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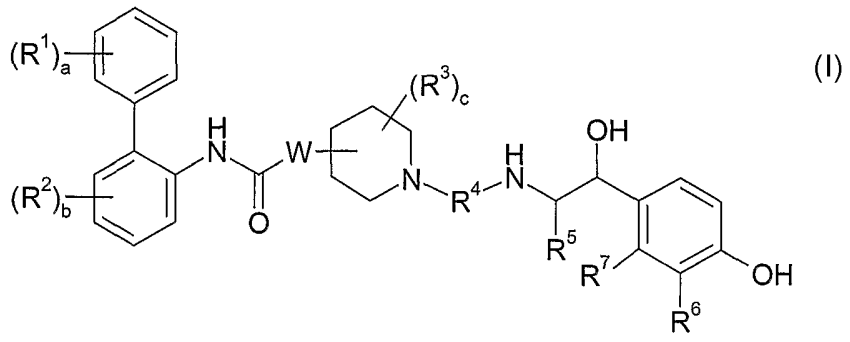
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(54) Title: LIBRARY OF BIPHENYL DERIVATIVES



(I)

(57) Abstract: This invention provides a library of biphenyl derivatives of formula I: wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, W, a, b and c are as defined in the specification, or a salt or stereoisomer thereof. The library is useful for identifying compounds having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity. Accordingly, this invention also provides methods of evaluating or screening a library of biphenyl derivatives to identifying compounds having such bifunctional activity.

WO 2004/074812 A2

LIBRARY OF BIPHENYL DERIVATIVES

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a library or collection of novel biphenyl derivatives. This invention also relates to methods of using the library of biphenyl derivatives to identify compounds having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity. Compounds having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity are useful for treating pulmonary disorders.

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 β_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.

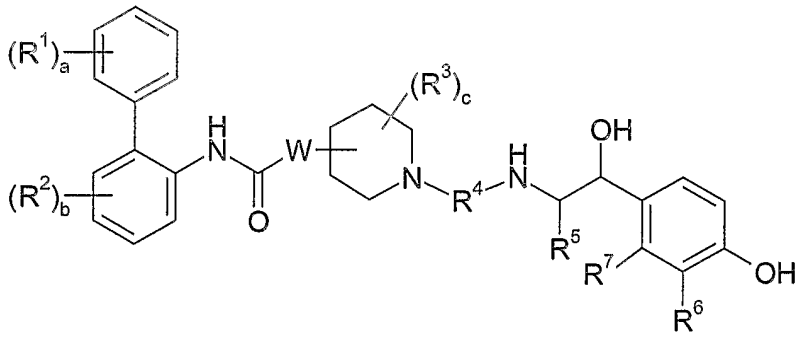
Pharmaceutical compositions containing both a β_2 adrenergic receptor agonist and a muscarinic receptor antagonist are also known in the art for use in treating pulmonary disorders. For example, U.S. Patent No. 6,433,027 discloses medicament compositions containing a muscarinic receptor antagonist, such as tiotropium bromide, and a β_2 adrenergic receptor agonist, such as formoterol fumarate.

Although compounds having either β_2 adrenergic receptor agonist or muscarinic receptor antagonist activity are known, no compound having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity has been previously disclosed. Compounds possessing both β_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. Accordingly, a need exists for methods of identifying compounds having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity.

SUMMARY OF THE INVENTION

The present invention provides a library or collection of novel biphenyl derivatives useful for identifying compounds having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity. This inventioin also provides methods of evaluating or screening such a library to identifying compounds having bifunctional activity.

Accordingly, in one of its composition aspects, the present invention is directed to a library comprising compounds of formula I:



I

wherein:

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

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

each of R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f} and R^{1g} is independently hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl;

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

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

each of R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f} and R^{2g} is independently hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl;

W is attached to the 3- or 4-position with respect to the nitrogen atom in the piperidine ring and represents O or NW^a;

W^a is hydrogen or (1-4C)alkyl;

c is 0 or an integer of from 1 to 4;

each R^3 is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, $-OR^{3a}$, $-C(O)OR^{3b}$, $-SR^{3c}$, $-S(O)R^{3d}$, $-S(O)_2R^{3e}$ and $-NR^{3f}R^{3g}$; or two R^3 groups are joined to form (1-3C)alkylene, (2-3C)alkenylene or oxiran-2,3-diyl;

each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^{3e}, R^{3f} and R^{3g} is independently hydrogen or (1-4C)alkyl;

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;

