formula I, or 20 pharmaceutically acceptable salt or solvate or stereoisomer thereof. For example, the pharmaceutical compositions of this invention may further comprise one or more therapeutic agents selected from other bronchodilators (e.g., PDE<sub>3</sub> inhibitors, adenosine 2b modulators and  $\beta_2$  adrenergic receptor agonists); anti-inflammatory agents (e.g. steroidal anti-inflammatory agents, such as corticosteroids; non-steroidal anti-inflammatory agents 25 (NSAIDs), and PDE<sub>4</sub> inhibitors); other muscarinic receptor antagonists (i.e., anticholinergic agents); antiinfective agents (e.g. Gram positive and Gram negative antibiotics or antivirals); antihistamines; protease inhibitors; and afferent blockers (e.g., D<sub>2</sub> agonists and neurokinin modulators). The other therapeutic agents can be used in the form of pharmaceutically acceptable salts or solvates. Additionally, if appropriate, the other 30 therapeutic agents can be used as optically pure stereoisomers.

Representative  $\beta_2$  adrenergic receptor agonists that can be used in combination with, and in addition to, the compounds of this invention include, but are not limited to, salmeterol, salbutamol, formoterol, salmefamol, fenoterol, terbutaline, albuterol,

isoetharine, metaproterenol, bitolterol, pirbuterol, levalbuterol and the like, or pharmaceutically acceptable salts thereof. Other  $\beta_2$  adrenergic receptor agonists that can be used in combination with the compounds of this invention include, but are not limited to, 3-(4-{{6-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)-hexyl]oxy}butyl)benzenesulfonamide and 3-(-3-{{7-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)heptyl]oxy}propyl)benzenesulfonamide and related compounds disclosed in WO 02/066422, published on August 29, 2002; 3-[3-(4-{{6-(((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy}butyl)-phenyl]imidazolidine-2,4-dione and related compounds disclosed in WO 02/070490, 10 published September 12, 2002; 3-(4-{{6-((2*R*)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl)amino)hexyl]oxy}butyl)-benzenesulfonamide, 3-(4-{{6-((2*S*)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl)amino)hexyl]oxy}butyl)-benzenesulfonamide, 3-(4-{{6-((2*R/S*)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl)amino)hexyl]oxy}butyl)-benzenesulfonamide, *N*-(*tert*-butyl)-3-(4-{{6-(((2*R*)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl)amino)hexyl]-oxy}butyl)benzenesulfonamide, *N*-(*tert*-butyl)-3-(4-{{6-((2*S*)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl)amino)-hexyl]oxy}butyl)-benzenesulfonamide, *N*-(*tert*-butyl)-3-(4-{{6-((2*R/S*)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl)amino)hexyl]-oxy}butyl)benzenesulfonamide and related compounds 20 disclosed in WO 02/076933, published on October 3, 2002; 4-{{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol and related compounds disclosed in WO 03/024439, published on March 27, 2003; and pharmaceutically acceptable salts thereof. When employed, the  $\beta_2$ -adrenoreceptor agonist will be present in the pharmaceutical composition in a therapeutically effective amount. 25 Typically, the  $\beta_2$ -adrenoreceptor agonist will be present in an amount sufficient to provide from about 0.05  $\mu\text{g}$  to about 500  $\mu\text{g}$  per dose.

Representative steroidal anti-inflammatory agents that can be used in combination with the compounds of this invention include, but are not limited to, methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxoandrost-1,4-diene-17-carbothioic acid 30 *S*-fluoromethyl ester, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androst-1,4-diene-17-carbothioic acid *S*-(2-oxo-tetrahydrofuran-3*S*-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester),

budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, ST-126 and the like, or pharmaceutically-acceptable salts thereof. In a particular embodiment, the steroidal anti-inflammatory agent is 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$  -[(2-furanylcarbonyl)oxy]-11 $\beta$ -hydroxy-  
5 16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid *S*-fluoromethyl ester or a pharmaceutically acceptable salt or solvate thereof. When employed, the steroidal anti-inflammatory agent will be present in the pharmaceutical composition in a therapeutically effective amount. Typically, the steroidal anti-inflammatory agent will be present in an amount sufficient to provide from about 0.05  $\mu$ g to about 500  $\mu$ g per dose.

10 Other suitable combinations include, for example, other anti-inflammatory agents, e.g., NSAIDs (such as sodium cromoglycate; nedocromil sodium; phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors); leukotriene antagonists (e.g. monteleukast); inhibitors of leukotriene synthesis; iNOS inhibitors; protease inhibitors, such as tryptase and elastase inhibitors; beta-2 integrin  
15 antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists); cytokine antagonists (e.g. chemokine antagonists such as, an interleukin antibody ( IL antibody), specifically, an IL-4 therapy, an IL-13 therapy, or a combination thereof); or inhibitors of cytokine synthesis.

For example, representative phosphodiesterase-4 (PDE4) inhibitors or mixed  
20 PDE3/PDE4 inhibitors that can be used in combination with the compounds of this invention include, but are not limited to *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one; *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; *cis*-4-cyano-4-[3-  
25 (cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid and the like, or pharmaceutically acceptable salts thereof. Other representative PDE4 or mixed PDE4/PDE3 inhibitors include AWD-12-281 (elbion); NCS-613 (INSERM); D-4418 (Chiroscience and Schering-Plough); CI-1018 or PD-168787 (Pfizer); benzodioxole compounds disclosed in WO99/16766 (Kyowa Hakko); K-34 (Kyowa Hakko); V-11294A  
30 (Napp); roflumilast (Byk-Gulden); pthalazinone compounds disclosed in WO99/47505 (Byk-Gulden); Pumafentrine (Byk-Gulden, now Altana); arofylline (Almirall-Prodesfarma); VM554/UM565 (Vernalis); T-440 (Tanabe Seiyaku); and T2585 (Tanabe Seiyaku).

Representative muscarinic antagonists (i.e., anticholinergic agents) that can be used in combination with, and in addition to, the compounds of this invention include, but are not limited to, atropine, atropine sulfate, atropine oxide, methylatropine nitrate, homatropine hydrobromide, hyoscyamine (*d, l*) hydrobromide, scopolamine hydrobromide, 5 ipratropium bromide, oxitropium bromide, tiotropium bromide, methantheline, propantheline bromide, anisotropine methyl bromide, clidinium bromide, copyrrolate (Robinul), isopropamide iodide, mepenzolate bromide, tridihexethyl chloride (Pathilone), hexocyclium methylsulfate, cyclopentolate hydrochloride, tropicamide, trihexyphenidyl hydrochloride, pirenzepine, telenzepine, AF-DX 116 and methoctramine and the like, or a 10 pharmaceutically acceptable salt thereof; or, for those compounds listed as a salt, alternate pharmaceutically acceptable salt thereof.

Representative antihistamines (i.e., H<sub>1</sub>-receptor antagonists) that can be used in combination with the compounds of this invention include, but are not limited to, ethanolamines, such as carbinoxamine maleate, clemastine fumarate, diphenylhydramine 15 hydrochloride and dimenhydrinate; ethylenediamines, such as pyrilamine amleate, tripeleminamine hydrochloride and tripeleminamine citrate; alkylamines, such as chlorpheniramine and acrivastine; piperazines, such as hydroxyzine hydrochloride, hydroxyzine pamoate, cyclizine hydrochloride, cyclizine lactate, meclizine hydrochloride and cetirizine hydrochloride; piperidines, such as astemizole, levocabastine hydrochloride, 20 loratadine or its descarboethoxy analogue, terfenadine and fexofenadine hydrochloride; azelastine hydrochloride; and the like, or a pharmaceutically acceptable salt thereof; or, for those compounds listed as a salt, alternate pharmaceutically acceptable salt thereof.

Suitable doses for the other therapeutic agents administered in combination with a compound of the invention are in the range of about 0.05 µg/day to about 100 mg/day.

25 The following formulations illustrate representative pharmaceutical compositions of the present invention:



Formulation Example A

A dry powder for administration by inhalation is prepared as follows:

Ingredients	Amount
Compound of the invention	0.2 mg
Lactose	25 mg

5

10

Representative Procedure: The compound of the invention is micronized and then blended with lactose. This blended mixture is then loaded into a gelatin inhalation cartridge. The contents of the cartridge are administered using a powder inhaler.

Formulation Example B

A dry powder formulation for use in a dry powder inhalation device is prepared as follows:

15

Representative Procedure: A pharmaceutical composition is prepared having a bulk formulation ratio of micronized compound of the invention to lactose of 1:200. The composition is packed into a dry powder inhalation device capable of delivering between about 10  $\mu\text{g}$  and about 100  $\mu\text{g}$  of the compound of the invention per dose.

20

Formulation Example C

A dry powder for administration by inhalation in a metered dose inhaler is prepared as follows:

25

Representative Procedure: A suspension containing 5 wt. % of a compound of the invention and 0.1 wt. % lecithin is prepared by dispersing 10 g of the compound of the invention as micronized particles with mean size less than 10  $\mu\text{m}$  in a solution formed from 0.2 g of lecithin dissolved in 200 mL of demineralized water. The suspension is spray dried and the resulting material is micronized to particles having a mean diameter less than 1.5  $\mu\text{m}$ . The particles are loaded into cartridges with pressurized 1,1,1,2-tetrafluoroethane.

30

Formulation Example D

A pharmaceutical composition for use in a metered dose inhaler is prepared as follows:

Representative Procedure: A suspension containing 5 wt. % compound of the invention, 0.5 wt. % lecithin, and 0.5 wt. % trehalose is prepared by dispersing 5 g of active ingredient as micronized particles with mean size less than 10  $\mu\text{m}$  in a colloidal solution formed from 0.5 g of trehalose and 0.5 g of lecithin dissolved in 100 mL of demineralized water. The suspension is spray dried and the resulting material is micronized to particles having a mean diameter less than 1.5  $\mu\text{m}$ . The particles are loaded into canisters with pressurized 1,1,1,2-tetrafluoroethane.

Formulation Example E

A pharmaceutical composition for use in a nebulizer inhaler is prepared as follows:

Representative Procedure: An aqueous aerosol formulation for use in a nebulizer is prepared by dissolving 0.1 mg of the compound of the invention in 1 mL of a 0.9 % sodium chloride solution acidified with citric acid. The mixture is stirred and sonicated until the active ingredient is dissolved. The pH of the solution is adjusted to a value in the range of from 3 to 8 by the slow addition of NaOH.

Formulation Example F

Hard gelatin capsules for oral administration are prepared as follows:

Ingredients	Amount
Compound of the invention	250 mg
Lactose (spray-dried)	200 mg
Magnesium stearate	10 mg

Representative Procedure: The ingredients are thoroughly blended and then loaded into a hard gelatin capsule (460 mg of composition per capsule).

Formulation Example G

A suspension for oral administration is prepared as follows:

	Ingredients	Amount
5	Compound of the invention	1.0 g
	Fumaric acid	0.5 g
	Sodium chloride	2.0 g
	Methyl paraben	0.15 g
	Propyl paraben	0.05 g
10	Granulated sugar	25.5 g
	Sorbitol (70% solution)	12.85 g
	Veegum k (Vanderbilt Co.)	1.0 g
	Flavoring	0.035 mL
	Colorings	0.5 mg
15	Distilled water	q.s. to 100 mL

Representative Procedure: The ingredients are mixed to form a suspension containing 100 mg of active ingredient per 10 mL of suspension.

20 Formulation Example H

An injectable formulation is prepared as follows:

	Ingredients	Amount
	Compound of the invention	0.2 g
25	Sodium acetate buffer solution (0.4 M)	2.0 mL
	HCl (0.5 N) or NaOH (0.5 N)	q.s. to pH 4
	Water (distilled, sterile)	q.s. to 20 mL

30 Representative Procedure: The above ingredients are blended and the pH is adjusted to  $4 \pm 0.5$  using 0.5 N HCl or 0.5 N NaOH.

### Utility

The compounds of this invention possess both  $\beta_2$  adrenergic receptor agonist and muscarinic receptor antagonist activity and therefore, such compounds are expected to be useful as therapeutic agents for treating medical conditions mediated by  $\beta_2$  adrenergic receptors or muscarinic receptors, i.e., medical conditions that are ameliorated by treatment with a  $\beta_2$  adrenergic receptor agonist or a muscarinic receptor antagonist. See, for example, Eglen et al., *Muscarinic Receptor Subtypes: Pharmacology and Therapeutic Potential*, *DN&P* **10**(8), 462-469 (1997); Emilien et al., *Current Therapeutic Uses and Potential of beta-Adrenoceptor Agonists and Antagonists*, *European J. Clinical Pharm.*, **53**(6), 389-404 (1998); and references cited therein. Such medical conditions include, by way of example, pulmonary disorders or diseases associated with reversible airway obstruction, such as chronic obstructive pulmonary disease (e.g., chronic and wheezy bronchitis and emphysema), asthma, pulmonary fibrosis and the like. Other conditions include premature labor, depression, congestive heart failure, skin diseases (e.g., inflammatory, allergic, psoriatic and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g., peptic and gastric ulceration) and muscle wasting disease.

Accordingly, in one embodiment, this invention is directed to a method for treating a pulmonary disorder, the method comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer thereof. When used to treat a pulmonary disorder, the compounds of this invention will typically be administered by inhalation in multiple doses per day, in a single daily dose or a single weekly dose. Generally, the dose for treating a pulmonary disorder will range from about 10  $\mu\text{g}/\text{day}$  to about 200  $\mu\text{g}/\text{day}$ .

When administered by inhalation, the compounds of this invention typically have the effect of producing bronchodilation. Accordingly, in another of its method aspects, this invention is directed to a method of producing bronchodilation in a patient, the method comprising administering to a patient requiring bronchodilation a bronchodilation-producing amount of a compound of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer thereof. Generally, the dose for producing bronchodilation will range from about 10  $\mu\text{g}/\text{day}$  to about 200  $\mu\text{g}/\text{day}$ .

In one embodiment, this invention is directed to a method of treating chronic obstructive pulmonary disease or asthma, the method comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt or solvate or stereoisomer thereof. When used to treat a COPD or asthma, the compounds of this invention will typically be administered by inhalation in multiple doses per day or in a single daily dose. Generally, the dose for treating COPD or asthma will range from about 10  $\mu\text{g/day}$  to about 200  $\mu\text{g/day}$ .

As used herein, COPD includes chronic obstructive bronchitis and emphysema (see, for example, Barnes, Chronic Obstructive Pulmonary Disease, *N Engl J Med* 2000: 343:269-78).

When used to treat a pulmonary disorder, the compounds of this invention are optionally administered in combination with other therapeutic agents. In particular, by combining the compounds of this invention with a steroidal anti-inflammatory agent (e.g. a corticosteroid), the pharmaceutical compositions of this invention can provide triple therapy, i.e.,  $\beta_2$  adrenergic receptor agonist, muscarinic receptor antagonist and anti-inflammatory activity, using only two active components. Since pharmaceutical compositions containing two active components are typically easier to formulate compared to compositions containing three active components, such two component compositions provide a significant advantage over compositions containing three active components. Accordingly, in a particular embodiment, the pharmaceutical compositions and methods of this invention further comprise a therapeutically effective amount of a steroidal anti-inflammatory agent.

Compounds of this invention exhibit both muscarinic receptor antagonist and  $\beta_2$  adrenergic receptor agonist activity. Accordingly, among other properties, compounds of particular interest are those that demonstrate an inhibitory constant  $K_i$  value for binding at the  $M_3$  muscarinic receptor and an  $EC_{50}$  value for  $\beta_2$  adrenergic receptor agonist activity of less than about 100 nM; particularly less than 10 nM. Among these compounds, compounds of special interest include those having muscarinic activity, expressed in terms of the inhibitory constant  $K_i$  for binding at the  $M_3$  muscarinic receptor, that is about equal to the compound's  $\beta_2$  adrenergic agonist activity, expressed in terms of the half maximal effective concentration  $EC_{50}$ , as determined in the *in vitro* assays described herein, or in similar assays. For example, compounds of particular interest are those having a ratio of the inhibitory constant  $K_i$  for the  $M_3$  muscarinic receptor to the  $EC_{50}$  for the  $\beta_2$  adrenergic

receptor ranging from about 30:1 to about 1:30; including about 20:1 to about 1:20; such as about 10:1 to about 1:10.

Since compounds of this invention possess both  $\beta_2$  adrenergic agonist activity and muscarinic receptor antagonist activity, such compounds are also useful as research tools  
5 for investigating or studying biological systems or samples having  $\beta_2$  adrenergic receptors or muscarinic receptors, or for discovering new compounds having both  $\beta_2$  adrenergic agonist activity and muscarinic receptor antagonist activity. Such biological systems or samples may comprise  $\beta_2$  adrenergic receptors and/or muscarinic receptors. Any suitable biological system or sample having  $\beta_2$  adrenergic and/or muscarinic receptors may be  
10 employed in such studies which may be conducted either *in vitro* or *in vivo*. Representative biological systems or samples suitable for such studies include, but are not limited to, cells, cellular extracts, plasma membranes, tissue samples, mammals (such as mice, rats, guinea pigs, rabbits, dogs, pigs, etc.), and the like.

In this embodiment, a biological system or sample comprising a  $\beta_2$  adrenergic  
15 receptor or a muscarinic receptor is contacted with a  $\beta_2$  adrenergic receptor-agonizing or muscarinic receptor-antagonizing amount of a compound of this invention. The effects are then determined using conventional procedures and equipment, such as radioligand binding assays and functional assays. Such functional assays include ligand-mediated changes in intracellular cyclic adenosine monophosphate (cAMP), ligand-mediated changes in activity  
20 of the enzyme adenylyl cyclase (which synthesizes cAMP), ligand-mediated changes in incorporation of guanosine 5'-O-( $\gamma$ -thio)triphosphate ( $[^{35}\text{S}]\text{GTP S}$ ) into isolated membranes via receptor catalyzed exchange of  $[^{35}\text{S}]\text{GTP S}$  for GDP, ligand-mediated changes in free intracellular calcium ions (measured, for example, with a fluorescence-linked imaging plate reader or FLIPR<sup>®</sup> from Molecular Devices, Inc.). A compound of this invention will  
25 agonize or cause activation of a  $\beta_2$  adrenergic receptor and antagonize or decrease the activation of muscarinic receptors in any of the functional assays listed above, or assays of a similar nature. The amount of compound used in these studies will typically range from about 0.1 nanomolar to about 100 nanomolar.

Additionally, the compounds of this invention can be used as research tools for  
30 discovering new compounds that have both a  $\beta_2$  adrenergic receptor agonist and muscarinic receptor antagonist activity. In this embodiment, a  $\beta_2$  adrenergic receptor and muscarinic receptor binding data (for example, as determined by *in vitro* radioligand displacement

assays) for a test compound or a group of test compounds is compared to the  $\beta_2$  adrenergic receptor and muscarinic receptor binding data for a compound of this invention to identify those test compounds that have about equal or superior  $\beta_2$  adrenergic receptor and/or muscarinic receptor binding, if any. This aspect of the invention includes, as separate  
 5 embodiments, both the generation of comparison data (using the appropriate assays) and the analysis of the test data to identify test compounds of interest.

In some cases, compounds of this invention may possess either weak muscarinic receptor antagonist activity or weak  $\beta_2$  adrenergic receptor agonist activity. In these cases, those of ordinary skill in the art will recognize that such compounds still have utility as  
 10 primarily either a  $\beta_2$  adrenergic receptor agonist or a muscarinic receptor antagonist, respectively.

The properties and utility of the compounds of this invention can be demonstrated using various *in vitro* and *in vivo* assays well-known to those skilled in the art. For example, representative assays are described in further detail in the following Examples.

15

### EXAMPLES

The following Preparations and Examples are provided to illustrate specific embodiments of this invention. These specific embodiments, however, are not intended to limit the scope of this invention in any way unless specifically indicated.

20 The following abbreviations have the following meanings unless otherwise indicated and any other abbreviations used herein and not defined have their standard meaning:

25	AC	adenylyl cyclase
	Ach	acetylcholine
	ATCC	American Type Culture Collection
	BSA	bovine serum albumin
	cAMP	3'-5' cyclic adenosine monophosphate
	CHO	Chinese hamster ovary
30	cM <sub>5</sub>	cloned chimpanzee M <sub>5</sub> receptor
	DCM	dichloromethane (i.e., methylene chloride)
	DIPEA	<i>N,N</i> -diisopropylethylamine
	dPBS	Dulbecco's phosphate buffered saline
	DMEM	Dulbecco's Modified Eagle's Medium
35	DMSO	dimethyl sulfoxide
	EDTA	ethylenediaminetetraacetic acid
	Emax	maximal efficacy

	EtOAc	ethyl acetate
	EtOH	ethanol
	FBS	fetal bovine serum
	FLIPR	fluorometric imaging plate reader
5	Gly	glycine
	HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
	HBSS	Hank's buffered salt solution
	HEK	human embryonic kidney cells
10	HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
	hM <sub>1</sub>	cloned human M <sub>1</sub> receptor
	hM <sub>2</sub>	cloned human M <sub>2</sub> receptor
	hM <sub>3</sub>	cloned human M <sub>3</sub> receptor
	hM <sub>4</sub>	cloned human M <sub>4</sub> receptor
15	hM <sub>5</sub>	cloned human M <sub>5</sub> receptor
	HPLC	high-performance liquid chromatography
	IBMX	3-isobutyl-1-methylxanthine
	%Eff	% efficacy
	PBS	phosphate buffered saline
20	PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
	rpm	rotations per minute
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
25	Tris	tris(hydroxymethyl)aminomethane

Unless noted otherwise, reagents, starting materials and solvents were purchased from commercial suppliers (such as Aldrich, Fluka, Sigma and the like) and were used without further purification.

In the examples described below, HPLC analysis was conducted using an Agilent (Palo Alto, CA) Series 1100 instrument with Zorbax Bonus RP 2.1 x 50 mm columns, supplied by Agilent, (a C14 column), having a 3.5 micron particle size. Detection was by UV absorbance at 214 nm. HPLC 10-70 data was obtained with a flow rate of 0.5 mL/minute of 10%-70% B over 6 minutes. Mobile phase A was 2 % - 98 % - 0.1% ACN-H<sub>2</sub>O-TFA; and mobile phase B was 90 % - 10 % - 0.1 % ACN-H<sub>2</sub>O-TFA. Using the mobile phases A and B described above, HPLC 5-35 data and HPLC 10-90 data were obtained with a 5 minute gradient.

Liquid chromatography mass spectrometry (LCMS) data were obtained with an Applied Biosystems (Foster City, CA) model API-150EX instrument. LCMS 10-90 data was obtained with a 10 % - 90 % mobile phase B over a 5 minute gradient.



Small scale purification was conducted using an API 150EX Prep Workstation system from Applied Biosystems. The mobile phase was A: water + 0.05% v/v TFA; and B: acetonitrile + 0.05% v/v TFA. For arrays (typically about 3 to 50 mg recovered sample size) the following conditions were used: 20 mL/min flow rate; 15 min gradients and a 20 mm x 50 mm Prism RP column with 5 micron particles (Thermo Hypersil-Keystone, Bellefonte, PA). For larger scale purifications (typically greater than 100 mg crude sample), the following conditions were used: 60 mL/min flow rate; 30 min gradients and a 41.4 mm x 250 mm Microsorb BDS column with 10 micron particles (Varian, Palo Alto, CA).

10 The specific rotation for chiral compounds (indicated as  $[\alpha]_D^{20}$ ) was measured using a Jasco Polarimeter (Model P-1010) with a tungsten halogen light source and a 589 nm filter at 20°C. Samples of test compounds were typically measured at 1 mg/mL water.

### Preparation 1

#### 15 **8-Benzyloxy-5-(2-bromoacetyl)-1*H*-quinolin-2-one**

##### (a) **8-Acetoxy-1*H*-quinolin-2-one**

8-Hydroxyquinoline-*N*-oxide (160.0 g, 1.0 mol), commercially-available from Aldrich, Milwaukee, WI, and acetic anhydride (800 mL, 8.4 mol) were heated at 100 °C for 3 h and then cooled in ice. The product was collected on a Buchner funnel, washed  
20 with acetic anhydride (2 x 100mL) and dried under reduced pressure to give 8-acetoxy-1*H*-quinolin-2-one (144 g) as a solid.

##### (b) **5-Acetyl-8-hydroxy-1*H*-quinolin-2-one**

A slurry of aluminum chloride (85.7 g, 640 mmol) in 1,2-dichloroethane (280 mL)  
25 was cooled in ice, and the product from step (a) (56.8 g, 280 mmol) was added. The mixture was warmed to room temperature and then heated at 85 °C. After 30 min, acetyl chloride (1.5 mL, 21 mmol) was added and the mixture was heated an additional 60 min. The reaction mixture was then cooled and added to 1N hydrochloric acid (3 L) at 0 °C with good stirring. After stirring for 2 h, the solids were collected on a Buchner funnel, washed  
30 with water (3 x 250 mL) and dried under reduced pressure. The crude product isolated from several batches (135 g) was combined and triturated with dichloromethane (4 L) for 6 h. The resulting solid was collected on a Buchner funnel and dried under reduced pressure to give the title compound (121 g).

**(c) 5-Acetyl-8-benzyloxy-1*H*-quinolin-2-one**

To the product from step (b) (37.7 g, 186 mmol) was added *N,N*-dimethylformamide (200 mL) and potassium carbonate (34.5 g, 250 mmol) followed by  
5 benzyl bromide (31.8 g, 186 mmol). The mixture was stirred at room temperature for 2.25 hour and then poured into saturated sodium chloride (3.5 L) at 0 °C and stirred for 1 hour. The product was collected and dried on a Buchner funnel for 1 hour, and the resulting solids were dissolved in dichloromethane (2 L) and this mixture was dried over sodium sulfate. The solution was filtered through a pad of Celite which was then washed with  
10 dichloromethane (5 x 200 mL). The combined filtrate was then concentrated to dryness and the resulting solids were triturated with ether (500 mL) for 2 h. The product was collected on a Buchner funnel, washed with ether (2 x 250 mL) and dried under reduced pressure to give the title compound (44 g) as a powder.

**15 (d) 8-Benzyloxy-5-(2-bromoacetyl)-1*H*-quinolin-2-one**

The product from step (c) (20.0 g, 68.2 mmol) was dissolved in dichloromethane (200 mL) and cooled to 0 °C. Boron trifluoride diethyl etherate (10.4 mL, 82.0 mmol) was added via syringe and the mixture was warmed to room temperature to give a thick  
20 suspension. The suspension was heated at 45 °C (oil bath) and a solution of bromine (11.5 g, 72.0 mmol) in dichloromethane (100 mL) was added over 40 min. The mixture was kept at 45 °C for an additional 15 min and then cooled to room temperature. The mixture was concentrated under reduced pressure and then triturated with 10% aqueous sodium carbonate (200 mL) for 1 hour. The solids were collected on a Buchner funnel, washed with water (4 x 100 mL) and dried under reduced pressure. The product of two runs was  
25 combined for purification. The crude product (52 g) was triturated with 50% methanol in chloroform (500 mL) for 1 hour. The product was collected on a Buchner funnel and washed with 50% methanol in chloroform (2 x 50 mL) and methanol (2 x 50 mL). The solid was dried under reduced pressure to give the title compound (34.1 g) as a powder.

**Preparation 2****8-Benzyloxy-5-[(*R*)-2-bromo-1-(*tert*-butyldimethylsilyloxy)ethyl]-1*H*-quinolin-2-one****(a) 8-Benzyloxy-5-((*R*)-2-bromo-1-hydroxyethyl)-1*H*-quinolin-2-one**

(*R*)-(+)- $\alpha,\alpha$ -Diphenylprolinol (30.0 g, 117 mmol) and trimethylboroxine (11.1 mL, 78 mmol) were combined in toluene (300 mL) and stirred at room temperature for 30 min. The mixture was placed in a 150 °C oil bath and liquid was distilled off. Toluene was added in 20 mL aliquots and distillation was continued for 4 h. A total of 300 mL toluene was added. The mixture was then cooled to room temperature. A 500  $\mu$ L aliquot was evaporated to dryness and weighed (246 mg) to determine that the concentration of catalyst was 1.8 M.

8-Benzyloxy 5-(2-bromoacetyl)-1*H*-quinolin-2-one (90.0 g, 243 mmol) was placed under nitrogen and tetrahydrofuran (900 mL) was added followed by the catalyst described above (1.8 M in toluene, 15 mL, 27 mmol). The suspension was cooled to  $-10\pm 5$  °C in an ice/isopropanol bath. Borane (1.0 M in THF, 294 mL, 294 mmol) was added over 4 h. The reaction was then stirred an additional 45 min at  $-10$  °C and then methanol (250 mL) was added slowly. The mixture was concentrated under vacuum and the residue was dissolved in boiling acetonitrile (1.3 L), filtered while hot and then cooled to room temperature. The crystals were filtered, washed with acetonitrile and dried under vacuum to give the title compound (72.5 g, 196 mmol, 81% yield, 95% ee, 95% pure by HPLC).

20

**(b) 8-Benzyloxy-5-[(*R*)-2-bromo-1-(*tert*-butyldimethylsilyloxy)ethyl]-1*H*-quinolin-2-one**

To the product of step (b) (70.2 g, 189 mmol) was added *N,N*-dimethylformamide (260 mL) and this mixture was cooled in an ice bath under nitrogen. 2,6-Lutidine (40.3 g, 376 mmol) was added over 5 min and then *tert*-butyldimethylsilyl trifluoromethanesulfonate (99.8 g, 378 mmol) was added slowly while maintaining the temperature below 20 °C. The mixture was allowed to warm to room temperature for 45 min. Methanol (45 mL) was added to the mixture dropwise over 10 min and the mixture was partitioned between ethyl acetate/cyclohexane(1:1, 500 mL) and water/brine (1:1, 500mL). The organics were washed twice more with water/brine (1:1, 500 mL each). The combined organics were evaporated under reduced pressure to give a light yellow oil. Two separate portions of cyclohexane (400 mL) were added to the oil and distillation continued until a thick white slurry was formed. Cyclohexane (300 mL) was added to the slurry and

30

the resulting white crystals were filtered, washed with cyclohexane (300 mL) and dried under reduced pressure to give the title compound (75.4 g, 151 mmol, 80% yield, 98.6 % ee).

### 5 Preparation 3A

#### **8-Benzyloxy-5-[(R)-2-(N-benzylamino)-1-(tert-butyldimethylsilyloxy)ethyl]-1H-quinolin-2-one**

A stirred solution of the product of Preparation 2 (1.00 g, 2.05 mmol) and benzylamine (493  $\mu$ L, 4.51 mmol) in DMSO (1.7 mL) was heated at 105 °C for 4 h. The reaction mixture was allowed to cool and was then diluted with EtOAc (10 mL) and the organic layer was washed with saturated aqueous ammonium chloride solution (5 mL) and 1N sodium hydroxide (5 mL), dried (MgSO<sub>4</sub>) and solvent removed under reduced pressure. The crude residue was purified by column chromatography (50% EtOAc/hexanes) to give the title compound (700 mg, 67%). MS *m/z*: [M + H<sup>+</sup>] calcd for C<sub>31</sub>H<sub>38</sub>N<sub>2</sub>O<sub>3</sub>Si 515.27; found 515.5.

### Preparation 3B

#### **8-Benzyloxy-5-[(R)-2-(N-benzylamino)-1-(tert-butyldimethylsilyloxy)ethyl]-1H-quinolin-2-one**

To a 500 mL three-necked round-bottom flask was added 8-benzyloxy-5-[(R)-2-bromo-1-(tert-butyldimethylsilyloxy)ethyl]-1H-quinolin-2-one (43 g, 0.124 mol, about 95% chiral purity), 1-methyl-2-pyrrolidinone (210 mL) and benzylamine (28.3 g, 0.37 mol). The resulting mixture was flushed with nitrogen and then stirred at 90 °C for 6 hours. The mixture was then cooled to room temperature and water (300 mL) and ethyl acetate (300 mL) were added. The layers were separated and the organic layer was washed with water (200 mL), a 1:1 mixture of water and aqueous saturated sodium chloride solution (200 mL), and water (200 mL). The organic layer was then dried over magnesium sulfate, filtered and concentrated under reduced pressure to provide the title compound as an orange oil.

To the orange oil was added heptane (200 mL) and ethyl acetate (200 mL) and the resulting mixture was heated to 65 °C to produce a clear solution. This solution was cooled to room temperature and allowed to stand overnight (about 16 hours) at which time a precipitate had formed. The precipitate was collected by filtration to give

stereochemically-impure title compound (8.85 g, 79.6% ee). The filtrate was concentrated under reduced pressure to give the title compound (38.6 g, 99.4% ee). This material was combined with a previous batch of material (19.2 g, 99.5% ee) and heptane (250 mL) and ethyl acetate (100 mL) were added. This mixture was heated to 80 °C (hazy to clear solution) and then cooled to room temperature and allowed to stand overnight. The resulting precipitate was collected by filtration to afford the title compound as a white solid (36.8 g, 98.4% ee, 99.9% chemical purity). The filtrate was concentrated under reduced pressure and the residue was dissolved in heptane (100 mL). The resulting solids were collected to give the title compound as a tan solid (24 g, 100% chiral purity, 95% ee).

10

#### Preparation 4

##### **5-[(*R*)-2-Amino-1-(*tert*-butyldimethylsilyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one Acetic Acid Salt**

8-Benzyloxy-5-[(*R*)-2-(*N*-benzylamino)-1-(*tert*-butyldimethylsilyloxy)ethyl]-1H-quinolin-2-one (100 g, 194 mmol) and acetic acid (17.5 mL, 291 mmol) were dissolved in methanol (1 L). The clear solution was purged with nitrogen and then palladium hydroxide on carbon (20 g, 20 wt. % Pd (dry basis), wet (about 50% water)) was added. Hydrogen gas was bubbled through the stirred solution at room temperature for 6 hours during which time a thick slurry developed. The reaction mixture was then purged with nitrogen and methanol (1 L) was added. The resulting mixture was stirred for about 30 minutes (to dissolve the product) and then the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to a volume of about 500 mL and, to the resulting slurry, was added ethanol (500 mL). The resulting mixture was again concentrated under reduced pressure to a volume of about 500 mL and the resulting precipitate was collected by filtration and dried to provide the title compound as a yellow-white solid (65g, 85% yield, >98% purity).

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#### Preparation 5

##### **Ethyl 3-(*N*-Benzyl-*N*-*tert*-butoxycarbonylamino)propionate**

Ethyl 3-benzylaminopropionate (10 g, 48.2 mmol) was dissolved in dichloromethane (100 mL) and to this solution was added triethylamine (6.72 mL, 53 mmol). This mixture was flushed with dry nitrogen and di-*tert*-butyl dicarbonate (11 g, 51 mmol) was added. The resulting mixture was stirred at room temperature for 3 hours. The

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reaction was then concentrated under reduced pressure and the residue was dissolved in ethyl acetate. This solution was washed with aqueous hydrochloric acid (1N, × 2), aqueous sodium hydroxide (1N, × 2) and brine (×1). The organic layer was then dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the title  
5 compound as a clear colorless oil (15.6 g). <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ) 7.4-7.2 (m, 5H), 4.45 (br s, 2H), 4.1 (q, 2H), 3.5 (m, 2H), 2.55 (m, 2H), 1.5 (m, 9H), 1.25 (t, 3H).

### Preparation 6

#### 4-(*N*-Benzyl-*N*-*tert*-butoxycarbonylamino)-2-methylbutan-2-ol

10 Under nitrogen, THF (30 mL) and methyllithium (1.6 M in diethyl ether, 35 mL) were added via a cannula to a dry 500 mL round-bottomed flask equipped with a stir bar and a 60 mL graduated dropping funnel. The cannula was then rinsed with a further portion of THF (10 mL). The flask was cooled to -78 °C and a solution of the product of Preparation 5 (6.16 g, 20 mmol) in THF (30 mL) was added dropwise from the dropping  
15 funnel over a period of 25 minutes. The resulting reaction mixture was stirred at -78 °C for 1.5 hours and then quenched with water. This mixture was warmed to room temperature and diluted with ethyl acetate. The resulting mixture was stirred at room temperature overnight. The mixture was then transferred to a separatory funnel and the layers were separated. The organic layer was washed with saturated aqueous sodium  
20 bicarbonate solution (×2) and brine (×1). The organic layer was then dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the title compound as a clear colorless oil (6 g). LCMS *m/z*: 294.3 (MH<sup>+</sup>).

### Preparation 7

#### 25 4-(Benzylmethylamino)-2-methylbutan-2-ol

The product of Preparation 6 (2.4 g, 8.2 mmol) was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was added. The resulting mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane. The solution was transferred into a separatory  
30 funnel and washed with aqueous sodium hydroxide solution (1N, × 3) and brine (×1). The organic layer was then dried over magnesium sulfate, filtered and concentrated under reduced pressure.

The resulting oil was dissolved in methanol (10 mL) and to this solution was added paraformaldehyde (2.5 g, 82 mmol). This mixture was heated at reflux for 3 hours and then cooled to room temperature. Sodium triacetoxymethylborohydride (5.2 g, 24.8 mmol) was added and the reaction mixture was stirred at room temperature overnight. The methanol  
5 was evaporated under reduced pressure and the residue was dissolved in dichloromethane. This solution was washed with aqueous sodium hydroxide solution (1N, × 3) and brine (×1). The organic layer was then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 10% methanol/chloroform to give the title compound as a clear pale yellow oil  
10 (1.49 g). <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ): 7.3 (m, 5H), 3.5 (s, 2H), 2.65 (m, 2H), 2.2 (s, 2H), 1.65 (m, 2H), 1.1 (s, 6H).

### Preparation 8

#### Biphenyl-2-ylcarbamic Acid 3-(Benzylmethylamino)-1,1-dimethylpropyl Ester

The product of Preparation 7 (500 mg, 2.4 mmol) was dissolved in *N,N*-  
15 dimethylformamide (1.3 mL) and to this solution was added biphenylisocyanate (455 μL, 2.65 mmol). The resulting mixture was heated at 70 °C overnight and then ethyl acetate was added. This mixture was washed with aqueous sodium hydroxide solution (1N, × 2) and brine (×1). The organic layer was then dried over magnesium sulfate, filtered and  
20 concentrated under reduced pressure to provide the title compound as an oil. LCMS *m/z*: 403.5 (MH<sup>+</sup>).

### Preparation 9

#### Biphenyl-2-ylcarbamic Acid 3-[(9-Hydroxynonyl)methylamino]-1,1-dimethylpropyl 25 Ester

The product of Preparation 8 (970 mg, 2.4 mmol) was dissolved in ethanol (10 mL) and nitrogen gas was bubbled through this solution for 5 minutes. Palladium on carbon (10%, degussa type, 1g) was added and the reaction mixture was stirred at room  
30 temperature overnight under a hydrogen-filled balloon. Nitrogen gas was then bubbled through the reaction mixture. The mixture was then filtered through a pad of Celite and the Celite pad was washed with ethanol. The filtrate was concentrated under reduced pressure.

The residue was dissolved in acetonitrile (10 mL) and to this solution was added 9-bromo-1-nonanol (642 mg, 2.88 mmol) and diisopropylethylamine (627 μL, 3.6 mmol).

The reaction mixture was heated at 60 °C overnight and then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane and the resulting solution was washed with aqueous sodium dihydrogenphosphate solution (1M, ×2), dried over magnesium sulfate, filtered and concentrated under reduced pressure.

5 The resulting oil was then chromatographed over silica gel eluting with 5% methanol/chloroform/ 0.5% NH<sub>4</sub>OH to afford the title compound (284 mg). LCMS *m/z*: 455.3 (MH<sup>+</sup>).