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

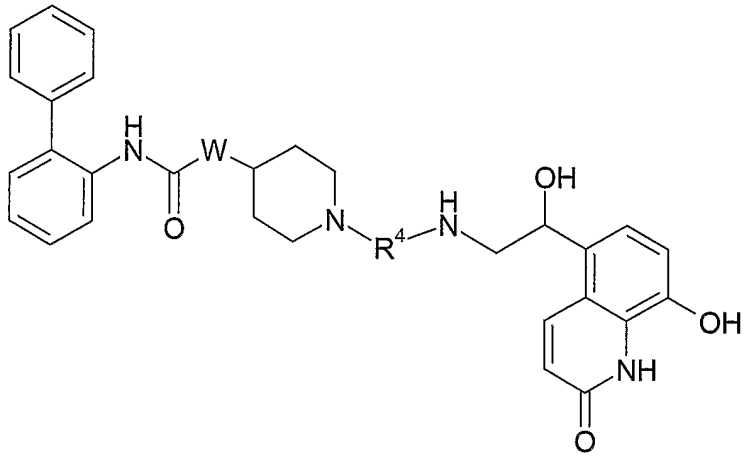
R^6 is $-NR^{6a}CR^{6b}(O)$ or $-CR^{6c}R^{6d}OR^{6e}$ and R^7 is hydrogen; or R^6 and R^7 together form $-NR^{7a}C(O)-CR^{7b}=CR^{7c}-$, $-CR^{7d}=CR^{7e}-C(O)-NR^{7f}-$, $-NR^{7g}C(O)-CR^{7h}R^{7i}-CR^{7j}R^{7k}-$ or $-CR^{7l}R^{7m}-CR^{7n}R^{7o}-C(O)-NR^{7p}-$;

each of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} is independently hydrogen or (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 hydrogen or (1-4C)alkyl;

or a salt or stereoisomer thereof.

In one embodiment, this invention is directed to a library that contains a compound of formula II:



II

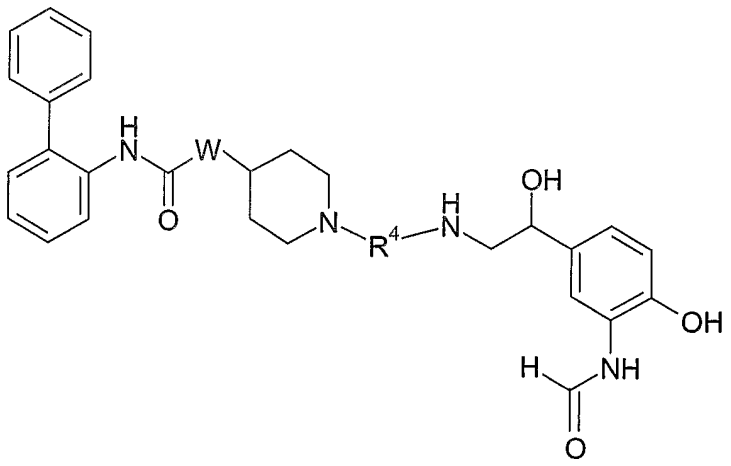
wherein

R^4 is as defined herein (including any specific or preferred embodiments);

W represents O or NH;

or a salt or stereoisomer thereof.

In another embodiment, this invention is directed to a library that contains a compound of formula III:



III

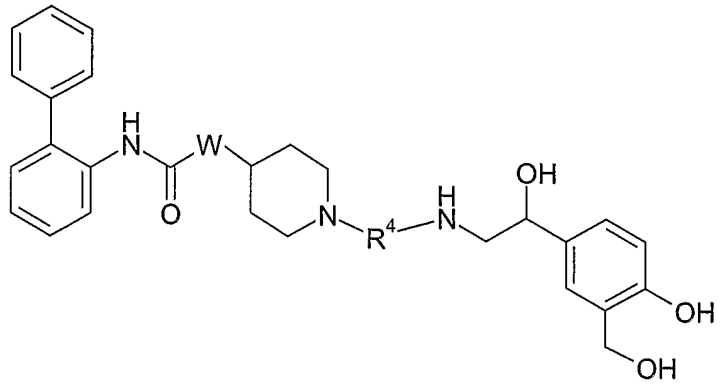
wherein

R^4 is as defined herein (including any specific or preferred embodiments);

W represents O or NH;

or a salt or solvate or stereoisomer thereof.

In yet another embodiment, this invention is directed to a library that contains a compound of formula IV:



IV

wherein

R^4 is as defined herein (including any specific or preferred embodiments);

W represents O or NH;

or a salt or stereoisomer thereof.

The libraries or collections of this invention are useful for identifying or finding or discovering compounds having both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity. Specifically, by evaluating or screening the members of the library in the appropriate assays, those members having bifunctional activity, if any, can be identified.

Accordingly, in one of its method aspects, this invention provides a method of identifying a compound of formula I having both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity; the method comprising:

evaluating a library comprising compounds of formula I to determine whether a compound in the library has both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity.

In another of its method aspects, this invention provides a method of identifying a compound of formula I having both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity; the method comprising:

(a) preparing a library comprising compounds of formula I;

(b) evaluating the compounds of formula I in the library to determine whether a compound has both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity.

When identifying compounds having both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity, it is often desirable to first identify compounds that bind to both a β_2 adrenergic receptor and a muscarinic receptor. Accordingly, in another of its method aspects, this invention provides a method of identifying a compound of formula I that binds to a β_2 adrenergic receptor and a muscarinic receptor; the method comprising:

evaluating a library comprising compounds of formula I to determine whether a compound in the library has a K_i value of less than about 300 nM for a β_2 adrenergic receptor and a K_i value less than 300 nM for a muscarinic receptor.

In still another of its method aspects, this invention provides a method of identifying a compound of formula I that binds to a β_2 adrenergic receptor and a muscarinic receptor; the method comprising:

(a) preparing a library comprising compounds of formula I;

(b) evaluating the compounds of formula I in the library to determine whether a compound has a K_i value of less than about 300 nM for a β_2 adrenergic receptor and a K_i value less than 300 nM for a muscarinic receptor.

In yet another of its method aspects, this invention provides a method of identifying a compound of formula I that binds to a β_2 adrenergic receptor and a muscarinic receptor; the method comprising:

evaluating a library comprising compounds of formula I to determine whether a compound in the library has an EC_{50} value of less than about 100 nM for a β_2 adrenergic receptor and a K_i value less than 100 nM for a muscarinic receptor.

In still another of its method aspects, this invention provides a method of identifying a compound of formula I that binds to a β_2 adrenergic receptor and a muscarinic receptor; the method comprising:

(a) preparing a library comprising compounds of formula I;

(b) evaluating the compounds of formula I in the library to determine whether a compound has a EC_{50} value of less than about 100 nM for a β_2 adrenergic receptor and a K_i value less than 100 nM for a muscarinic receptor.

This invention is also directed to processes for preparing a library of compounds of formula I. Accordingly, in another of its method aspects, this invention is directed to a process of preparing a library comprising compounds 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 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;

(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; and

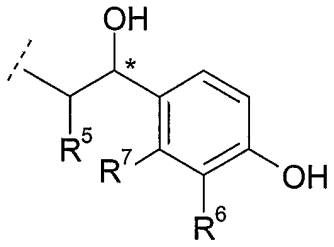
(h) removing any protecting groups to form a compound of formula I; wherein the compounds of formula **1**-**11** are as defined therein;

(i) repeating step (a), (b), (c), (d), (e), (f) or (g) and step (h) to prepare a library comprising compounds of formula I.

DETAILED DESCRIPTION OF THE INVENTION

In one of its aspects, the present invention is directed to a library or collection comprising novel biphenyl derivatives useful for identifying compounds having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity. In this regard, the compounds of formula I which comprise the library contain one or more chiral centers and therefore, this invention is directed a libraries containing racemic mixtures; pure stereoisomers (i.e., enantiomers or diastereomers); stereoisomer-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 the utility of the composition as a whole is not eliminated by the presence of such other isomers.

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



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 β_2 adrenergic agonist activity of the compounds of formula I, 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 formula I 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 biphenyl-2-ylcarbamic acid; and compounds of formula I wherein W is NW^a have been named as urea derivatives.

Representative Embodiments

The following substituents and values are intended to provide representative 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 indicated.

The libraries or collections of this invention are comprised of compounds of formula I or salts or stereoisomers thereof.

In particular embodiments of the compounds of formula I, a and b are independently 0, 1 or 2; including 0 or 1. In one embodiment, both a and b are 0.

When present, each R^1 may be at the 2, 3, 4, 5 or 6-position of the phenyl ring to which it is attached. In one embodiment, each R^1 is independently selected from (1-4C)alkyl, halo, $-OR^{1a}$ and $-NR^{1f}R^{1g}$; such as methyl, fluoro, chloro, bromo, hydroxy, methoxy, amino, methylamino, dimethylamino and the like. Particular values for R^1 are fluoro or chloro.