### Example 1

#### 10 **Biphenyl-2-ylcarbamic Acid 3-({9-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl)methylamino)-1,1-dimethylpropyl Ester**

The product of Preparation 9 (284 mg, 0.63 mmol) was dissolved in dichloromethane (5 mL) to this solution was added diisopropylethylamine (330 μL, 1.88 mmol) and dimethyl sulfoxide (135 μL, 1.88 mmol). The flask was sealed under a  
15 nitrogen atmosphere and cooled to -15 °C. Pyridine sulfur trioxide complex (300 mg, 1.88 mmol) was added and the reaction mixture was stirred at -15 °C for 1h. The reaction was then quenched by adding water and the layers were separated. The organic layer was washed with water (× 3), aqueous saturated sodium bicarbonate solution (×1) and brine (×1). The organic layer was then dried over magnesium sulfate, filtered and concentrated  
20 under reduced pressure.

The residue was dissolved in a 1:1 mixture of dichloromethane (1 mL) and methanol (1 mL) and to this solution was added the product of Preparation 4 (316 mg, 0.94 mmol) and sodium triacetoxyborohydride (400 mg, 1.88 mmol). The reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure.

25 The residue was dissolved in dichloromethane (5 mL) and to this solution was added triethylamine trihydrofluoride (1.03 mL, 6.3 mmol). The reaction mixture was stirred at room temperature overnight and then the solvent was evaporated under reduced pressure. The resulting foam was dissolved in a 1:1 mixture of acetic acid (3 mL) and water (3 mL) and this mixture was purified by reverse phase preparative HPLC to afford  
30 the title compound as a white lyophilized solid (18.0 mg). LCMS *m/z*: 657.5 (MH<sup>+</sup>).



**Preparation 10****(2-Bromophenyl)carbamic Acid 3-(Benzylmethylamino)-1,1-dimethylpropyl Ester**

Following the procedure of Preparation 8 and using 2-bromophenylisocyanate in place of biphenylisocyanate, the title compound is prepared.

5

**Preparation 11****(2-Thien-3-ylphenyl)carbamic Acid 3-(Benzylmethylamino)-1,1-dimethylpropyl Ester**

The product of Preparation 10 (0.41 mmol) is dissolved in a 1:1 mixture of ethylene glycol dimethyl ether and *N,N*-dimethylformamide (2 mL total) and to this solution is added 3-thiopheneboronic acid (80 mg, 0.62 mmol) and aqueous potassium carbonate solution (4M, 205  $\mu$ L, 0.82 mmol). The vial is flushed with nitrogen and then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (catalytic amount) is added and the vial is sealed and heated on a shaker block at 86 °C overnight. The solvent is removed under reduced pressure and the residue is dissolved in dichloromethane and washed with aqueous sodium bisulfate (1M  $\times$  2), aqueous sodium hydroxide (1N  $\times$  2), brine ( $\times$ 1) and the organic layer is dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue is purified by silica gel chromatography to provide the title compound.

20 **Example 2****(2-Thien-3-ylphenyl)carbamic Acid 3-({9-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}methylamino)-1,1-dimethylpropyl Ester**

Using the product of Preparation 11 and the procedures of Preparation 9 and Example 1, the title is prepared.

25

**Preparation 12****Biphenyl-2-ylcarbamic Acid 3-[(2-*tert*-Butoxycarbonylaminoethyl)methylamino]-1,1-dimethylpropyl Ester**

To a stirred solution of the debenzylated product of Preparation 9 (6.76 mmol) and DIPEA (3.54 mL, 20.3 mmol) in acetonitrile (67.6 mL) at 50 °C is added 2-*tert*-butoxycarbonylaminoethyl bromide (1.82 g, 8.11 mmol) and the reaction mixture is heated at 50 °C overnight. The solvent is then removed under reduced pressure and the residue is purified by flash chromatography to yield the title compound.

**Preparation 13****Biphenyl-2-ylcarbamic Acid 3-[(2-Aminoethyl)methylamino]-1,1-dimethylpropyl Ester**

5           The product of Preparation 12 is dissolved in TFA/DCM (25%, 52 mL) and stirred at room temperature for 2 h. The solvent is then removed under reduced pressure and the residue is purified by flash chromatography to yield the title compound.

**Preparation 14****10   Biphenyl-2-ylcarbamic Acid 3-{[2-(4-Aminomethylbenzoylamino)ethyl]methylamino}-1,1-dimethylpropyl Ester**

          To a stirred solution of the product of Preparation 13 (1 mmol), 4-(*tert*-butoxycarbonylaminoethyl)benzoic acid (301 mg, 1.2 mmol) and HATU (456 mg, 1.2 mmol) in DMF (2 mL) is added DIPEA (226  $\mu$ L, 1.3 mmol). The reaction mixture is stirred at room temperature overnight and then the solvent is removed under reduced  
15   pressure. The resulting residue is dissolved in TFA/DCM (25%, 10 mL) and this mixture is stirred at room temperature for 2 h. The solvent is removed under reduced pressure and the residue is purified by flash chromatography to yield the title compound.

**20   Preparation 15****Biphenyl-2-ylcarbamic Acid 3-{[2-(4-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilyloxy)ethylamino)methyl]benzoylamino)ethyl]methylamino}-1,1-dimethylpropyl Ester**

          A solution of the product of Preparation 14 (1.1 mmol), the product of Preparation  
25   2 (634 mg, 1.3 mmol), sodium bicarbonate (277 mg, 3.3 mmol) and sodium iodide (215 mg, 1.43 mmol) in THF (0.55 mL) is heated at 80 °C for 12 h. The solvent is removed under reduced pressure and the crude residue is purified by flash chromatography to give the title compound.

**30   Preparation 16****Biphenyl-2-ylcarbamic Acid 3-{[2-(4-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino)methyl]benzoylamino)ethyl]methylamino}-1,1-dimethylpropyl ester**

To a stirred solution of the product of Preparation 15 (0.36 mmol) in dichloromethane (3.6 mL) is added triethylamine trihydrofluoride (117  $\mu$ L, 0.72 mmol). The reaction mixture is stirred for 10 h and is then diluted with dichloromethane (10 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL). The organic  
5 phase is dried ( $\text{MgSO}_4$ ) and the solvent is removed under reduced pressure to give the title compound.

### Example 3

**Biphenyl-2-ylcarbamic Acid 3-{{2-(4-{{(R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-  
10 dihydroquinolin-5-yl)ethylamino)methyl}benzoylamino)ethyl)methylamino}-1,1-  
dimethylpropyl Ester**

To a stirred solution of the product of Preparation 16 (0.36 mmol) in ethanol (3.6 mL) is added palladium (10 wt. % (dry basis) on activated carbon) (275 mg) and the reaction mixture is placed under a hydrogen atmosphere and stirred overnight. The reaction  
15 mixture is then filtered and the solvent is removed under reduced pressure. The crude residue is purified by preparative HPLC to yield the title compound as the ditrifluoroacetate salt.

### Preparation 17

20 **Methyl 4-Iodophenylacetate**

To a stirred solution of 4-iodophenylacetic acid (5.0 g, 19.1 mmol) in MeOH (200 mL) was added 4N hydrochloric acid in dioxane (10 mL). The reaction mixture was stirred for 24 h at room temperature and then the solvent was removed under reduced pressure to give the title compound (5.17 g, 98% yield), which was used without further purification.

25

### Preparation 18

**Methyl [4-(4-Hydroxybut-1-ynyl)phenyl]acetate**

To a stirred solution of the product of Preparation 17 (4.5 g, 16.3 mmol) in diethylamine (100 mL) was added but-3-yn-1-ol (1.9 mL, 32.6 mmol),  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (500  
30 mg, 1.63 mmol) and  $\text{CuI}$  (154 mg, 0.815 mmol) and resulting mixture was stirred for 17 h at room temperature. The solvent was then removed under reduced pressure and the residue was dissolved in diethyl ether (200 mL) and this solution was filtered to remove salts. The solvent was then removed under reduced pressure and the crude product was

purified by silica gel chromatography (60 % EtOAc/Hexane) to afford the title intermediate (3.03 g, 91% yield).

### Preparation 19

#### 5 Methyl [4-(4-Hydroxybutyl)phenyl]acetate .

A stirred solution of the product of Preparation 18 (2.8 g, 12.8 mmol) in methanol (50 mL) was flushed with nitrogen and then 10% palladium on carbon (400 mg, 20% wt/wt) was added. The reaction flask was then alternately placed under vacuum and flushed with hydrogen for cycles and then stirred under hydrogen for 14 h. The reaction  
10 mixture was flushed with nitrogen and then filtered and the solvent removed under reduced pressure to give the title compound (2.75 g, 97% yield), which was used without further purification.

### Preparation 20

#### 15 Methyl [4-(4-{[3-(Biphenyl-2-ylcarbamoxy)-3-methylbutyl]methylamino}butyl)-phenyl]acetate

##### (a) Methyl {4-[4-(Toluene-4-sulfonyloxy)butyl]phenyl}acetate

To a stirred solution of the product of Preparation 19 (2.6 g, 12.5 mmol) in THF (100 mL) was added DABCO (2.6 g, 25.0 mmol) and then *p*-toluenesulfonyl chloride (2.44  
20 g, 13.75 mmol). The reaction mixture was stirred at room temperature for 23 h and then solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (200 mL). The organic layer was then washed with water (2 X 100 mL), 1N hydrochloric acid (100 mL), aqueous saturated sodium chloride solution (100 mL), dried (MgSO<sub>4</sub>), filtered and the solvent removed under reduced pressure to give the title  
25 compound, which was used without further purification.

##### (b) Methyl [4-(4-{[3-(Biphenyl-2-ylcarbamoxy)-3-methylbutyl]methylamino}butyl)-phenyl]acetate

To the crude product from step (a) is added DMF (50 mL), diisopropylethylamine  
30 (3.0 mL, 17.3 mmol) and the debenzylated product of Preparation 9 (8.1 mmol). The reaction mixture is stirred at room temperature for 18 h and then the solvent is removed under reduced pressure to give the title compound.

**Preparation 21****Biphenyl-2-ylcarbamic Acid 3-({4-[4-(2-Hydroxyethyl)phenyl]butyl}methylamino)-1,1-dimethylpropyl Ester**

To a stirred solution of the product of Preparation 20 (4.0 mmol) in THF (100 mL) is added dropwise DIBAL-H (24 mL, 24 mmol, 1.0 M in THF). After the addition is complete, the reaction mixture is stirred for 3 h and then quenched by slow addition of methanol (until gas evolution ceased). The mixture is then concentrated to dryness and the residue is purified by flash chromatography to give the title compound.

10 **Example 4****Biphenyl-2-ylcarbamic Acid 3-{{4-(4-{2-[(R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenyl)butyl}methylamino}-1,1-dimethylpropyl Ester**

Using the product of Preparation 21 and the procedures of Example 1, the title compound is prepared.

**Preparation 22****Methyl 4-Amino-5-chloro-2-methoxybenzoate**

To a solution of 4-amino-5-chloro-3-methoxybenzoic acid (1.008 g, 5.0 mmol) in a mixture of toluene (9 mL) and methanol (1 mL) at 0 °C was added (trimethylsilyl)diazomethane (2.0 M in hexane, 3.0 mL, 6.0 mmol) dropwise. The reaction mixture was then warmed to room temperature and stirred for 16 h. Excess (trimethylsilyl)diazomethane was quenched by adding acetic acid until the bright yellow color of the reaction mixture disappeared. The mixture was then concentrated *in vacuo* to give the title compound as an off-white solid, which was used without further purification.

**Preparation 23****Methyl 4-Acryloylamino-5-chloro-2-methoxybenzoate**

To crude product of Preparation 22 was added dichloromethane (10 mL, 0.5 M) and triethylamine (2.1 mL, 15 mmol). This mixture was cooled to 0 °C and acryloyl chloride (812 µL, 10 mmol) was added dropwise with stirring. After 2 h, the reaction was quenched by adding methanol (about 2 mL) at 0 °C and the resulting mixture was stirred at room temperature for 15 min and then concentrated *in vacuo*. Dichloromethane (30 mL)

and water (30 mL) were added to the residue and this mixture was mixed thoroughly. The layers were separated and the aqueous layer was extracted with dichloromethane (20 mL). The organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent was removed *in vacuo* to give the title compound as a brown foamy solid.

5

**Preparation 24****Methyl 4-(3-{{3-(Biphenyl-2-ylcarbamoxyloxy)-3-methylbutyl}methylamino}propionylamino)-5-chloro-2-methoxybenzoate**

To the crude product from Preparation 23 is added the debenzylated product of Preparation 9 (4.5 mmol) and a mixture of THF (22.5 mL) and methanol (2.5 mL). This mixture is heated at 50 °C with stirring for 16 h and then the solvent is removed *in vacuo*. The residue is chromatographed to give the title compound.

**Preparation 25****15 Biphenyl-2-ylcarbamic Acid 3-{{2-(2-Chloro-4-hydroxymethyl-5-methoxy-phenylcarbamoxy)ethyl}methylamino}-1,1-dimethylpropyl Ester**

To a solution of the product of Preparation 24 (1.45 mmol) in a mixture of THF (4.5 mL) and methanol (0.5 mL) at 0 °C is added lithium borohydride (32 mg, 1.45 mmol). The reaction mixture is allowed to warm to room temperature and is stirred for 41 h. The reaction is then quenched by adding 1N aqueous hydrochloric acid at 0 °C until no more bubbling is observed and this mixture is stirred for 10 min. The solvent is removed *in vacuo* and the residue is dissolved in acetonitrile (about 2 mL). This solution is purified by prep-RP-HPLC. The appropriate fractions are collected and combined and lyophilized to give the title compound as a trifluoroacetate salt. This salt is treated with isopropyl acetate (10 mL) and 1N aqueous sodium hydroxide (10 mL) and the organic layer is collected, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent is removed *in vacuo* to give the title compound.

**Example 5****30 Biphenyl-2-ylcarbamic Acid 3-{{2-(2-Chloro-4-{{(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino}methyl}-5-methoxyphenylcarbamoxy)ethyl}methylamino}-1,1-dimethylpropyl Ester**

Using the product of Preparation 25 and the procedures of Example 1, the title compound is prepared.

**Preparation 26*****N*-{2-Benzyloxy-5-[(*R*)-2-bromo-1-(*tert*-butyldimethylsilyloxy)ethyl]phenyl}-formamide**

5           (*R*)-2-Bromo-1-(3-formamido-4-benzyloxyphenyl)ethanol (9.9 g, 28 mmol) was dissolved in dimethylformamide (36 mL). Imidazole (2.3 g, 34 mmol) and *tert*-butyldimethylsilyl chloride (4.7 g, 31 mmol) were added. The solution was stirred under nitrogen atmosphere for 72 h. Additional imidazole (0.39 g, 5.7 mmol) and *tert*-butyldimethylsilyl chloride (0.64 g, 4.3 mmol) were added and the reaction was stirred  
10 for an additional 20 h. The reaction mixture was then diluted with a mixture of isopropyl acetate (53 mL) and hexanes (27 mL) and transferred to a separatory funnel. The organic layer was washed twice with a mixture of water (27 mL) and saturated aqueous sodium chloride (27 mL) followed by a final wash with saturated aqueous sodium chloride (27 mL). The organic layer was dried over sodium sulfate. Silica gel (23.6 g) and hexanes  
15 (27 mL) were added and the suspension was stirred for 10 min. The solids were removed by filtration and the filtrate concentrated under vacuum. The residue was crystallized from hexanes (45 mL) to afford 8.85 g (19 mmol, 68 %) of the title compound as a solid. MS *m/z*: [M + H<sup>+</sup>] calcd for C<sub>22</sub>H<sub>30</sub>NO<sub>3</sub>SiBr 464.1; found 464.2.

The starting material, (*R*)-2-bromo-1-(3-formamido-4-benzyloxyphenyl)ethanol,  
20 can be prepared as described in U.S. Patent No. 6,268,533 B1; or R. Hett et al., *Organic Process Research and Development*, **1998**, 2:96-99; or using procedures similar to those described in Hong et al., *Tetrahedron Lett.*, **1994**, 35:6631; or similar to those described in U.S. Patent No. 5,495,054.

By using this compound in the examples above, additional compounds of this  
25 invention can be prepared.

**Preparation 27****6-(2-Bromo-(*R*)-1-*tert*-butyldimethylsilyloxy)ethyl-2,2-dimethyl-1,3-benzodioxan****(a) 6-Bromo-2,2-dimethyl-4H-benzo[1,3]dioxine**

30           To 5-bromo-2-hydroxybenzyl alcohol (93 g, 0.46 mol, available from Sigma-Aldrich) in 2.0 L of 2,2-dimethoxypropane was added 700 mL of acetone, followed by zinc chloride (170 g). After stirring for 18 hours, 1.0 M aqueous sodium hydroxide was added until the aqueous phase was basic. Diethyl ether (1.5 L) was added to the slurry and the

organic phase was decanted into a separatory funnel. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the title compound as an oil.

5           **(b) 6-Acetyl-2,2-dimethyl-4H-benzo[1,3]dioxine**

To the product of step (a) (110 g, 0.46 mol) in 1.0 L of THF at -78 °C was added 236 mL (0.51 mol) of 2.14 M *n*-butyllithium in hexanes via a dropping funnel. After 30 minutes, *N*-methyl-*N*-methoxy acetamide (71 g, 0.69 mol, available from TCI) was added. After 2 hours, the reaction mixture was quenched with water, diluted with 2.0 L of  
10 1.0 M aqueous phosphate buffer (pH = 7.0) and extracted once with diethyl ether. The diethyl ether phase was washed once with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a light orange oil. The oil was dissolved in a minimum volume of ethyl acetate, diluted with hexanes, and to give the title compound as a crystalline solid.

15

**(c) 6-Bromoacetyl-2,2-dimethyl-4H-benzo[1,3]dioxine**

To the product of step (b) (23.4 g, 0.113 mol) in 600 mL of THF at -78 °C was added 135 mL of 1.0 M sodium hexamethyldisilazane in THF (Sigma-Aldrich). After 1 hour, trimethylsilyl chloride (15.8 mL, 0.124 mol) was added. After another 30 minutes,  
20 bromine (5.82 mL, 0.113 mol) was added. After 10 minutes, the reaction was quenched by diluting the reaction mixture with diethyl ether and pouring it onto 500 mL of 5% aqueous Na<sub>2</sub>SO<sub>3</sub> premixed with 500 mL of 5% aqueous NaHCO<sub>3</sub>. The phases were separated and the organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the title compound as an oil that solidified upon storage in  
25 the freezer.

**(d) (*R*)-2-Bromo-1-(2,2-dimethyl-4H-benzo[1,3]dioxin-6-yl)ethanol**

To the product of step (c) (10 g, 35.1 mmol) in 100 mL of THF was added the solid catalyst of Preparation 13, step (c)(1) (0.97 g, 3.5 mmol). The solution was cooled to  
30 between -20 °C and -10 °C and BH<sub>3</sub>-THF (35 mL, 35 mmol) diluted with 50 mL THF was added dropwise via a dropping funnel. After the addition was complete, the reaction mixture was allowed to warm to ambient temperature. After 30 minutes, the reaction mixture was quenched by slow addition of 50 mL of methanol and then concentrated to a



thick oil. The oil was purified by silica gel chromatography eluted with 1:2 ethyl acetate/hexanes. The fractions were combined and concentrated to give the title compound as an off-white solid.

5           (e)     **[(R)-2-Bromo-1-(2,2-dimethyl-4H-benzo[1,3]dioxin-6-yl)ethoxy]-tert-butyl dimethylsilane**

To the product of step (d) (10 g, 34.8 mmol) and imidazole (4.7 g, 69.7 mmol) dissolved in 100 mL DMF was added *tert*-butyldimethylsilyl chloride (5.78 g, 38.3 mmol). The reaction mixture was stirred for 18 hours. The reaction mixture was then partitioned  
10 between 200 mL of saturated sodium chloride and 200 mL of diethyl ether. The aqueous layer was extracted with 200 mL of diethyl ether. The organic layers were then combined, washed with saturated sodium chloride (3 x 100 mL), dried over MgSO<sub>4</sub> and concentrated. The product was purified by silica gel chromatography, eluting with hexanes followed by 5% ethyl acetate in hexanes. The desired fractions were combined and concentrated to  
15 give the title compound as an oil.

By using this compound in the examples above, additional compounds of this invention can be prepared.