When present, each R^2 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^2 is independently selected from (1-4C)alkyl, halo, $-OR^{2a}$ and $-NR^{2f}R^{2g}$; such as methyl, fluoro, chloro, bromo, hydroxy, methoxy, amino, methylamino, dimethylamino and the like. Particular values for R^2 are fluoro or chloro.

Each R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f} and R^{1g} 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; such as hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl and 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 one embodiment of this invention, W is O. In another embodiment, W is NW^a.

Generally, it has been found that compounds in which W represents O exhibit particularly high affinity for muscarinic and β_2 adrenergic receptors. Accordingly, in a particular embodiment of this invention, W preferably represents O.

When referring to W, particular mention may be made of compounds wherein W is attached to the piperidine ring at the 4-position with respect to the nitrogen atom of the piperidine ring.

When W is NW^a, W^a 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^a is hydrogen or (1-3C)alkyl. In another embodiment, W^a is hydrogen, methyl or ethyl; such as hydrogen or methyl. In yet another embodiment, W^a is hydrogen and NW^a is NH.

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

In one embodiment, each R^3 is at the 3, 4 or 5-position on the piperidine ring (where the nitrogen atom of the piperidine ring is position 1). In another embodiment, R^3 is at 4-position on the piperidine ring. In a particular aspect of these embodiments, each R^3 is independently selected from (1-4C)alkyl; such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl and *tert*-butyl. In another aspect, each R^3 is independently methyl or ethyl.

In another embodiment, R^3 is at the 1-position of the piperidine ring, i.e., on the nitrogen atom of the piperidine ring thus forming a quaternary amine salt. In a particular aspect of this embodiment, each R^3 is independently selected from (1-4C)alkyl; such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl and *tert*-butyl. In another aspect, each R^3 is independently methyl or ethyl.

In yet another embodiment, two R^3 groups are joined to form a (1-3C)alkylene or (2-3C)alkenylene group. For example, two R^3 groups at the 2 and 6-positions on the piperidine ring can be joined to form an ethylene bridge (i.e., the piperidine ring and the R^3 groups form an 8-azabicyclo[3.2.1]octane ring); or two R^3 groups at the 1 and 4-positions on the piperidine ring can be joined to form an ethylene bridge (i.e., the piperidine ring and the R^3 groups form an 1-azabicyclo[2.2.2]octane ring). In this embodiment, other R^3 groups as defined herein may also be present.

In still another embodiment, two R^3 groups are joined to form a oxiran-2,3-diyl group. For example, two R^3 groups at the 2 and 6-positions on the piperidine ring can be joined to form a 3-oxatricyclo[3.3.1.$0^{2,4}$]nonane ring). In this embodiment, other R^3 groups as defined herein may also be present.

Each R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^{3e}, R^{3f} and R^{3g} as used in R^3 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.

In one embodiment of the compounds of formula I, R^5 is hydrogen or (1-4C)alkyl; such as hydrogen, methyl, 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 of this invention, R^6 is $-NR^{6a}CR^{6b}(O)$ 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 $-NR^{7a}C(O)-CR^{7b}=CR^{7c}-$, $-CR^{7d}=CR^{7e}-C(O)-NR^{7f}-$, $-NR^{7g}C(O)-CR^{7h}R^{7i}-CR^{7j}R^{7k}-$ or $-CR^{7l}R^{7m}-CR^{7n}R^{7o}-C(O)-NR^{7p}-$; 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-, $-CH_2-CH_2-C(O)NH-$ or $-NHC(O)-CH_2-CH_2-$; 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 the compounds of formula I, R^4 is 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. 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, 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 formula I is a divalent group of the formula:

$$-(R^{4a})_d-(A^1)_e-(R^{4b})_f-Q-(R^{4c})_g-(A^2)_h-(R^{4d})_i-$$

wherein

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

R^{4a}, R^{4b}, R^{4c} and R^{4d} 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;

A^1 and A^2 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 substitutents 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, $-S(O)_2$-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy;

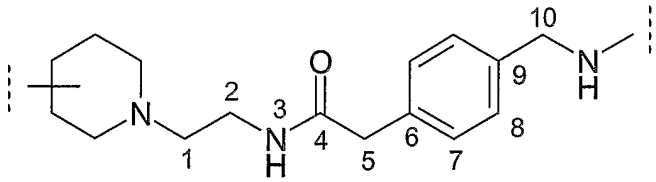
Q is selected from a bond, -O-, -C(O)O-, -OC(O)-, -S-, -S(O)-, $-S(O)_2$-, $-N(Q^a)C(O)$-, $-C(O)N(Q^b)$-, $-N(Q^c)S(O)_2$-, $-S(O)_2N(Q^d)$-, $-N(Q^e)C(O)N(Q^f)$-, $-N(Q^g)S(O)_2N(Q^h)$-, $-OC(O)N(Q^i)$-, $-N(Q^j)C(O)O$- and $-N(Q^k)$;

Q^a, Q^b, Q^c, Q^d, Q^e, Q^f, Q^g, Q^h, Q^i, Q^j and Q^k are each independently selected from hydrogen, (1-6C)alkyl, A^3 and (1-4C)alkylene-A^4, 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^{4b} or R^{4c} to which they are attached, form a 4-6 membered azacycloalkylene group;

A^3 and A^4 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 substitutents 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 a particular embodiment, 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 of the piperidine ring 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 of the piperidine ring ending with the last atom in the R^4 group adjacent to the nitrogen of the aminohydroxyethyl group as shown below:



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 $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$,

$-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_8-$, $-(CH_2)_9-$, $-(CH_2)_{10}-$, $-(CH_2)CH(CH_3)-$, $-(CH_2)C(CH_3)_2-$, and $-(CH_2)_2C(phenyl)_2-$. In another aspect, R^{4a} is $-(CH_2)C(=CH_2)-$.

In one embodiment, d is 1.

In one embodiment, A^1 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^1 is an optionally substituted (6-10C)arylene group, 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 napth-1,5-ylene.

In yet another embodiment, A^1 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^1 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^1 is an optionally substituted phenylene, thienylene, cyclopentylene, cyclohexylene or piperidinylene.

In one embodiment, e is 0.

In a particular embodiment, R^{4b} is (1-5C)alkylene. Representative examples of particular values for R^{4b} are $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$; including methylene, ethylene and propylene.

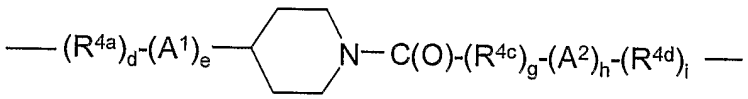
In one embodiment, f is 0.

In a particular embodiment, Q is selected from a bond, $-N(Q^a)C(O)-$, $-C(O)N(Q^b)-$, $-N(Q^c)S(O)_2-$, $-S(O)_2N(Q^d)-$, $-N(Q^e)C(O)N(Q^f)-$, $-OC(O)N(Q^j)-$, $-N(Q^j)C(O)O-$ or $-N(Q^k)$; such as where Q is a bond, $-N(Q^a)C(O)-$ or $-C(O)N(Q^b)-$. Representative examples of particular values for Q are a bond, O, NH, $-C(O)NH-$, $-C(O)N(CH_3)-$, $-NHC(O)-$, $-N(CH_3)C(O)-$, $-S(O)_2NH-$, $-S(O)_2N(CH_3)-$, $-NHS(O)_2-$, $-N(CH_3)S(O)_2-$ and $-NHC(O)NH-$. Another example of a value for Q, together with R^{4c}, is -C(O)(piperidin-1,4-ylene).

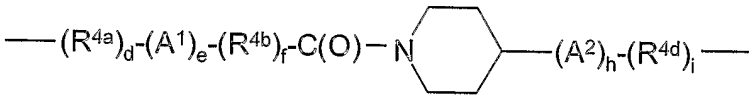
In one embodiment, Q^a, Q^b, Q^c, Q^d, Q^e, Q^f, Q^g, Q^h, Q^i, Q^j and Q^k are each independently selected from hydrogen and (1-6C)alkyl, wherein the alkyl group is unsubstituted or substituted with from 1 to 3 substituents independently selected from

fluoro, hydroxy and (1-4C)alkoxy. For example, Q^a, Q^b, Q^c, Q^d, Q^e, Q^f, Q^g, Q^h, Q^i, Q^j and Q^k 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^a, Q^b, Q^c, Q^d, Q^e, Q^f, Q^g, Q^h, Q^i, Q^j and Q^k is hydrogen.

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



Similarly, when Q represents $-C(O)N(Q^b)-$ and Q^b together with the nitrogen atom and the group R^{4c} to which it is attached, forms a piperidin-4-ylene group, R^4 is a group of formula:



In a particular embodiment, R^{4c} is (1-5C)alkylene. Representative examples of particular values for R^{4c} are $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$; including methylene, ethylene and propylene.