### Preparation A

20     **Cell Culture and Membrane Preparation From Cells Expressing Human  $\beta_1$ ,  $\beta_2$  or  $\beta_3$  Adrenergic Receptors**

Chinese hamster ovarian (CHO) cell lines stably expressing cloned human  $\beta_1$ ,  $\beta_2$  or  $\beta_3$  adrenergic receptors, respectively, were grown to near confluency in Hams F-12 media with 10% FBS in the presence of 500  $\mu$ g/mL Geneticin. The cell monolayer was lifted  
25 with 2mM EDTA in PBS. Cells were pelleted by centrifugation at 1,000 rpm, and cell pellets were either stored frozen at  $-80$  °C or membranes were prepared immediately for use. For preparation of  $\beta_1$  and  $\beta_2$  receptor expressing membranes, cell pellets were re-suspended in lysis buffer (10 mM HEPES/HCl, 10mM EDTA, pH 7.4 at 4°C) and homogenized using a tight-fitting Dounce glass homogenizer (30 strokes) on ice. For the  
30 more protease-sensitive  $\beta_3$  receptor expressing membranes, cell pellets were homogenated in lysis buffer (10mM Tris/HCl, pH 7.4) supplemented with one tablet of "Complete Protease Inhibitor Cocktail Tablets with 2 mM EDTA" per 50 mL buffer (Roche Catalog No. 1697498, Roche Molecular Biochemicals, Indianapolis, IN). The homogenate was

centrifuged at 20,000 x g, and the resulting pellet was washed once with lysis buffer by re-suspension and centrifugation as above. The final pellet was then re-suspended in ice-cold binding assay buffer (75 mM Tris/HCl pH 7.4, 12.5mM MgCl<sub>2</sub>, 1 mM EDTA). The protein concentration of the membrane suspension was determined by the methods  
5 described in Lowry et al., **1951**, *Journal of Biological Chemistry*, **193**, 265; and Bradford, *Analytical Biochemistry*, **1976**, **72**, 248-54. All membranes were stored frozen in aliquots at -80 °C or used immediately.

### **Preparation B**

#### **10 Cell Culture and Membrane Preparation From Cells Expressing Human M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub> and M<sub>4</sub> Muscarinic Receptors**

CHO cell lines stably expressing cloned human hM<sub>1</sub>, hM<sub>2</sub>, hM<sub>3</sub> and hM<sub>4</sub> muscarinic receptor subtypes, respectively, were grown to near confluency in HAM's F-12 media supplemented with 10% FBS and 250 µg/mL Geneticin. The cells were grown in a 5%  
15 CO<sub>2</sub>, 37 °C incubator and lifted with 2 mM EDTA in dPBS. Cells were collected by 5 minute centrifugation at 650 x g, and cell pellets were either stored frozen at -80 °C or membranes were prepared immediately for use. For membrane preparation, cell pellets were resuspended in lysis buffer and homogenized with a Polytron PT-2100 tissue disrupter (Kinematica AG; 20 seconds x 2 bursts). Crude membranes were centrifuged at  
20 40,000 x g for 15 minutes at 4°C. The membrane pellet was then resuspended with re-suspension buffer and homogenized again with the Polytron tissue disrupter. The protein concentration of the membrane suspension was determined by the method described in Lowry et al., **1951**, *Journal of Biochemistry*, **193**, 265. All membranes were stored frozen in aliquots at -80 °C or used immediately. Aliquots of prepared hM<sub>5</sub> receptor membranes  
25 were purchased directly from Perkin Elmer and stored at -80 °C until use.

### **Assay Test Procedure A**

#### **Radioligand Binding Assay for Human β<sub>1</sub>, β<sub>2</sub> and β<sub>3</sub> Adrenergic Receptors**

Binding assays were performed in 96-well microtiter plates in a total assay volume  
30 of 100 µL with 10-15 µg of membrane protein containing the human β<sub>1</sub>, β<sub>2</sub> or β<sub>3</sub> adrenergic receptors in assay buffer (75 mM Tris/HCl pH 7.4 at 25°C, 12.5 mM MgCl<sub>2</sub>, 1 mM EDTA, 0.2% BSA). Saturation binding studies for determination of K<sub>d</sub> values of the radioligand were done using [<sup>3</sup>H]-dihydroalprenolol (NET-720, 100 Ci/mmol, PerkinElmer Life

Sciences Inc., Boston, MA) for the  $\beta_1$  and  $\beta_2$  receptors and [ $^{125}$ I]-(-)-iodocyanopindolol (NEX-189, 220 Ci/mmol, PerkinElmer Life Sciences Inc., Boston, MA) at 10 or 11 different concentrations ranging from 0.01 nM to 20 nM. Displacement assays for determination of  $K_i$  values of test compounds were done with [ $^3$ H]-dihydroalprenolol at 1 nM and [ $^{125}$ I]-(-)-iodocyanopindolol at 0.5 nM for 10 or 11 different concentrations of test compound ranging from 10 pM to 10  $\mu$ M. Non-specific binding was determined in the presence of 10  $\mu$ M propranolol. Assays were incubated for 1 hour at 37°C, and then binding reactions were terminated by rapid filtration over GF/B for the  $\beta_1$  and  $\beta_2$  receptors or GF/C glass fiber filter plates for the  $\beta_3$  receptors (Packard BioScience Co., Meriden, CT) presoaked in 0.3% polyethyleneimine. Filter plates were washed three times with filtration buffer (75 mM Tris/HCl pH 7.4 at 4°C, 12.5 mM MgCl<sub>2</sub>, 1 mM EDTA) to remove unbound radioactivity. The plates were then dried and 50  $\mu$ L of Microscint-20 liquid scintillation fluid (Packard BioScience Co., Meriden, CT) was added and plates were counted in a Packard Topcount liquid scintillation counter (Packard BioScience Co., Meriden, CT). Binding data were analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the 3-parameter model for one-site competition. The curve minimum was fixed to the value for nonspecific binding, as determined in the presence of 10  $\mu$ M propranolol.  $K_i$  values for test compounds were calculated from observed IC<sub>50</sub> values and the  $K_d$  value of the radioligand using the Cheng-Prusoff equation (Cheng Y, and Prusoff WH., *Biochemical Pharmacology*, 1973, 22, 23, 3099-108).

In this assay, a lower  $K_i$  value indicates that a test compound has a higher binding affinity for the receptor tested. Exemplified compound of this invention that were tested in this assay typically were found to have a  $K_i$  value of less than about 300 nM for the  $\beta_2$  adrenergic receptor. For example, the compound of Example 1 was found to have  $K_i$  values of less than 300 nM.

If desired, the receptor subtype selectivity for a test compound can be calculated as the ratio of  $K_i(\beta_1)/K_i(\beta_2)$  or  $K_i(\beta_3)/K_i(\beta_2)$ . Typically, compounds of this invention demonstrated greater binding at the  $\beta_2$  adrenergic receptor compared to the  $\beta_1$  or  $\beta_3$  adrenergic receptor, i.e.  $K_i(\beta_1)$  or  $K_i(\beta_3)$  is typically greater than  $K_i(\beta_2)$ . Generally, compounds having selectivity for the  $\beta_2$  adrenergic receptor over the  $\beta_1$  or  $\beta_3$  adrenergic receptors are preferred; especially compounds having a selectivity greater than about 5.

## Assay Test Procedure B

### Radioligand Binding Assay for Muscarinic Receptors

Radioligand binding assays for cloned human muscarinic receptors were performed in 96-well microtiter plates in a total assay volume of 100  $\mu$ L. CHO cell membranes stably expressing either the hM<sub>1</sub>, hM<sub>2</sub>, hM<sub>3</sub>, hM<sub>4</sub> or hM<sub>5</sub> muscarinic subtype were diluted in assay buffer to the following specific target protein concentrations ( $\mu$ g/well): 10  $\mu$ g for hM<sub>1</sub>, 10-15  $\mu$ g for hM<sub>2</sub>, 10-20  $\mu$ g for hM<sub>3</sub>, 10-20  $\mu$ g for hM<sub>4</sub>, and 10-12  $\mu$ g for hM<sub>5</sub> to get similar signals (cpm). The membranes were briefly homogenized using a Polytron tissue disruptor (10 seconds) prior to assay plate addition. Saturation binding studies for determining  $K_D$  values of the radioligand were performed using L-[N-methyl-<sup>3</sup>H]scopolamine methyl chloride ([<sup>3</sup>H]-NMS) (TRK666, 84.0 Ci/mmol, Amersham Pharmacia Biotech, Buckinghamshire, England) at concentrations ranging from 0.001 nM to 20 nM. Displacement assays for determination of  $K_i$  values of test compounds were performed with [<sup>3</sup>H]-NMS at 1 nM and eleven different test compound concentrations. The test compounds were initially dissolved to a concentration of 400  $\mu$ M in dilution buffer and then serially diluted 5x with dilution buffer to final concentrations ranging from 10 pM to 100  $\mu$ M. The addition order and volumes to the assay plates were as follows: 25  $\mu$ L radioligand, 25  $\mu$ L diluted test compound, and 50  $\mu$ L membranes. Assay plates were incubated for 60 minutes at 37°C. Binding reactions were terminated by rapid filtration over GF/B glass fiber filter plates (PerkinElmer Inc., Wellesley, MA) pre-treated in 1% BSA. Filter plates were rinsed three times with wash buffer (10 mM HEPES) to remove unbound radioactivity. The plates were then air dried and 50  $\mu$ L Microscint-20 liquid scintillation fluid (PerkinElmer Inc., Wellesley, MA) was added to each well. The plates were then counted in a PerkinElmer Topcount liquid scintillation counter (PerkinElmer Inc., Wellesley, MA). Binding data were analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the one-site competition model.  $K_i$  values for test compounds were calculated from observed IC<sub>50</sub> values and the  $K_D$  value of the radioligand using the Cheng-Prusoff equation (Cheng Y; Prusoff WH. (1973) *Biochemical Pharmacology*, 22(23):3099-108).  $K_i$  values were converted to pK<sub>i</sub> values to determine the geometric mean and 95% confidence intervals. These summary statistics were then converted back to  $K_i$  values for data

reporting.

In this assay, a lower  $K_i$  value indicates that the test compound has a higher binding affinity for the receptor tested. Exemplified compound of this invention that were tested in this assay typically were found to have a  $K_i$  value of less than about 300 nM for the  $M_3$  muscarinic receptor. For example, the compound of Example 1 was found to have  $K_i$  values of less than 300 nM for the  $M_3$  muscarinic receptor.

### Assay Test Procedure C

#### Whole-cell cAMP Flashplate Assay in CHO Cell Lines Heterologously Expressing Human $\beta_1$ , $\beta_2$ or $\beta_3$ Adrenergic Receptors

cAMP assays are performed in a radioimmunoassay format using the Flashplate Adenylyl Cyclase Activation Assay System with [ $^{125}$ I]-cAMP (NEN SMP004, PerkinElmer Life Sciences Inc., Boston, MA), according to the manufacturers instructions. For the determination of  $\beta$  receptor agonist potency ( $EC_{50}$ ), CHO-K1 cell lines stably expressing cloned human  $\beta_1$ ,  $\beta_2$  or  $\beta_3$  adrenergic receptors are grown to near confluency in HAM's F-12 media supplemented with 10% FBS and Geneticin (250  $\mu$ g/mL). Cells are rinsed with PBS and detached in dPBS (Dulbecco's Phosphate Buffered Saline, without  $CaCl_2$  and  $MgCl_2$ ) containing 2 mM EDTA or Trypsin-EDTA solution (0.05% trypsin/0.53 mM EDTA). After counting cells in Coulter cell counter, cells are pelleted by centrifugation at 1,000 rpm and re-suspended in stimulation buffer containing IBMX (PerkinElmer Kit) pre-warmed to room temperature to a concentration of  $1.6 \times 10^6$  to  $2.8 \times 10^6$  cells/mL. About 60,000 to 80,000 cells per well are used in this assay. Test compounds (10 mM in DMSO) are diluted into PBS containing 0.1% BSA in Beckman Biomek-2000 and tested at 11 different concentrations ranging from 100  $\mu$ M to 1 pM. Reactions are incubated for 10 min at 37 °C and stopped by adding 100  $\mu$ L of cold detection buffer containing [ $^{125}$ I]-cAMP (NEN SMP004, PerkinElmer Life Sciences, Boston, MA). The amount of cAMP produced (pmol/well) is calculated based on the counts observed for the samples and cAMP standards as described in the manufacturer's user manual. Data are analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) with the sigmoidal equation. The Cheng-Prusoff equation (Cheng Y, and Prusoff WH., *Biochemical Pharmacology*, 1973, 22, 23, 3099-108) is used to calculate the  $EC_{50}$  values.

In this assay, a lower EC<sub>50</sub> value indicates that the test compound has a higher functional activity at the receptor tested. When tested in this assay, compound of this invention are expected to have a EC<sub>50</sub> value of less than about 300 nM for the β<sub>2</sub> adrenergic receptor.

5 If desired, the receptor subtype selectivity for a test compound can be calculated as the ratio of EC<sub>50</sub>(β<sub>1</sub>)/EC<sub>50</sub>(β<sub>2</sub>) or EC<sub>50</sub>(β<sub>3</sub>)/EC<sub>50</sub>(β<sub>2</sub>). Typically, compounds of this invention demonstrated greater functional activity at the β<sub>2</sub> adrenergic receptor compared to the β<sub>1</sub> or β<sub>3</sub> adrenergic receptor, i.e. EC<sub>50</sub>(β<sub>1</sub>) or EC<sub>50</sub>(β<sub>3</sub>) is typically greater than EC<sub>50</sub>(β<sub>2</sub>). Generally, compounds having selectivity for the β<sub>2</sub> adrenergic receptor over the  
10 β<sub>1</sub> or β<sub>3</sub> adrenergic receptors are preferred; especially compounds having a selectivity greater than about 5; and in particular, greater than about 10.

#### Assay Test Procedure D

##### Functional Assays of Antagonism for Muscarinic Receptor Subtypes

###### 15 A. Blockade of Agonist-Mediated Inhibition of cAMP Accumulation

In this assay, the functional potency of a test compound is determined by measuring the ability of the test compound to block oxotremorine-inhibition of forskolin-mediated cAMP accumulation in CHO-K1 cells expressing the hM<sub>2</sub> receptor. cAMP assays are performed in a radioimmunoassay format using the Flashplate Adenylyl Cyclase  
20 Activation Assay System with <sup>125</sup>I-cAMP (NEN SMP004B, PerkinElmer Life Sciences Inc., Boston, MA), according to the manufacturer's instructions. Cells are rinsed once with dPBS and lifted with Trypsin-EDTA solution (0.05% trypsin/0.53 mM EDTA) as described in the Cell Culture and Membrane Preparation section above. The detached cells are washed twice by centrifugation at 650 x g for five minutes in 50 mL dPBS. The cell  
25 pellet is then re-suspended in 10 mL dPBS, and the cells are counted with a Coulter Z1 Dual Particle Counter (Beckman Coulter, Fullerton, CA). The cells are centrifuged again at 650 x g for five minutes and re-suspended in stimulation buffer to an assay concentration of 1.6 x 10<sup>6</sup> – 2.8 x 10<sup>6</sup> cells/mL.

The test compound is initially dissolved to a concentration of 400 μM in dilution  
30 buffer (dPBS supplemented with 1 mg/mL BSA (0.1%)), and then serially diluted with dilution buffer to final molar concentrations ranging from 100 μM to 0.1 nM. Oxotremorine is diluted in a similar manner.

To measure oxotremorine inhibition of adenylyl cyclase (AC) activity, 25  $\mu$ L forskolin (25  $\mu$ M final concentration diluted in dPBS), 25  $\mu$ L diluted oxotremorine, and 50  $\mu$ L cells are added to agonist assay wells. To measure the ability of a test compound to block oxotremorine-inhibited AC activity, 25  $\mu$ L forskolin and oxotremorine (25  $\mu$ M and 5  $\mu$ M final concentrations, respectively, diluted in dPBS), 25  $\mu$ L diluted test compound, and 50  $\mu$ L cells are added to remaining assay wells.

Reactions are incubated for 10 minutes at 37 °C and stopped by addition of 100  $\mu$ L ice-cold detection buffer. Plates are sealed, incubated overnight at room temperature and counted the next morning on a PerkinElmer TopCount liquid scintillation counter (PerkinElmer Inc., Wellesley, MA). The amount of cAMP produced (pmol/well) is calculated based on the counts observed for the samples and cAMP standards, as described in the manufacturer's user manual. Data is analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the non-linear regression, one-site competition equation. The Cheng-Prusoff equation is used to calculate the  $K_i$ , using the  $EC_{50}$  of the oxotremorine concentration-response curve and the oxotremorine assay concentration as the  $K_D$  and [L], respectively.

In this assay, a lower  $K_i$  value indicates that the test compound has a higher functional activity at the receptor tested. When tested in this assay, compounds of this invention are expected to have a  $K_i$  value of less than about 300 nM for blockade of oxotremorine-inhibition of forskolin-mediated cAMP accumulation in CHO-K1 cells expressing the hM<sub>2</sub> receptor.

#### **B. Blockade of Agonist-Mediated [<sup>35</sup>S]GTP $\gamma$ S Binding**

In a second functional assay, the functional potency of test compounds can be determined by measuring the ability of the compounds to block oxotremorine-stimulated [<sup>35</sup>S]GTP $\gamma$ S binding in CHO-K1 cells expressing the hM<sub>2</sub> receptor.

At the time of use, frozen membranes are thawed and then diluted in assay buffer with a final target tissue concentration of 5-10  $\mu$ g protein per well. The membranes are briefly homogenized using a Polytron PT-2100 tissue disrupter and then added to the assay plates.

The  $EC_{90}$  value (effective concentration for 90% maximal response) for stimulation of [<sup>35</sup>S]GTP $\gamma$ S binding by the agonist oxotremorine is determined in each experiment.

To determine the ability of a test compound to inhibit oxotremorine-stimulated [<sup>35</sup>S]GTP $\gamma$ S binding, the following is added to each well of 96 well plates: 25  $\mu$ L of assay buffer with [<sup>35</sup>S]GTP $\gamma$ S (0.4nM), 25  $\mu$ L of oxotremorine(EC<sub>90</sub>) and GDP (3 $\mu$ M), 25  $\mu$ L of diluted test compound and 25  $\mu$ L CHO cell membranes expressing the hM<sub>2</sub> receptor. The assay plates are then incubated at 37 °C for 60 minutes. The assay plates are filtered over 1% BSA-pretreated GF/B filters using a PerkinElmer 96-well harvester. The plates are rinsed with ice-cold wash buffer for 3 x 3 seconds and then air or vacuum dried. Microscint-20 scintillation liquid (50  $\mu$ L) is added to each well, and each plate is sealed and radioactivity counted on a Topcounter (PerkinElmer). Data are analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the non-linear regression, one-site competition equation. The Cheng-Prusoff equation is used to calculate the K<sub>i</sub>, using the IC<sub>50</sub> values of the concentration-response curve for the test compound and the oxotremorine concentration in the assay as the K<sub>D</sub> and [L], ligand concentration, respectively.

In this assay, a lower K<sub>i</sub> value indicates that the test compound has a higher functional activity at the receptor tested. When tested in this assay, compounds of this invention are expected to have a K<sub>i</sub> value of less than about 300 nM for blockade of oxotremorine-stimulated [<sup>35</sup>S]GTP $\gamma$ S binding in CHO-K1 cells expressing the hM<sub>2</sub> receptor.

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### C. Blockade of Agonist-Mediated Calcium Release via FLIPR Assays

Muscarinic receptor subtypes (M<sub>1</sub>, M<sub>3</sub> and M<sub>5</sub> receptors), which couple to G<sub>q</sub> proteins, activate the phospholipase C (PLC) pathway upon agonist binding to the receptor. As a result, activated PLC hydrolyzes phosphatyl inositol diphosphate (PIP<sub>2</sub>) to diacylglycerol (DAG) and phosphatidyl-1,4,5-triphosphate (IP<sub>3</sub>), which in turn generates calcium release from intracellular stores, i.e., endoplasmic and sarcoplasmic reticulum. The FLIPR (Molecular Devices, Sunnyvale, CA) assay capitalizes on this increase in intracellular calcium by using a calcium sensitive dye (Fluo-4AM, Molecular Probes, Eugene, OR) that fluoresces when free calcium binds. This fluorescence event is measured in real time by the FLIPR, which detects the change in fluorescence from a monolayer of cells cloned with human M<sub>1</sub> and M<sub>3</sub>, and chimpanzee M<sub>5</sub> receptors. Antagonist potency can be determined by the ability of antagonists to inhibit agonist-mediated increases in intracellular calcium.

30



For FLIPR calcium stimulation assays, CHO cells stably expressing the hM<sub>1</sub>, hM<sub>3</sub> and cM<sub>5</sub> receptors are seeded into 96-well FLIPR plates the night before the assay is done. Seeded cells are washed twice by Cellwash (MTX Labsystems, Inc.) with FLIPR buffer (10 mM HEPES, pH 7.4, 2 mM calcium chloride, 2.5 mM probenecid in Hank's Buffered  
5 Salt Solution (HBSS) without calcium and magnesium) to remove growth media and leaving 50 µL/well of FLIPR buffer. The cells are then incubated with 50 µL/well of 4 µM FLUO-4AM (a 2X solution was made) for 40 minutes at 37 °C, 5% carbon dioxide. Following the dye incubation period, cells are washed two times with FLIPR buffer, leaving a final volume of 50 µL/well.

10 To determine antagonist potency, the dose-dependent stimulation of intracellular Ca<sup>2+</sup> release for oxotremorine is first determined so that antagonist potency can later be measured against oxotremorine stimulation at an EC<sub>90</sub> concentration. Cells are first incubated with compound dilution buffer for 20 minutes, followed by agonist addition, which is performed by the FLIPR. An EC<sub>90</sub> value for oxotremorine is generated according  
15 to the method detailed in the FLIPR measurement and data reduction section below, in conjunction with the formula  $EC_F = ((F/100-F)^{1/H}) * EC_{50}$ . An oxotremorine concentration of 3 x EC<sub>F</sub> is prepared in stimulation plates such that an EC<sub>90</sub> concentration of oxotremorine is added to each well in the antagonist inhibition assay plates.

The parameters used for the FLIPR are: exposure length of 0.4 seconds, laser  
20 strength of 0.5 watts, excitation wavelength of 488 nm, and emission wavelength of 550 nm. Baseline is determined by measuring the change in fluorescence for 10 seconds prior to addition of agonist. Following agonist stimulation, the FLIPR continuously measured the change of fluorescence every 0.5 to 1 second for 1.5 minutes to capture the maximum fluorescence change.

25 The change of fluorescence is expressed as maximum fluorescence minus baseline fluorescence for each well. The raw data is analysed against the logarithm of drug concentration by nonlinear regression with GraphPad Prism (GraphPad Software, Inc., San Diego, CA) using the built-in model for sigmoidal dose-response. Antagonist K<sub>i</sub> values are determined by Prism using the oxotremorine EC<sub>50</sub> value as the K<sub>D</sub> and the oxotremorine  
30 EC<sub>90</sub> for the ligand concentration according to the Cheng-Prusoff equation (Cheng & Prusoff, 1973).

In this assay, a lower K<sub>i</sub> value indicates that the test compound has a higher functional activity at the receptor tested. When tested in this assay, compounds of this

invention are expected to have a  $K_i$  value of less than about 300 nM for blockade of agonist-mediated calcium release in CHO cells stably expressing the  $hM_1$ ,  $hM_3$  and  $cM_5$  receptors.

## 5 Assay Test Procedure E

### Whole-cell cAMP Flashplate Assay With a Lung Epithelial Cell Line Endogenously Expressing Human $\beta_2$ Adrenergic Receptor

For the determination of agonist potencies and efficacies (intrinsic activities) in a cell line expressing endogenous levels of the  $\beta_2$  adrenergic receptor, a human lung epithelial cell line (BEAS-2B) is used (ATCC CRL-9609, American Type Culture Collection, Manassas, VA) (January B, et al., *British Journal of Pharmacology*, 1998, 123, 4, 701-11). Cells are grown to 75-90% confluency in complete, serum-free medium (LHC-9 MEDIUM containing Epinephrine and Retinoic Acid, cat # 181-500, Biosource International, Camarillo, CA). The day before the assay, medium is switched to LHC-8 (no epinephrine or retinoic acid, cat # 141-500, Biosource International, Camarillo, CA). cAMP assays are performed in a radioimmunoassay format using the Flashplate Adenylyl Cyclase Activation Assay System with [ $^{125}$ I]-cAMP (NEN SMP004, PerkinElmer Life Sciences Inc., Boston, MA), according to the manufacturers instructions.

On the day of the assay, cells are rinsed with PBS, lifted by scraping with 5mM EDTA in PBS, and counted. Cells are pelleted by centrifugation at 1,000 rpm and re-suspended in stimulation buffer pre-warmed to 37 °C at a final concentration of 600,000 cells/mL. Cells are used at a final concentration of 100,000 to 120,000 cells/well in this assay. Test compounds are serially diluted into assay buffer (75 mM Tris/HCl pH 7.4 at 25°C, 12.5 mM  $MgCl_2$ , 1 mM EDTA, 0.2% BSA) in Beckman Biomek-2000. Test compounds are tested in the assay at 11 different concentrations, ranging from 10  $\mu$ M to 10 pM. Reactions are incubated for 10 min at 37 °C and stopped by addition of 100  $\mu$ L of ice-cold detection buffer. Plates are sealed, incubated over night at 4 °C and counted the next morning in a Topcount scintillation counter (Packard BioScience Co., Meriden, CT). The amount of cAMP produced per mL of reaction is calculated based on the counts observed for samples and cAMP standards, as described in the manufacturer's user manual. Data are analyzed by nonlinear regression analysis with the GraphPad Prism Software package

(GraphPad Software, Inc., San Diego, CA) using the 4-parameter model for sigmoidal dose-response.

In this assay, a lower EC<sub>50</sub> value indicates that the test compound has a higher functional activity at the receptor tested. When tested in this assay, compounds of this invention are expected to have an EC<sub>50</sub> value of less than about 300 nM for the  $\beta_2$  adrenergic receptor.

If desired, test compound efficacy (%Eff) is calculated from the ratio of the observed Emax (TOP of the fitted curve) and the maximal response obtained for isoproterenol dose response curve and is expressed as %Eff relative to isoproterenol. Compounds of this invention are expected to demonstrate a %Eff greater than about 40.

#### Assay Test Procedure F

##### Duration of Bronchoprotection In Guinea Pig Models of Acetylcholine-Induced or Histamine-Induced Bronchoconstriction

These *in vivo* assays are used to assess the bronchoprotective effects of test compounds exhibiting both muscarinic receptor antagonist and  $\beta_2$  adrenergic receptor agonist activity. To isolate muscarinic antagonist activity in the acetylcholine-induced bronchoconstriction model, the animals are administered propranolol, a compound that blocks  $\beta$  receptor activity, prior to the administration of acetylcholine. Duration of bronchoprotection in the histamine-induced bronchoconstriction model reflects  $\beta_2$  adrenergic receptor agonist activity.

Groups of 6 male guinea pigs (Duncan-Hartley (HsdPoc:DH) Harlan, Madison, WI) weighing between 250 and 350 g are individually identified by cage cards. Throughout the study, animals are allowed access to food and water *ad libitum*.

Test compounds are administered *via* inhalation over 10 minutes in a whole-body exposure dosing chamber (R&S Molds, San Carlos, CA). The dosing chambers are arranged so that an aerosol is simultaneously delivered to 6 individual chambers from a central manifold. Guinea pigs are exposed to an aerosol of a test compound or vehicle (WFI). These aerosols are generated from aqueous solutions using an LC Star Nebulizer Set (Model 22F51, PARI Respiratory Equipment, Inc. Midlothian, VA) driven by a mixture of gases (CO<sub>2</sub> = 5%, O<sub>2</sub> = 21% and N<sub>2</sub> = 74%) at a pressure of 22 psi. The gas flow through the nebulizer at this operating pressure is approximately 3 L/ minute. The generated aerosols are driven into the chambers by positive pressure. No dilution air

is used during the delivery of aerosolized solutions. During the 10 minute nebulization, approximately 1.8 mL of solution is nebulized. This value is measured gravimetrically by comparing pre-and post-nebulization weights of the filled nebulizer.

The bronchoprotective effects of test compounds administered *via* inhalation are  
5 evaluated using whole body plethysmography at 1.5, 24, 48 and 72 hours post-dose.

Forty-five minutes prior to the start of the pulmonary evaluation, each guinea pig is anesthetized with an intramuscular injection of ketamine (43.75 mg/kg), xylazine (3.50 mg/kg) and acepromazine (1.05 mg/kg). After the surgical site is shaved and cleaned with 70% alcohol, a 2-3 cm midline incision of the ventral aspect of the neck is made.  
10 Then, the jugular vein is isolated and cannulated with a saline-filled polyethylene catheter (PE-50, Becton Dickinson, Sparks, MD) to allow for intravenous infusions of acetylcholine (Ach) or histamine in saline. The trachea is then dissected free and cannulated with a 14G teflon tube (#NE- 014, Small Parts, Miami Lakes, FL). If required, anesthesia is maintained by additional intramuscular injections of the aforementioned anesthetic  
15 mixture. The depth of anesthesia is monitored and adjusted if the animal responds to pinching of its paw or if the respiration rate is greater than 100 breaths/minute.

Once the cannulations are completed, the animal is placed into a plethysmograph (#PLY3114, Buxco Electronics, Inc., Sharon, CT) and an esophageal pressure cannula (PE-160, Becton Dickinson, Sparks, MD) is inserted to measure pulmonary driving  
20 pressure (*pressure*). The teflon tracheal tube is attached to the opening of the plethysmograph to allow the guinea pig to breathe room air from outside the chamber. The chamber is then sealed. A heating lamp is used to maintain body temperature and the guinea pig's lungs are inflated 3 times with 4 mL of air using a 10 mL calibration syringe (#5520 Series, Hans Rudolph, Kansas City, MO) to ensure that the lower airways did not  
25 collapse and that the animal did not suffer from hyperventilation.

Once it was determined that baseline values are within the range of 0.3 - 0.9 mL/cm H<sub>2</sub>O for compliance and within the range of 0.1 - 0.199 cm H<sub>2</sub>O/mL per second for resistance, the pulmonary evaluation is initiated. A Buxco pulmonary measurement computer program enabled the collection and derivation of pulmonary values.  
30

Starting this program initiated the experimental protocol and data collection. The changes in volume over time that occur within the plethysmograph with each breath are measured *via* a Buxco pressure transducer. By integrating this signal over time, a measurement of *flow* is calculated for each breath. This signal, together with the

pulmonary driving *pressure* changes, which are collected using a Sensym pressure transducer (#TRD4100), is connected *via* a Buxco (MAX 2270) preamplifier to a data collection interface (#'s SFT3400 and SFT3813). All other pulmonary parameters are derived from these two inputs.

5 Baseline values are collected for 5 minutes, after which time the guinea pigs are challenged with Ach or histamine. When evaluating the muscarinic antagonist effects, propranolol (5 mg/Kg, iv) (Sigma-Aldrich, St. Louis, MO) is administered 15 minutes prior to challenge with Ach. Ach (Sigma-Aldrich, St. Louis, MO) (0.1 mg/mL) is infused intravenously for 1 minute from a syringe pump (sp210iw, World Precision Instruments,  
10 Inc., Sarasota, FL) at the following doses and prescribed times from the start of the experiment: 1.9  $\mu\text{g}/\text{minute}$  at 5 minutes, 3.8  $\mu\text{g}/\text{minute}$  at 10 minutes, 7.5  $\mu\text{g}/\text{minute}$  at 15 minutes, 15.0  $\mu\text{g}/\text{minute}$  at 20 minutes, 30  $\mu\text{g}/\text{minute}$  at 25 minutes and 60  $\mu\text{g}/\text{minute}$  at 30 minutes. Alternatively, bronchoprotection of test compounds is assessed in the acetylcholine challenge model without pretreatment with a beta blocking compound.

15 When evaluating the  $\beta_2$  adrenergic receptor agonist effects of test compounds, histamine (25  $\mu\text{g}/\text{mL}$ ) (Sigma-Aldrich, St. Louis, MO) is infused intravenously for 1 minute from a syringe pump at the following doses and prescribed times from the start of the experiment: 0.5  $\mu\text{g}/\text{minute}$  at 5 minutes, 0.9  $\mu\text{g}/\text{minute}$  at 10 minutes, 1.9  $\mu\text{g}/\text{minute}$  at 15 minutes, 3.8  $\mu\text{g}/\text{minute}$  at 20 minutes, 7.5  $\mu\text{g}/\text{minute}$  at 25 minutes and 15  $\mu\text{g}/\text{minute}$  at  
20 30 minutes. If resistance or compliance does not returned to baseline values at 3 minutes following each Ach or histamine dose, the guinea pig's lungs are inflated 3 times with 4 mL of air from a 10 mL calibration syringe. Recorded pulmonary parameters include respiration frequency (breaths/minute), compliance (mL/cm H<sub>2</sub>O) and pulmonary resistance (cm H<sub>2</sub>O/ mL per second). Once the pulmonary function measurements are  
25 completed at minute 35 of this protocol, the guinea pig is removed from the plethysmograph and euthanized by carbon dioxide asphyxiation.

The data are evaluated in one of two ways:

(a) Pulmonary resistance ( $R_L$ , cm H<sub>2</sub>O/mL per second) is calculated from the ratio of "change in pressure" to "the change in flow." The  $R_L$  response to ACh (60  $\mu\text{g}/\text{min}$ ,  
30 IH) is computed for the vehicle and the test compound groups. The mean ACh response in vehicle-treated animals, at each pre-treatment time, is calculated and used to compute % inhibition of ACh response, at the corresponding pre-treatment time, at each test compound dose. Inhibition dose-response curves for ' $R_L$ ' were fitted with a four parameter logistic

equation using GraphPad Prism, version 3.00 for Windows (GraphPad Software, San Diego, California) to estimate bronchoprotective ID<sub>50</sub> (dose required to inhibit the ACh (60 µg/min) bronchoconstrictor response by 50%). The equation used is as follows:

$$5 \quad Y = \text{Min} + (\text{Max} - \text{Min}) / (1 + 10^{((\log \text{ID}_{50} - X) * \text{Hillslope})})$$

where X is the logarithm of dose, Y is the response (% Inhibition of ACh induced increase in R<sub>L</sub>). Y starts at Min and approaches asymptotically to Max with a sigmoidal shape.

(b) The quantity PD<sub>2</sub>, which is defined as the amount of Ach or histamine needed to cause a doubling of the baseline pulmonary resistance, is calculated using the pulmonary resistance values derived from the *flow* and the *pressure* over a range of Ach or histamine challenges using the following equation (which was derived from an equation used to calculate PC<sub>20</sub> values described in American Thoracic Society. Guidelines for methacholine and exercise challenge testing - 1999. *Am J Respir Crit Care Med.* 2000; 15 161: 309-329):

$$\text{PD}_2 = \text{antilog} \left[ \log C_1 + \frac{(\log C_2 - \log C_1)(2R_0 - R_1)}{R_2 - R_1} \right]$$

where:

20 C<sub>1</sub> = concentration of Ach or histamine preceding C<sub>2</sub>

C<sub>2</sub> = concentration of Ach or histamine resulting in at least a 2-fold increase in pulmonary resistance (R<sub>L</sub>)

R<sub>0</sub> = Baseline R<sub>L</sub> value

R<sub>1</sub> = R<sub>L</sub> value after C<sub>1</sub>

25 R<sub>2</sub> = R<sub>L</sub> value after C<sub>2</sub>

Statistical analysis of the data is performed using a two tailed – Students t-test.

A P-value <0.05 was considered significant.

Exemplified compounds of this invention are expected to produce a dose-dependent bronchoprotective effect against MCh-induced bronchoconstriction and His-induced bronchoconstriction. Test compounds having a potency (ID<sub>50</sub> at 1.5 h post-dose) of less than about 300 µg/mL for ACh-induced bronchoconstriction and less than about 300 µg/mL for His-induced bronchoconstriction in this assay are generally preferred.

Additionally, test compounds having a duration (PD  $T_{1/2}$ ) of brochoprotective activity of at least about 24 hours in this assay are generally preferred.

### Assay Test Procedure G

#### 5 Einthoven Model for Measuring Changes in Ventilation in Guinea Pigs

The bronchodilator activity of test compounds is evaluated in an anesthetized guinea pig model (the Einthoven model), which uses ventilation pressure as a surrogate measure of airway resistance. See, for example, Einthoven (1892) *Pflugers Arch.* 51: 367 – 445; and Mohammed et al. (2000) *Pulm Pharmacol Ther.* 13(6):287-92. In this model, 10 muscarinic antagonist and  $\beta_2$  agonist activity is assessed by determining the protective effects against methacholine (MCh) and histamine (His)-induced bronchoconstriction.

This assay is conducted using Duncan-Hartley guinea pigs (Harlan, Indianapolis, IN), weighing between 300 and 400 g.

The test compound or vehicle (i.e., sterile water) is dosed by inhalation (IH) over a 15 10 minute time period in a whole body exposure dosing chamber (R+S Molds, San Carlos, CA) using 5 mL of dosing solution. Animals are exposed to an aerosol, which is generated from an LC Star Nebulizer Set (Model 22F51, PARI Respiratory Equipment, Inc. Midlothian, VA) driven by Bioblend a mixture of gasses (5% CO<sub>2</sub>; 21% O<sub>2</sub>; and 74% N<sub>2</sub>) at a pressure of 22 psi. Pulmonary function is evaluated at various time-points after 20 inhalation dosing.

Forty five minutes prior to the start of pulmonary function evaluation, the guinea pigs are anesthetized with an intramuscular (IM) injection of a mixture of ketamine (13.7 mg/kg/xylazine (3.5 mg/kg)/acepromazine (1.05 mg/kg). A supplemental dose of this mixture (50% of initial dose) is administered as needed. The jugular vein and carotid 25 artery are isolated and cannulated with saline-filled polyethylene catheters (micro-renathane and PE-50, respectively, Beckton Dickinson, Sparks, MD). The carotid artery is connected to a pressure transducer to allow the measurement of blood pressure and the jugular vein cannula is used for IV injection of either MCh or His. The trachea is then dissected free and cannulated with a 14G needle (#NE-014, Small Parts, Miami Lakes, 30 FL). Once the cannulations are complete, the guinea pigs are ventilated using a respirator (Model 683, Harvard Apparatus, Inc., MA) set at a stroke volume of 1 mL/100 g body weight but not exceeding 2.5 mL volume, and at a rate of 100 strokes per minute. Ventilation pressure (VP) is measured in the tracheal cannula using a Biopac transducer

that is connected to a Biopac (TSD 137C) pre-amplifier. Body temperature is maintained at 37 °C using a heating pad. Prior to initiating data collection, pentobarbital (25mg/kg) is administered intraperitoneally (IP) to suppress spontaneous breathing and obtain a stable baseline. The changes in VP are recorded on a Biopac Windows data collection interface.

- 5 Baseline values are collected for at least 5 minutes, after which time guinea pigs are challenged IV non-cumulatively with 2-fold incremental doses of the bronchoconstrictor (MCh or His). When MCh is used as the bronchoconstrictor agent, animals are pre-treated with propranolol (5 mg/kg, IV) to isolate the antimuscarinic effects of the test compound. Changes in VP are recorded using the Acknowledge Data Collection Software (Santa  
10 Barbara, CA). After the completion of study, the animals are euthanized.

Change in VP is measured in cm of water. Change in VP (cm H<sub>2</sub>O) = peak pressure (after bronchoconstrictor challenge) - peak baseline pressure. The dose-response curve to MCh or His is fitted to a four parameter logistic equation using GraphPad Prism, version 3.00 for Windows (GraphPad Software, San Diego, California). The equation used  
15 is as follows:

$$Y = \text{Min} + (\text{Max} - \text{Min}) / (1 + 10^{((\log \text{ID}_{50} - X) * \text{Hillslope})})$$

where X is the logarithm of dose, Y is the response. Y starts at Min and approaches  
20 asymptotically to Max with a sigmoidal shape.

The percent inhibition of the bronchoconstrictor response to a submaximal dose of MCh or His is calculated at each dose of the test compound using the following equation:  
% Inhibition of response = 100 - ((peak pressure (after bronchoconstrictor challenge, treated) - peak baseline pressure (treated)) \* 100% / (peak pressure (after bronchoconstrictor  
25 challenge, water) - peak baseline pressure (water))). Inhibition curves are fitted using the four parameter logistic equation from GraphPad software. ID<sub>50</sub> (dose required to produce 50% inhibition of the bronchoconstrictor response) and Emax (maximal inhibition) are also estimated wherever appropriate.

The magnitude of bronchoprotection at different time-points after inhalation of the  
30 test compound is used to estimate the pharmacodynamic half-life (PD T<sub>1/2</sub>). PD T<sub>1/2</sub> is determined using a non-linear regression fit using a one-phase exponential decay equation (GraphPad Prism, Version 4.00): Y = Span \* exp(-K \* X) + Plateau; Starts at Span + Plateau



and decays to Plateau with a rate constant K. The PD  $T_{1/2} = 0.69/K$ . Plateau is constrained to 0.

Exemplified compounds of this invention are expected to produce a dose-dependent bronchoprotective effect against MCh-induced bronchoconstriction and His-induced bronchoconstriction. Generally, test compounds having an  $ID_{50}$  less than about 300  $\mu\text{g/mL}$  for MCh-induced bronchoconstriction and an  $ID_{50}$  less than about 300  $\mu\text{g/mL}$  for His-induced bronchoconstriction at 1.5 hours post-dose in this assay are preferred. Additionally, test compounds having a duration (PD  $T_{1/2}$ ) of bronchoprotective activity of at least about 24 hours in this assay are generally preferred.

10

### Assay Test Procedure H

#### Inhalation Guinea Pig Salivation Assay

Guinea pigs (Charles River, Wilmington, MA) weighing 200-350 g are acclimated to the in-house guinea pig colony for at least 3 days following arrival. Test compound or vehicle are dosed via inhalation (IH) over a 10 minute time period in a pie shaped dosing chamber (R+S Molds, San Carlos, CA). Test solutions are dissolved in sterile water and delivered using a nebulizer filled with 5.0 mL of dosing solution. Guinea pigs are restrained in the inhalation chamber for 30 minutes. During this time, guinea pigs are restricted to an area of approximately 110 sq. cm. This space is adequate for the animals to turn freely, reposition themselves, and allow for grooming. Following 20 minutes of acclimation, guinea pigs are exposed to an aerosol generated from a LS Star Nebulizer Set (Model 22F51, PARI Respiratory Equipment, Inc. Midlothian, VA) driven by house air at a pressure of 22 psi. Upon completion of nebulization, guinea pigs are evaluated at 1.5, 6, 12, 24, 48, or 72 hrs after treatment.

Guinea pigs are anesthetized one hour before testing with an intramuscular (IM) injection of a mixture of ketamine 43.75 mg/kg, xylazine 3.5 mg/kg, and acepromazine 1.05 mg/kg at an 0.88 mL/kg volume. Animals are placed ventral side up on a heated (37°C) blanket at a 20 degree incline with their head in a downward slope. A 4-ply 2 x 2 inch gauze pad (Nu-Gauze General-use sponges, Johnson and Johnson, Arlington, TX) is inserted in the guinea pig's mouth. Five minutes later, the muscarinic agonist pilocarpine (3.0 mg/kg, s.c.) is administered and the gauze pad is immediately discarded and replaced by a new pre-weighed gauze pad. Saliva is collected for 10 minutes, at which point the gauze pad is weighed and the difference in weight recorded to determine the amount of

30

accumulated saliva (in mg). The mean amount of saliva collected for animals receiving the vehicle and each dose of test compound is calculated. The vehicle group mean is considered to be 100% salivation. Results are calculated using result means (n = 3 or greater). Confidence intervals (95%) are calculated for each dose at each time point using  
5 two-way ANOVA. This model is a modified version of the procedure described in Rechter, "Estimation of anticholinergic drug effects in mice by antagonism against pilocarpine-induced salivation" *Ata Pharmacol Toxicol*, **1996**, 24:243-254.

The mean weight of saliva in vehicle-treated animals, at each pre-treatment time, is calculated and used to compute % inhibition of salivation, at the corresponding pre-  
10 treatment time, at each dose. The inhibition dose-response data are fitted to a a four parameter logistic equation using GraphPad Prism, version 3.00 for Windows (GraphPad Software, San Diego, California) to estimate anti-sialagogue ID<sub>50</sub> (dose required to inhibit 50% of pilocarpine-evoked salivation). The equation used is as follows:

15 
$$Y = \text{Min} + (\text{Max} - \text{Min}) / (1 + 10^{((\log \text{ID}_{50} - X) * \text{Hillslope})})$$

where X is the logarithm of dose, Y is the response (% inhibition of salivation). Y starts at Min and approaches asymptotically to Max with a sigmoidal shape.

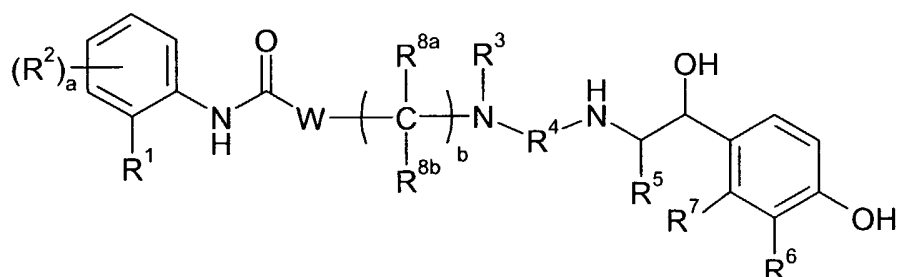
The ratio of the anti-sialagogue ID<sub>50</sub> to bronchoprotective ID<sub>50</sub> is used to compute  
20 the apparent lung-selectivity index of the test compound. Generally, compounds having an apparent lung-selectivity index greater than about 5 are preferred.

While the present invention has been described with reference to specific aspects or embodiments thereof, it will be understood by those of ordinary skilled in the art that various changes can be made or equivalents can be substituted without departing from the  
25 true spirit and scope of the invention. Additionally, to the extent permitted by applicable patent statutes and regulations, all publications, patents and patent applications cited herein are hereby incorporated by reference in their entirety to the same extent as if each document had been individually incorporated by reference herein.

30

**WHAT IS CLAIMED IS:**

1. A compound of formula I:



5

I

wherein

W represents O or NW<sup>a</sup>; where W<sup>a</sup> is hydrogen or (1-4C)alkyl;

R<sup>1</sup> is (6-10C)aryl, (2-9C)heteroaryl containing from 1 to 4 heteroatoms

- 10 independently selected from oxygen, nitrogen and sulfur or (3-7C)cycloalkyl; wherein the aryl, heteroaryl or cycloalkyl group is unsubstituted or substituted with from 1 to 3 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (6-10C)aryl, (2-9C)heteroaryl, (3-5C)heterocyclic, cyano, halo, -OR<sup>1a</sup>, -C(O)OR<sup>1b</sup>, -SR<sup>1c</sup>, -S(O)R<sup>1d</sup>, -S(O)<sub>2</sub>R<sup>1e</sup>, -NR<sup>1f</sup>R<sup>1g</sup>, -C(O)R<sup>1h</sup>, -NR<sup>1i</sup>C(O)OR<sup>1j</sup>,  
 15 -OC(O)NR<sup>1k</sup>R<sup>1l</sup>, -NR<sup>1m</sup>C(O)R<sup>1n</sup>, -C(O)NR<sup>1o</sup>R<sup>1p</sup> and -NHS(O)<sub>2</sub>R<sup>1q</sup>; where each of R<sup>1a</sup>, R<sup>1b</sup>, R<sup>1c</sup>, R<sup>1d</sup>, R<sup>1e</sup>, R<sup>1f</sup>, R<sup>1g</sup>, R<sup>1h</sup>, R<sup>1i</sup>, R<sup>1j</sup>, R<sup>1k</sup>, R<sup>1l</sup>, R<sup>1m</sup>, R<sup>1n</sup>, R<sup>1o</sup>, R<sup>1p</sup> and R<sup>1q</sup> is independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and where each (3-6C)cycloalkyl, (6-10C)aryl, (2-9C)heteroaryl and (3-5C)heterocyclic group is  
 20 unsubstituted or substituted with from 1 to 3 substituents selected from (1-4C)alkyl, halo and -OR<sup>1a</sup>; and where each alkyl group present in R<sup>1</sup> is unsubstituted or substituted with from 1 to 3 fluoro substituents;

- each R<sup>2</sup> is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, -OR<sup>2a</sup>, -C(O)OR<sup>2b</sup>, -SR<sup>2c</sup>, -S(O)R<sup>2d</sup>, -S(O)<sub>2</sub>R<sup>2e</sup> and -NR<sup>2f</sup>R<sup>2g</sup>; where each of R<sup>2a</sup>, R<sup>2b</sup>, R<sup>2c</sup>, R<sup>2d</sup>, R<sup>2e</sup>, R<sup>2f</sup> and R<sup>2g</sup> is independently selected from  
 25 hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and where each alkyl group present in R<sup>2</sup> is unsubstituted or substituted with from 1 to 3 fluoro substituents;

R<sup>3</sup> is selected from hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, or (3-6C)cycloalkyl, where the alkyl group is unsubstituted or substituted with from 1 to 3 fluoro substituents;

$R^4$  represents a divalent hydrocarbon group containing from 4 to 28 carbon atoms and optionally containing from 1 to 10 heteroatoms selected independently from halo, oxygen, nitrogen and sulfur, provided that the number of contiguous atoms in the shortest chain between the two nitrogen atoms to which  $R^4$  is attached is in the range of from 4 to

5 16;

$R^5$  represents hydrogen or (1-4C)alkyl;

$R^6$  is  $-N(R^{6a})C(O)R^{6b}$  or  $-CR^{6c}R^{6d}OR^{6e}$  and  $R^7$  is hydrogen; or  $R^6$  and  $R^7$  together form  $-N(R^{7a})C(O)C(R^{7b})=C(R^{7c})-$ ,  $-C(R^{7d})=C(R^{7e})C(O)N(R^{7f})-$ ,  $-N(R^{7g})C(O)CR^{7h}R^{7i}-CR^{7j}R^{7k}-$  or  $-CR^{7l}R^{7m}-CR^{7n}R^{7o}C(O)-N(R^{7p})-$ ; where each of  $R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$ ,  $R^{6d}$  and  $R^{6e}$  is independently selected from hydrogen and (1-4C)alkyl; and each of  $R^{7a}$ ,  $R^{7b}$ ,  $R^{7c}$ ,  $R^{7d}$ ,  $R^{7e}$ ,  $R^{7f}$ ,  $R^{7g}$ ,  $R^{7h}$ ,  $R^{7i}$ ,  $R^{7j}$ ,  $R^{7k}$ ,  $R^{7l}$ ,  $R^{7m}$ ,  $R^{7n}$ ,  $R^{7o}$  and  $R^{7p}$  is independently selected from hydrogen and (1-4C)alkyl;

each  $R^{8a}$  and  $R^{8b}$  is independently selected from hydrogen, (1-4C)alkyl, hydroxy and fluoro, or  $R^{8a}$  and  $R^{8b}$  are joined together with the atoms to which they are attached to form a (3-6C)cycloalkylene ring or a (2-5C)heterocyclene ring containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, or  $R^{8a}$  and  $W^a$  are joined together with the atoms to which they are attached to form a (2-6C)azacycloalkylene group;

a is 0 or an integer of from 1 to 3;

b is an integer of from 2 to 8;

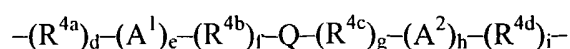
or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

2. The compound of Claim 1, wherein  $R^1$  is an unsubstituted or substituted aryl or heteroaryl group selected from a phenyl, naphthalene, pyrrole, imidazole, thiazole, oxazole, furan, thiophene, triazole, pyrazole, isoxazole, isothiazole, pyridine, pyridine N-oxide, pyrazine, pyridazine, pyrimidine, triazine, indole, benzofuran, benzothiophene, benzimidazole, benzthiazole, quinoline, isoquinoline, quinazoline and quinoxaline ring, where the point of attachment is at any available carbon or nitrogen ring atom.

3. The compound of Claim 2, wherein  $R^1$  is an unsubstituted or substituted phenyl group.

4. The compound of Claim 2, wherein  $R^1$  is an unsubstituted or substituted thienyl group.
5. The compound of Claim 2, wherein  $R^1$  is an unsubstituted or substituted thiazole group.
6. The compound of Claim 2, wherein  $R^1$  is an unsubstituted or substituted pyridyl or pyridyl N-oxide group.
7. The compound of any one of Claims 1 to 6, wherein W is O.
8. The compound of any one of Claims 1 to 7, wherein b is 2, 3 or 4.
9. The compound of any one of Claims 1 to 7, wherein b is 3, and  $R^{8a}$  and  $R^{8b}$  on the  $-CR^{8a}R^{8b}-$  unit attached to W are methyl, and the remaining  $R^{8a}$  and  $R^{8b}$  groups are hydrogen.
10. The compound of any one of Claims 1 to 9, wherein  $R^3$  is methyl.
11. The compound of any one of Claims 1 to 10, wherein  $R^6$  is  $-NHCHO$  or  $-CH_2OH$  and  $R^7$  is hydrogen; or  $R^6$  and  $R^7$  together form  $-NHC(O)CH=CH-$ ,  $-CH=CHC(O)NH-$ ,  $-CH_2CH_2C(O)NH-$  or  $-NHC(O)CH_2CH_2-$ .
12. The compound of Claim 11, wherein  $R^6$  and  $R^7$  together form  $-NHC(O)CH=CH-$ .
13. The compound of any one of Claims 1 to 12, wherein the number of contiguous atoms in the shortest chain between the two nitrogen atoms to which  $R^4$  is attached is in the range of from 8 to 14.
14. The compound of Claim 13, wherein the number of contiguous atoms in the shortest chain between the two nitrogen atoms to which  $R^4$  is attached is 8, 9, 10 or 11.

15. The compound of Claim 1, wherein R<sup>4</sup> is a divalent group of the formula:



5 wherein

d, e, f, g, h and i are each independently selected from 0 and 1;

R<sup>4a</sup>, R<sup>4b</sup>, R<sup>4c</sup> and R<sup>4d</sup> are each independently selected from (1-10C)alkylene, (2-10C)alkenylene and (2-10C)alkynylene, wherein each alkylene, alkenylene or alkynylene group is unsubstituted or substituted with from 1 to 5 substituents

10 independently selected from (1-4C)alkyl, fluoro, hydroxy, phenyl and phenyl-(1-4C)alkyl; or R<sup>4d</sup> represents (1-6C)alkylene-NHC(O)-(1-6C)alkylene;

A<sup>1</sup> and A<sup>2</sup> are each independently selected from (3-7C)cycloalkylene, (6-10C)arylene, -O-(6-10C)arylene, (6-10C)arylene-O-, (2-9C)heteroarylene, -O-(2-9C)heteroarylene, (2-9C)heteroarylene-O- and (3-6C)heterocyclene, wherein each  
15 cycloalkylene is unsubstituted or substituted with from 1 to 4 substituents selected independently from (1-4C)alkyl, and each arylene, heteroarylene or heterocyclene group is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, -S-(1-4C)alkyl, -S(O)-(1-4C)alkyl, -S(O)<sub>2</sub>-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy;

20 Q is selected from a bond, -O-, -C(O)O-, -OC(O)-, -S-, -S(O)-, -S(O)<sub>2</sub>-, -N(Q<sup>a</sup>)C(O)-, -C(O)N(Q<sup>b</sup>)-, -N(Q<sup>c</sup>)S(O)<sub>2</sub>-, -S(O)<sub>2</sub>N(Q<sup>d</sup>)-, -N(Q<sup>e</sup>)C(O)N(Q<sup>f</sup>)-, -N(Q<sup>g</sup>)S(O)<sub>2</sub>N(Q<sup>h</sup>)-, -OC(O)N(Q<sup>i</sup>)-, -N(Q<sup>j</sup>)C(O)O- and -N(Q<sup>k</sup>); where Q<sup>a</sup>, Q<sup>b</sup>, Q<sup>c</sup>, Q<sup>d</sup>, Q<sup>e</sup>, Q<sup>f</sup>, Q<sup>g</sup>, Q<sup>h</sup>, Q<sup>i</sup>, Q<sup>j</sup> and Q<sup>k</sup> are each independently selected from hydrogen, (1-6C)alkyl, A<sup>3</sup> and (1-4C)alkylene-A<sup>4</sup>, wherein the alkyl group is unsubstituted or substituted with from 1  
25 to 3 substituents independently selected from fluoro, hydroxy and (1-4C)alkoxy; or together with the nitrogen atom and the group R<sup>4b</sup> or R<sup>4c</sup> to which they are attached, form a 4 to 6 membered azacycloalkylene group; and

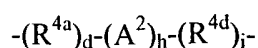
A<sup>3</sup> and A<sup>4</sup> are each independently selected from (3-6C)cycloalkyl, (6-10C)aryl, (2-9C)heteroaryl and (3-6C)heterocyclyl, wherein each cycloalkyl is unsubstituted or  
30 substituted with from 1 to 4 substituents selected independently from (1-4C)alkyl and each aryl, heteroaryl or heterocyclyl group is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl and (1-4C)alkoxy.

16. The compound of Claim 15, wherein  $R^4$  is a divalent group of the formula:  
 $-(R^{4a})_d-$  where  $R^{4a}$  is (4-10C)alkylene.

17. The compound of Claim 16, wherein  $R^4$  is  $-(CH_2)_8-$ ,  $-(CH_2)_9$ , and  $-(CH_2)_{10}-$ .

5

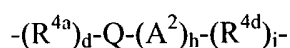
18. The compound of Claim 15, wherein  $R^4$  is a divalent group of the formula:



10 wherein  $R^{4a}$  is (1-10C)alkylene;  $A^2$  is (6-10C)arylene or (2-9C)heteroarylene; and  
 $R^{4d}$  is (1-10C)alkylene.

19. The compound of Claim 15, wherein  $R^4$  is a divalent group of the formula:

15

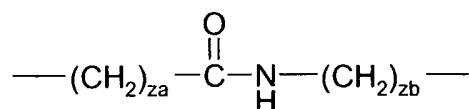


wherein Q is -O- or  $-N(Q^k)-$ ;  $Q^k$  is hydrogen or (1-3C)alkyl;  $R^{4a}$  is (1-10C)alkylene;  $A^2$  is (6-10C)arylene or (2-9C)heteroarylene; and  $R^{4d}$  is (1-10C)alkylene.

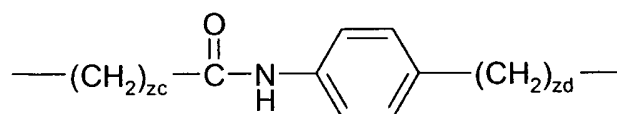
20. The compound of Claim 15, wherein Q is  $-N(Q^a)C(O)-$  or  
 $-C(O)N(Q^b)-$ .

21. The compound of Claim 20, wherein  $R^4$  is selected from:

25

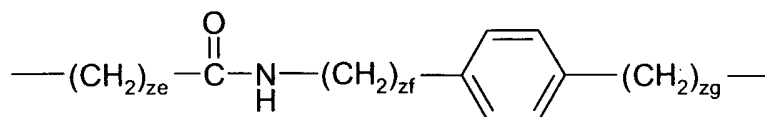


where  $za$  is an integer from 2 to 10; and  $zb$  is an integer from 2 to 10; provided that  
 $za + zb$  is an integer from 4 to 12;



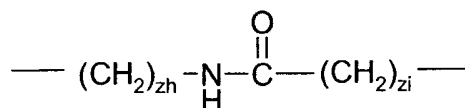
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where  $zc$  is an integer from 2 to 7; and  $zd$  is an integer from 1 to 6; provided that  $zc + zd$  is an integer from 3 to 8; and wherein the phen-1,4-ylene group is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, -S-(1-4C)alkyl, -S(O)-(1-4C)alkyl, -S(O)<sub>2</sub>-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy;



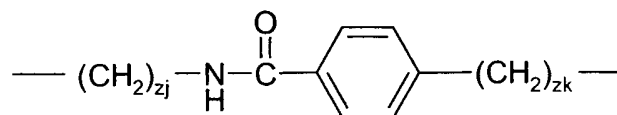
where  $ze$  is an integer from 2 to 6;  $zf$  is an integer from 1 to 5; and  $zg$  is an integer from 1 to 5; provided that  $ze + zf + zg$  is an integer from 4 to 8; and wherein the phen-1,4-ylene group is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, -S-(1-4C)alkyl, -S(O)-(1-4C)alkyl, -S(O)<sub>2</sub>-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy;

15



where  $zh$  is an integer from 2 to 10; and  $zi$  is an integer from 2 to 10; provided that  $zh + zi$  is an integer from 4 to 12;

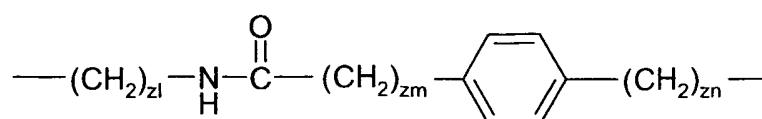
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where  $zj$  is an integer from 2 to 7; and  $zk$  is an integer from 1 to 6; provided that  $zj + zk$  is an integer from 3 to 8; and wherein the phen-1,4-ylene group is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, -S-(1-4C)alkyl, -S(O)-(1-4C)alkyl, -S(O)<sub>2</sub>-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy; and

25





where  $zl$  is an integer from 2 to 6;  $zm$  is an integer from 1 to 5; and  $zn$  is an integer from 1 to 5; provided that  $zl + zm + zn$  is an integer from 4 to 8; and wherein the phen-1,4-ylene group is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy,  $-\text{S}-(1-4\text{C})\text{alkyl}$ ,  $-\text{S}(\text{O})-(1-4\text{C})\text{alkyl}$ ,  $-\text{S}(\text{O})_2-(1-4\text{C})\text{alkyl}$ ,  $-\text{C}(\text{O})\text{O}(1-4\text{C})\text{alkyl}$ , carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy.

10            22.    The compound of any one of Claims 1 to 12, wherein  $\text{R}^4$  is selected from:

$-(\text{CH}_2)_7-$ ;

$-(\text{CH}_2)_8-$ ;

$-(\text{CH}_2)_9-$ ;

$-(\text{CH}_2)_{10}-$ ;

15  $-(\text{CH}_2)_{11}-$ ;

$-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{CH}_2)_5-$ ;

$-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(\text{CH}_2)_5-$ ;

$-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{phen-1,4-ylene})\text{CH}_2-$ ;

$-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{phen-1,4-ylene})\text{CH}_2-$ ;

20  $-(\text{CH}_2)_2\text{NHC}(\text{O})\text{NH}(\text{CH}_2)_5-$ ;

$-(\text{CH}_2)_3\text{NHC}(\text{O})\text{NH}(\text{CH}_2)_5-$ ;

$-(\text{CH}_2)_2\text{C}(\text{O})\text{NHCH}_2(\text{cyclohex-1,3-ylene})\text{CH}_2-$ ;

$-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{cyclopent-1,3-ylene})-$ ;

$-(\text{CH}_2)_2\text{NHC}(\text{O})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;

25  $1-[-(\text{CH}_2)_2\text{C}(\text{O})](\text{piperidin-4-yl})(\text{CH}_2)_2-$ ;

$-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{trans-cyclohex-1,4-ylene})\text{CH}_2-$ ;

$-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{cis-cyclopent-1,3-ylene})-$ ;

$-(\text{CH}_2)_2\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;

$1-[-(\text{CH}_2)_2\text{NHC}(\text{O})](\text{piperidin-4-yl})(\text{CH}_2)_2-$ ;

30  $-\text{CH}_2(\text{phen-1,4-ylene})\text{NH}(\text{phen-1,4-ylene})\text{CH}_2-$ ;

$-(\text{CH}_2)_2\text{C}(\text{O})\text{NHCH}_2(\text{phen-1,3-ylene})\text{CH}_2-$ ;

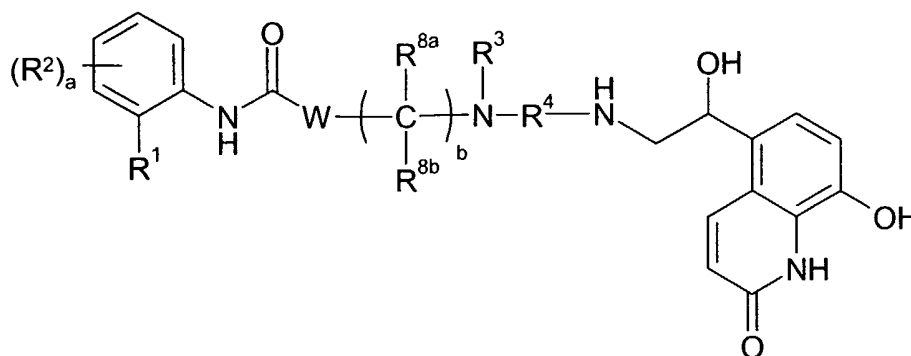
- $-(\text{CH}_2)_2\text{C}(\text{O})\text{NHCH}_2(\text{pyrid-2,6-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{cis-cyclohex-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{trans-cyclohex-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{cis-cyclopent-1,3-ylene})\text{CH}_2-$ ;  
5  $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(\text{phen-1,3-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(\text{trans-cyclohex-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{phen-1,4-ylene})\text{C}^*\text{H}(\text{CH}_3)- ((S)\text{-isomer})$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{phen-1,4-ylene})\text{C}^*\text{H}(\text{CH}_3)- ((R)\text{-isomer})$ ;  
 $2-[(S)-(-\text{CH}_2-)](\text{pyrrolidin-1-yl})\text{C}(\text{O})(\text{CH}_2)_4-$ ;  
10  $2-[(S)-(-\text{CH}_2-)](\text{pyrrolidin-1-yl})\text{C}(\text{O})(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(4\text{-chlorophen-1,3-ylene})\text{CH}_2-$ ;  
 $-\text{CH}_2(2\text{-fluorophen-1,3-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(4\text{-methylphen-1,3-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(6\text{-chlorophen-1,3-ylene})\text{CH}_2-$ ;  
15  $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2\text{-chlorophen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(2,6\text{-dichlorophen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})\text{NHCH}_2(\text{phen-1,3-ylene})\text{CH}_2-$ ;  
 $4-[-\text{CH}_2-](\text{piperidin-1-yl})\text{C}(\text{O})(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{N}(\text{CH}_2\text{CH}_3)(\text{phen-1,4-ylene})\text{CH}_2-$ ;  
20  $1-[-(\text{CH}_2)_2\text{NHC}(\text{O})](\text{piperidin-4-yl})-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_2\text{NHC}(\text{O})(\text{thien-2,5-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(3\text{-nitrophen-1,4-ylene})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{C}(\text{O})(\text{trans-cyclohex-1,4-ylene})-$ ;  
25  $1-[-\text{CH}_2(2\text{-fluorophen-1,3-ylene})\text{CH}_2](\text{piperidin-4-yl})-$ ;  
 $5-[-(\text{CH}_2)_2\text{NHC}(\text{O})](\text{pyrid-2-yl})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $-(\text{CH}_2)_3(\text{thien-2,5-ylene})(\text{CH}_2)_3-$ ;  
 $-(\text{CH}_2)_2(\text{phen-1,4-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
30  $-\text{CH}_2(\text{phen-1,2-ylene})\text{NH}(\text{phen-1,4-ylene})(\text{CH}_2)_2-$ ;  
 $1-[-\text{CH}_2(2\text{-fluorophen-1,3-ylene})\text{CH}_2](\text{piperidin-4-yl})(\text{CH}_2)_2-$ ;  
 $1-[-\text{CH}_2(2\text{-fluorophen-1,3-ylene})\text{CH}_2](\text{piperidin-4-yl})\text{CH}_2-$ ;  
 $-(\text{CH}_2)_2\text{C}(\text{O})\text{NH}(3\text{-chlorophen-1,4-ylene})\text{CH}_2-$

- (CH<sub>2</sub>)<sub>2</sub>C(O)NH(2-(CF<sub>3</sub>O-)phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,3-ylene)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>S(O)<sub>2</sub>NH(CH<sub>2</sub>)<sub>5</sub>-;  
 -CH<sub>2</sub>(phen-1,3-ylene)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 5 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2-iodophen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2-chloro-5-methoxyphen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2-chloro-6-methylphen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)S(O)<sub>2</sub>(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2-bromophen-1,4-ylene)CH<sub>2</sub>-;  
 10 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,4-ylene)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,2-ylene)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 1-[-CH<sub>2</sub>(2-fluorophen-1,3-ylene)CH<sub>2</sub>](piperidin-4-yl)(CH<sub>2</sub>)<sub>3</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2-methoxyphen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>5</sub>NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 15 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(phen-1,4-ylene)CH(CH<sub>3</sub>)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>-(*trans*-cyclohex-1,4-ylene)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2-fluorophen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,3-ylene)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 20 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2,5-difluorophen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>NHC(O)(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 1-[-CH<sub>2</sub>(pyrid-2,6-ylene)CH<sub>2</sub>](piperidin-4-yl)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>NH(naphth-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 25 -(CH<sub>2</sub>)<sub>3</sub>O(phen-1,4-ylene)CH<sub>2</sub>-;  
 1-[-(CH<sub>2</sub>)<sub>3</sub>](piperidin-4-yl)CH<sub>2</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,4-ylene)NHC(O)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>O(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 30 2-[-(CH<sub>2</sub>)<sub>2</sub>](benzimidazol-5-yl)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>-(*trans*-cyclohex-1,4-ylene)NHC(O)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>-(*trans*-cyclohex-1,4-ylene)NHC(O)(CH<sub>2</sub>)<sub>4</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>-(*trans*-cyclohex-1,4-ylene)NHC(O)(CH<sub>2</sub>)<sub>5</sub>-;

- 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>NHC(O)NH(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>)<sub>2</sub>(*cis*-cyclohex-1,4-ylene)-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2,3,5,6-tetrafluorophen-1,4-ylene)CH<sub>2</sub>-;
- 5 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2,6-diiodophen-1,4-ylene)CH<sub>2</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(CH<sub>2</sub>)<sub>3</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(CH<sub>2</sub>)<sub>4</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(CH<sub>2</sub>)<sub>5</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NHCH<sub>2</sub>(phen-1,4-ylene)CH<sub>2</sub>-;
- 10 -(CH<sub>2</sub>)<sub>2</sub>NHC(O)NHCH<sub>2</sub>(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(2-methylphen-1,4-ylene)CH<sub>2</sub>-;  
 1-[-(CH<sub>2</sub>)<sub>3</sub>O(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>](piperidin-4-yl)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NHCH<sub>2</sub>(phen-1,3-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;
- 15 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)CH<sub>2</sub>O(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)CH<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)(fur-2,5-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)(thien-2,5-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,4-ylene)O(CH<sub>2</sub>)<sub>2</sub>-;
- 20 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,2-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)(fur-2,5-ylene)CH<sub>2</sub>-;
- 25 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)(thien-2,5-ylene)CH<sub>2</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)CH<sub>2</sub>O(phen-1,2-ylene)CH<sub>2</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)CH<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)CH<sub>2</sub>O(phen-1,4-ylene)CH<sub>2</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(fur-2,5-ylene)CH<sub>2</sub>-;
- 30 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)(thien-2,5-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)(phen-1,3-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,2-ylene)CH<sub>2</sub>-;

- (CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)CH<sub>2</sub>O(phen-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)(fur-2,5-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>(phen-1,4-ylene)NHC(O)(thien-2,5-ylene)CH<sub>2</sub>-;  
 5 -(CH<sub>2</sub>)<sub>2</sub>(*trans*-cyclohex-1,4-ylene)NHC(O)(phen-1,3-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>O(phen-1,3-ylene)CH<sub>2</sub>-;  
 -CH<sub>2</sub>CH(OH)CH<sub>2</sub>NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>4</sub>NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(phen-1,4-ylene)CH<sub>2</sub>NHC(O)CH<sub>2</sub>-;  
 10 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>NHC(O)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NHCH<sub>2</sub>(*trans*-cyclohex-1,4-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>NHC(O)(CH<sub>2</sub>)<sub>5</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,3-ylene)O(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,2-ylene)O(CH<sub>2</sub>)<sub>2</sub>-;  
 15 -CH<sub>2</sub>(phen-1,2-ylene)O(phen-1,2-ylene)CH<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>C(O)NH(CH<sub>2</sub>)<sub>6</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,4-ylene)(CH<sub>2</sub>)<sub>3</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>4</sub>(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 20 -(CH<sub>2</sub>)<sub>3</sub>(furan-2,5-ylene)(CH<sub>2</sub>)<sub>3</sub>-;  
 -(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)C(O)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 4-[-(CH<sub>2</sub>)<sub>2</sub>](piperidin-1-yl)C(O)NH(phen-1,4-ylene)(CH<sub>2</sub>)<sub>2</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(phen-1,3-ylene)(CH<sub>2</sub>)<sub>3</sub>-;  
 -(CH<sub>2</sub>)<sub>3</sub>(tetrahydrofuran-2,5-ylene)(CH<sub>2</sub>)<sub>3</sub>-; and  
 25 -(CH<sub>2</sub>)<sub>2</sub>O(phen-1,4-ylene)C(O)(CH<sub>2</sub>)<sub>2</sub>-

23. The compound of any one of Claims 1-7, 13-22, wherein the compound is a compound of formula II:

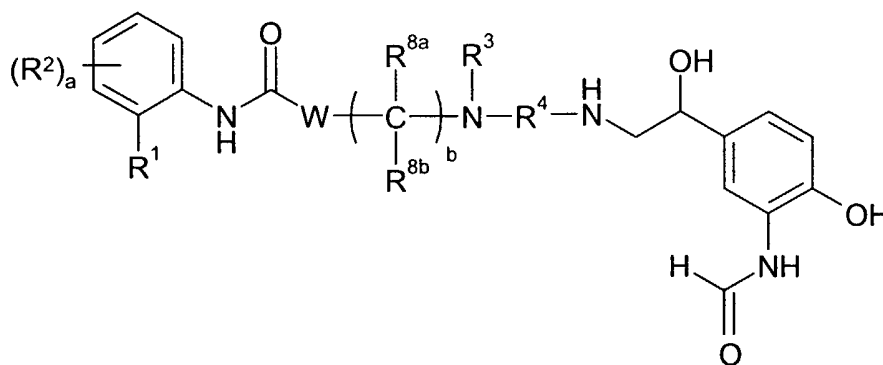


5

II

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

24. The compound of any one of Claims 1-7, 13-22, wherein the compound is a  
10 compound of formula III:

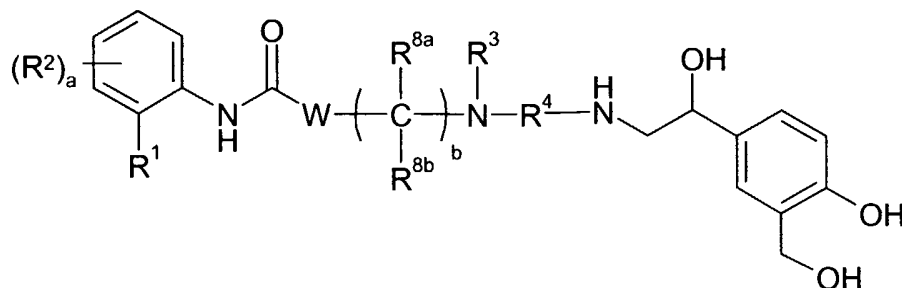


III

15

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

25. The compound of any one of Claims 1-7, 13-22, wherein the compound is a compound of formula IV:

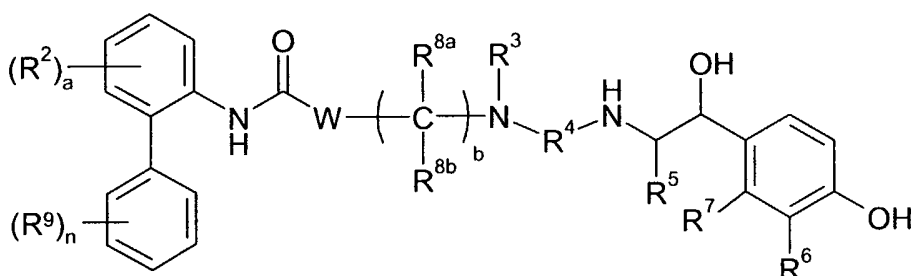


5

IV

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

26. The compound of any one of Claims 1, 7-22, wherein the compound is a compound of formula V:



V

15

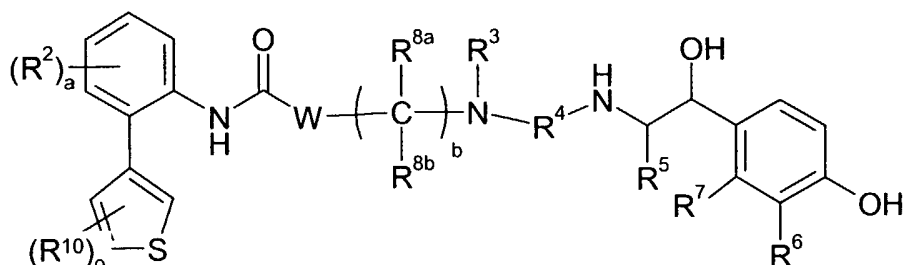
wherein each  $R^9$  is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo,  $-OR^{9a}$ ,  $-C(O)OR^{9b}$ ,  $-SR^{9c}$ ,  $-S(O)R^{9d}$ ,  $-S(O)_2R^{9e}$  and  $-NR^{9f}R^{9g}$ ; wherein  $R^{9a}$ ,  $R^{9b}$ ,  $R^{9c}$ ,  $R^{9d}$ ,  $R^{9e}$ ,  $R^{9f}$  and  $R^{9g}$  are independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and

20

n is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

27. The compound of any one of Claims 1, 7-22, wherein the compound is a compound of formula VI:



5

VI

wherein each  $R^{10}$  is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo,  $-OR^{10a}$ ,  $-C(O)OR^{10b}$ ,  $-SR^{10c}$ ,  $-S(O)R^{10d}$ ,  $-S(O)_2R^{10e}$  and  $-NR^{10f}R^{10g}$ ; wherein  $R^{10a}$ ,  $R^{10b}$ ,  $R^{10c}$ ,  $R^{10d}$ ,  $R^{10e}$ ,  $R^{10f}$  and  $R^{10g}$  are

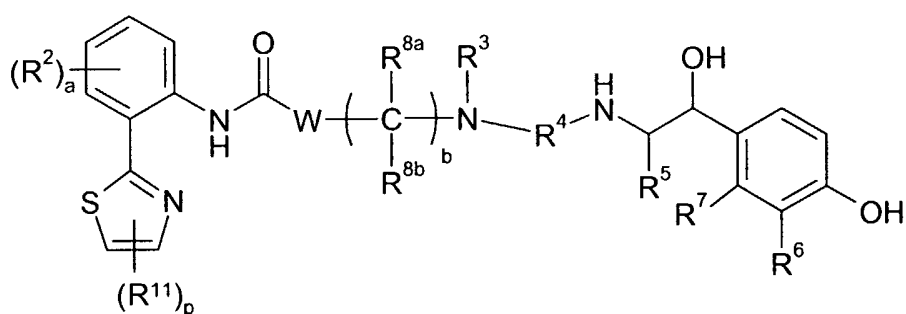
10 independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and

$o$  is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

28. The compound of any one of Claims 1, 13-22, wherein the compound is a

15 compound of formula VII:



VII

20 wherein each  $R^{11}$  is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo,  $-OR^{11a}$ ,  $-C(O)OR^{11b}$ ,  $-SR^{11c}$ ,  $-S(O)R^{11d}$ ,  $-S(O)_2R^{11e}$  and  $-NR^{11f}R^{11g}$ ; wherein  $R^{11a}$ ,  $R^{11b}$ ,  $R^{11c}$ ,  $R^{11d}$ ,  $R^{11e}$ ,  $R^{11f}$  and  $R^{11g}$  are

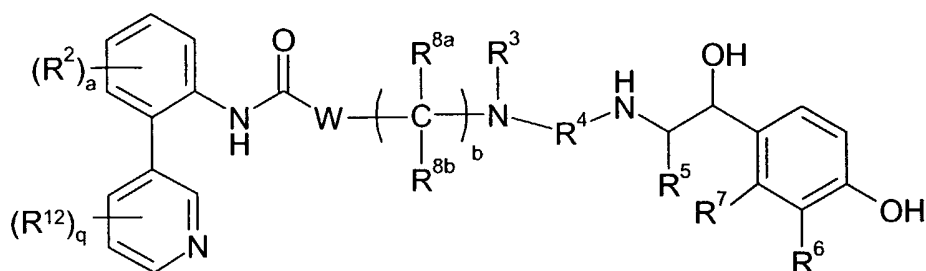
independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and



p is 0, 1 or 2;

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

29. The compound of any one of Claims 1, 7-22, wherein the compound is a  
5 compound of formula VIII:



VIII

- 10 or the corresponding pyridine N-oxide, wherein each R<sup>12</sup> is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, -OR<sup>12a</sup>, -C(O)OR<sup>12b</sup>, -SR<sup>12c</sup>, -S(O)R<sup>12d</sup>, -S(O)<sub>2</sub>R<sup>12e</sup> and -NR<sup>12f</sup>R<sup>12g</sup>; wherein R<sup>12a</sup>, R<sup>12b</sup>, R<sup>12c</sup>, R<sup>12d</sup>, R<sup>12e</sup>, R<sup>12f</sup> and R<sup>12g</sup> are independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and

- 15 q is 0, 1 or 2;

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

30. The compound of Claim 1, wherein the compound is selected from:

- 20 biphenyl-2-ylcarbamic acid 3-({9-[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}methylamino)-1,1-dimethylpropyl ester;

(2-thien-3-ylphenyl)carbamic acid 3-({9-[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}methylamino)-1,1-dimethylpropyl ester;

biphenyl-2-ylcarbamic acid 3-{[2-(4-{{(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino}methyl}benzoylamino)ethyl]methylamino}-1,1-

- 25 dimethylpropyl ester;

biphenyl-2-ylcarbamic acid 3-{[4-(4-{2-[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenyl)butyl]methylamino}-1,1-dimethylpropyl ester; and

biphenyl-2-ylcarbamic acid 3-{{2-(2-chloro-4-{{(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino}methyl}-5-methoxyphenylcarbonyl)ethyl}-methylamino}-1,1-dimethylpropyl ester.

5           31.     A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of any one of Claims 1 to 30.

            32.     The pharmaceutical composition of Claim 31, wherein the composition further comprises a therapeutically effective amount of a steroidal anti-inflammatory agent.  
10

            33.     The pharmaceutical composition of Claim 31, wherein the composition further comprises a therapeutically effective amount of a PDE<sub>4</sub> inhibitor.

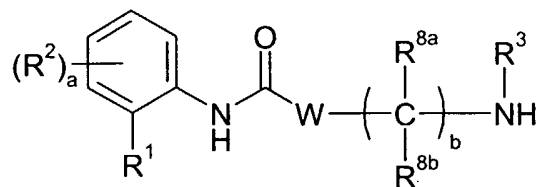
            34.     A method for treating a pulmonary disorder, the method comprising  
15 administering to a patient in need of treatment a therapeutically effective amount of a compound of any one of Claims 1 to 30.

            35.     A method of producing bronchodilation in a patient, the method comprising administering to a patient a bronchodilation-producing amount of a compound of any one  
20 of Claims 1 to 30.

            36.     A method of treating chronic obstructive pulmonary disease or asthma, the method comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of any one of Claims 1 to 30.  
25

            37.     A method of studying a biological system or sample comprising a muscarinic receptor or a  $\beta_2$  adrenergic receptor, the method comprising:  
            (a)     contacting the biological system or sample with a muscarinic receptor antagonizing or a  $\beta_2$  adrenergic receptor agonizing amount of a compound of any one of  
30 Claims 1 to 30; and  
            (b)     determining or measuring the effects caused by the compound on the biological system or sample.

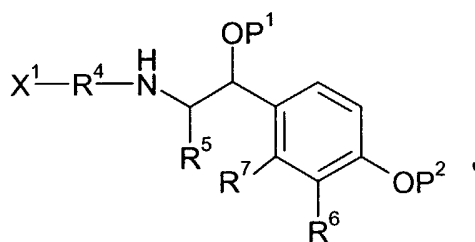
38. A process for preparing a compound of Claim 1, the process comprising:  
 (a) reacting a compound of formula 1:



5

1

or a salt thereof; with a compound of formula 2:

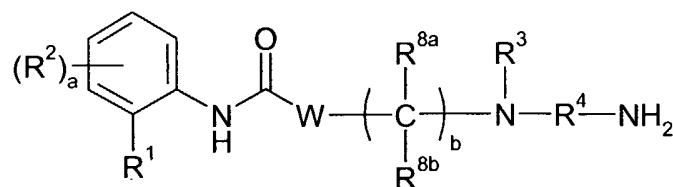


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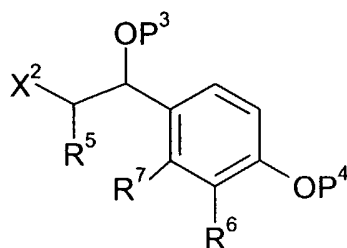
2

wherein  $X^1$  represents a leaving group, and  $P^1$  and  $P^2$  each independently represent a hydrogen atom or a hydroxyl-protecting group;

- 15 (b) reacting a compound of formula 3:

3

or salt thereof; with a compound of formula 4:



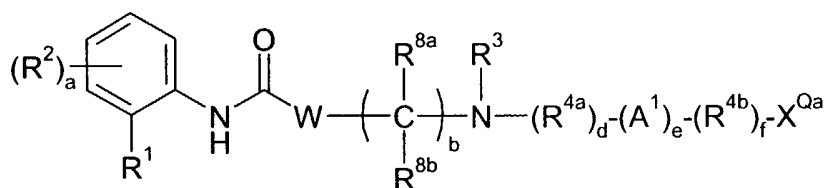
5

4

wherein  $X^2$  represents a leaving group, and  $P^3$  and  $P^4$  each independently represent a hydrogen atom or a hydroxyl-protecting group;

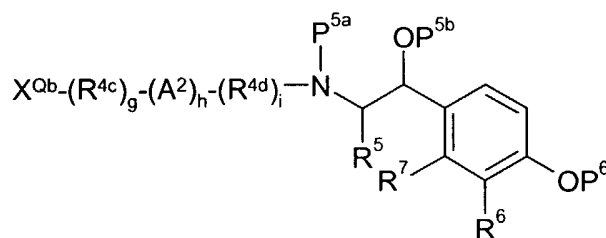
(c) coupling a compound of formula 5:

10

5

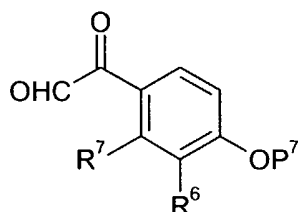
with a compound of formula 6:

15

6

wherein  $X^{Qa}$  and  $X^{Qb}$  each independently represent functional groups that couple to form a group Q,  $P^{5a}$  represents a hydrogen atom or an amino-protecting group; and  $P^{5b}$  and  $P^6$  each independently represent a hydrogen atom or a hydroxyl-protecting group;

(d) for a compound of formula 1 wherein R<sup>5</sup> represents a hydrogen atom, reacting a compound of formula 3 with a compound of formula 7:



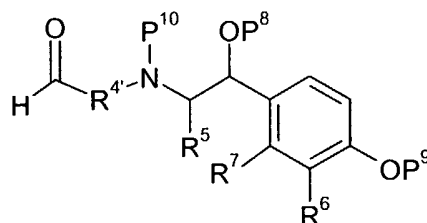
5

7

or a hydrate thereof (e.g., a glyoxal), in the presence of a reducing agent, wherein P<sup>7</sup> represents a hydrogen atom or a hydroxyl-protecting group;

(e) reacting a compound of formula 1 with a compound of formula 8:

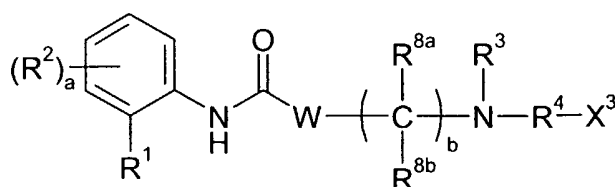
10

8

or a hydrate thereof, in the presence of a reducing agent, wherein P<sup>8</sup> and P<sup>9</sup> each independently represent a hydrogen atom or a hydroxyl-protecting group, P<sup>10</sup> represents a hydrogen atom or an amino-protecting group, and R<sup>4'</sup> represents a residue that, together with the carbon to which it is attached, affords a group R<sup>4</sup> upon completion of the reaction;

15

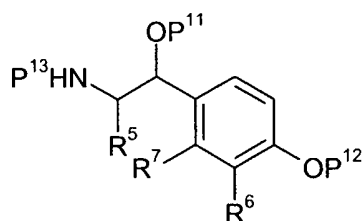
(f) reacting a compound of formula 9:



20

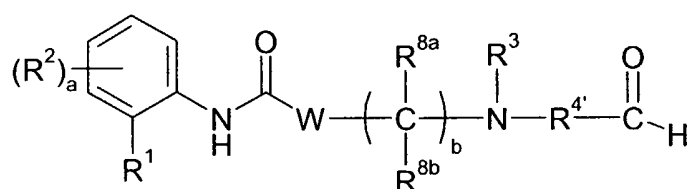
9

wherein X<sup>3</sup> represents a leaving group, with a compound of formula 10:

**10**

wherein P<sup>11</sup> and P<sup>12</sup> each independently represent a hydrogen atom or a hydroxyl-protecting group, and P<sup>13</sup> represents a hydrogen atom or an amino-protecting group; or

(g) reacting a compound of formula **11**:

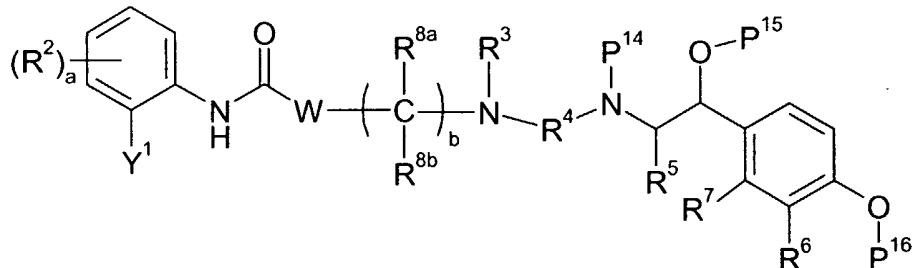
**11**

10

or a hydrate thereof; wherein R<sup>4'</sup> represents a residue that, together with the carbon to which it is attached, affords a group R<sup>4</sup> upon completion of the reaction; with a compound of formula **10** in the presence of a reducing agent;

(h) reacting a compound of formula **12**:

15

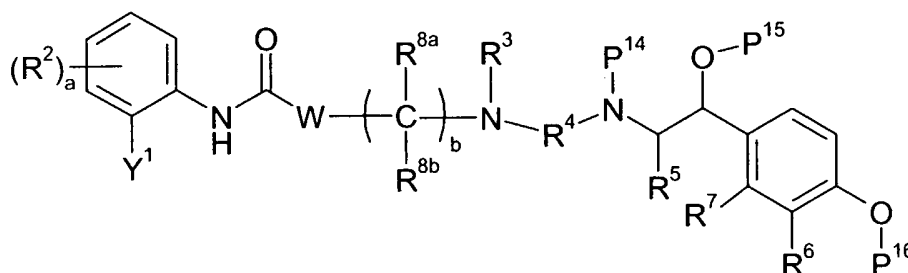
**12**

wherein Y<sup>1</sup> represents chloro, bromo, iodo or CF<sub>3</sub>SO<sub>2</sub>O-, P<sup>14</sup> represents a hydrogen atom or an amino-protecting group; and P<sup>15</sup> and P<sup>16</sup> each independently represent a hydroxyl-protecting group; with a compound of the formula: R<sup>1</sup>-B(OH)<sub>2</sub> in the presence of a coupling catalyst; and then

removing any protecting group P<sup>1</sup>, P<sup>2</sup>, P<sup>3</sup>, P<sup>4</sup>, P<sup>5a</sup>, P<sup>5b</sup>, P<sup>6</sup>, P<sup>7</sup>, P<sup>8</sup>, P<sup>9</sup>, P<sup>10</sup>, P<sup>11</sup>, P<sup>12</sup>, P<sup>13</sup>, P<sup>14</sup>, P<sup>15</sup> and P<sup>16</sup> to provide a compound of formula I, or a salt thereof.

39. The process of Claim 38, wherein the process further comprises forming a  
5 pharmaceutically acceptable salt of the compound of formula I.

40. A compound of formula 12:



10

12

wherein

Y<sup>1</sup> represents chloro, bromo, iodo or CF<sub>3</sub>SO<sub>2</sub>O-;

W represents O or NW<sup>a</sup>; where W<sup>a</sup> is hydrogen or (1-4C)alkyl;

15 R<sup>1</sup> is (6-10C)aryl or (2-9C)heteroaryl containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur; wherein the aryl or heteroaryl group is unsubstituted or substituted with from 1 to 3 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, -OR<sup>1a</sup>, -C(O)OR<sup>1b</sup>, -SR<sup>1c</sup>, -S(O)R<sup>1d</sup>, -S(O)<sub>2</sub>R<sup>1e</sup> and -NR<sup>1f</sup>R<sup>1g</sup>; where each of R<sup>1a</sup>, R<sup>1b</sup>, R<sup>1c</sup>, R<sup>1d</sup>, R<sup>1e</sup>,  
20 R<sup>1f</sup> and R<sup>1g</sup> is independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and where each alkyl group present in R<sup>1</sup> is unsubstituted or substituted with from 1 to 3 fluoro substituents;

each R<sup>2</sup> is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, -OR<sup>2a</sup>, -C(O)OR<sup>2b</sup>, -SR<sup>2c</sup>, -S(O)R<sup>2d</sup>, -S(O)<sub>2</sub>R<sup>2e</sup> and  
25 -NR<sup>2f</sup>R<sup>2g</sup>; where each of R<sup>2a</sup>, R<sup>2b</sup>, R<sup>2c</sup>, R<sup>2d</sup>, R<sup>2e</sup>, R<sup>2f</sup> and R<sup>2g</sup> is independently selected from hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl; and where each alkyl group present in R<sup>2</sup> is unsubstituted or substituted with from 1 to 3 fluoro substituents;

$R^3$  is selected from hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, or (3-6C)cycloalkyl, where the alkyl group is unsubstituted or substituted with from 1 to 3 fluoro substituents;

$R^4$  represents a divalent hydrocarbon group containing from 4 to 28 carbon atoms and optionally containing from 1 to 10 heteroatoms selected independently from halo, oxygen, nitrogen and sulfur, provided that the number of contiguous atoms in the shortest chain between the two nitrogen atoms to which  $R^4$  is attached is in the range of from 4 to 16;

$R^5$  represents hydrogen or (1-4C)alkyl;

$R^6$  is  $-N(R^{6a})C(O)R^{6b}$  or  $-CR^{6c}R^{6d}OR^{6e}$  and  $R^7$  is hydrogen; or  $R^6$  and  $R^7$  together form  $-N(R^{7a})C(O)C(R^{7b})=C(R^{7c})-$ ,  $-C(R^{7d})=C(R^{7e})C(O)N(R^{7f})-$ ,  $-N(R^{7g})C(O)CR^{7h}R^{7i}-CR^{7j}R^{7k}-$  or  $-CR^{7l}R^{7m}-CR^{7n}R^{7o}C(O)-N(R^{7p})-$ ; where each of  $R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$ ,  $R^{6d}$  and  $R^{6e}$  is independently selected from hydrogen and (1-4C)alkyl; and each of  $R^{7a}$ ,  $R^{7b}$ ,  $R^{7c}$ ,  $R^{7d}$ ,  $R^{7e}$ ,  $R^{7f}$ ,  $R^{7g}$ ,  $R^{7h}$ ,  $R^{7i}$ ,  $R^{7j}$ ,  $R^{7k}$ ,  $R^{7l}$ ,  $R^{7m}$ ,  $R^{7n}$ ,  $R^{7o}$  and  $R^{7p}$  is independently selected from hydrogen and (1-4C)alkyl;

each  $R^{8a}$  and  $R^{8b}$  is independently selected from hydrogen and (1-4C)alkyl, or  $R^{8a}$  and  $R^{8b}$  are joined together with the atoms to which they are attached to form a (3-6C)cycloalkylene ring or a (2-5C)heterocyclene ring containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, or  $R^{8a}$  and  $W^a$  are joined together with the atoms to which they are attached to form a (2-6C)azacycloalkylene group;

$P^{14}$  represents a hydrogen atom or an amino-protecting group;

$P^{15}$  and  $P^{16}$  each independently represent a hydrogen atom or a hydroxyl-protecting group;

a is 0 or an integer of from 1 to 3;

b is an integer of from 2 to 8;

or a salt or solvate or stereoisomer thereof.

41. The compound of Claim 40, wherein  $Y^1$  is bromo.

42. A compound of any one of Claims 1 to 30 for use in therapy or as a medicament.



43. A compound of any one of Claims 1 to 30 as a medicament for treatment of a pulmonary disorder.

44. Medicament containing a compound of any one of Claims 1 to 30.

5

45. Use of a compound of any one of Claims 1 to 30 for the manufacture of a medicament.

46. The use of Claim 45, wherein the medicament is for the treatment of a  
10 pulmonary disorder.

**INTERNATIONAL SEARCH REPORT**

International Application No PCT/US2005/029018
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**A. CLASSIFICATION OF SUBJECT MATTER**  
 C07C271/08 C07C271/24 C07C275/28 A61K31/00

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)  
 C07C A61K

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, BEILSTEIN Data, CHEM ABS Data, PAJ, 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	WO 02/076933 A (GLAXO GROUP LIMITED; BIGGADIKE, KEITH; FIELD, RITA; GUNTRIP, STEPHEN,) 3 October 2002 (2002-10-03) the whole document	1-46
A	WO 02/070490 A (GLAXO GROUP LIMITED; COE, DIANE, MARY; MONTEITH, MICHAEL, JOHN; PROCOP) 12 September 2002 (2002-09-12) the whole document	1-46

Further documents are listed in the continuation of box C.       Patent family members are listed in annex.

\* Special categories of cited documents :

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

Date of the actual completion of the international search  19 December 2005	Date of mailing of the international search report  28/12/2005
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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Slootweg, A
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/029018

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	REITZ A B ET AL: "CONJUGATES OF CATECHOLAMINES. 6. SYNTHESIS AND BETA-ADRENERGIC ACTIVITY N-(HYDROCYALKYL)CATECHOLAMINE DERIVATIVES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 28, no. 5, May 1985 (1985-05), pages 642-647, XP002014818 ISSN: 0022-2623 compounds 12,13	1-46
P,A	----- WO 2004/074276 A1 (USA) 2 September 2004 (2004-09-02) the whole document	1-46
P,A	----- US 2005/113417 A1 (MAMMEN MATHAI ET AL) 26 May 2005 (2005-05-26) the whole document -----	1-46

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2005/029018

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

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

1.  Claims Nos.: 34-37, 42(part)  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/029018

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
WO 02076933	A	03-10-2002	EP 1370521 A1	17-12-2003
			JP 2004538259 T	24-12-2004
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			CA 2515777 A1	02-09-2004
			EP 1594860 A2	16-11-2005
			EP 1592685 A1	09-11-2005
			WO 2004074812 A2	02-09-2004
			WO 2004074246 A2	02-09-2004
US 2005113417	A1	26-05-2005	NONE	