In one embodiment, A^2 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^2 is an optionally substituted (6-10C)arylene group, 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 napth-1,5-ylene.

In yet another embodiment, A^2 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^2 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^2 is optionally substituted phenylene, thienylene, cyclopentylene, cyclohexylene or piperidinylene.

By way of illustration, either A^1 or A^2 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, -$S(O)_2$-(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^1 or A^2 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^1 or A^2 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^{4d} 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^{4d} are -(CH_2)-, -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$(CH_2)_7$-, -$(CH_2)_8$-, -$(CH_2)_9$-, -$(CH_2)_{10}$- and -(CH_2)CH(CH_3)-(CH_2)-C$(CH_3)_2$-$(CH_2)_2$-.

In a particular embodiment, R^4 is a divalent group of the formula: $-(R^{4a})_d-$ where R^{4a} is (4-10C)alkylene. In one aspect of this embodiment, R^4 is a divalent group of the formula: $-(CH_2)_j-$ where j is 8, 9 or 10. Examples of particular values for R^4 in this embodiment are $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_8-$, $-(CH_2)_9$, and $-(CH_2)_{10}-$; including $-(CH_2)_8-$, $-(CH_2)_9$, and $-(CH_2)_{10}-$.

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

$$-(R^{4a})_d-(A^2)_h-(R^{4d})_i-$$

where R^{4a} is (1-10C)alkylene, such as $-(CH_2)-$, $-(CH_2)_2-$, $-(CH_2)_3-$; 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 $-(CH_2)-$, $-(CH_2)_2-$, $-(CH_2)_3-$. Examples of particular values for R^4 in this embodiment are $-(CH_2)$-(phen-1,4-ylene)-$(CH_2)-$; $-(CH_2)$-(phen-1,4-ylene)-$(CH_2)_2-$; $-(CH_2)$-(phen-1,4-ylene)-$(CH_2)_3-$; $-(CH_2)_2$-(phen-1,4-ylene)-$(CH_2)-$; $-(CH_2)_2$-(phen-1,4-ylene)-$(CH_2)_2-$; $-(CH_2)_2$-(phen-1,4-ylene)-$(CH_2)_3-$; $-(CH_2)_3$-(phen-1,4-ylene)-$(CH_2)-$; $-(CH_2)_3$-(phen-1,4-ylene)-$(CH_2)_2-$, $-(CH_2)_3$-(phen-1,4-ylene)-$(CH_2)_3-$, $-(CH_2)_4$-(phen-1,4-ylene)-$(CH_2)-$; $-(CH_2)_4$-(phen-1,4-ylene)-$(CH_2)_2-$ and $-(CH_2)_4$-(phen-1,4-ylene)-$(CH_2)_3-$.

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

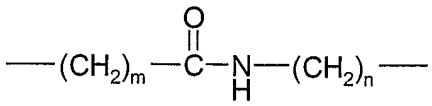
$$-(R^{4a})_d-Q-(A^2)_h-(R^{4d})_i-$$

where Q is -O- or $-N(Q^k)-$; Q^k is hydrogen or (1-3C)alkyl, such as methyl or ethyl; R^{4a} is (1-10C)alkylene, such as $-(CH_2)-$, $-(CH_2)_2-$, $-(CH_2)_3-$; 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 $-(CH_2)-$, $-(CH_2)_2-$, $-(CH_2)_3-$. Examples of particular values for R^4 in this embodiment are $-(CH_2)_2$-O-(phen-1,4-ylene)-$(CH_2)-$; $-(CH_2)_2$-O-(phen-1,4-ylene)-$(CH_2)_2-$; $-(CH_2)_2$-O-(phen-1,4-ylene)-$(CH_2)_3-$; $-(CH_2)_3$-O-(phen-1,4-ylene)-$(CH_2)-$; $-(CH_2)_3$-O-(phen-1,4-ylene)-$(CH_2)_2-$; $-(CH_2)_3$-O-(phen-1,4-ylene)-$(CH_2)_3-$; $-(CH_2)_2$-NH-(phen-1,4-ylene)-$(CH_2)-$; $-(CH_2)_2$-NH-(phen-1,4-ylene)-$(CH_2)_2-$; $-(CH_2)_2$-NH-(phen-1,4-ylene)-$(CH_2)_3-$; $-(CH_2)_3$-NH-(phen-1,4-ylene)-$(CH_2)-$; $-(CH_2)_3$-NH-(phen-1,4-ylene)-$(CH_2)_2-$ and $-(CH_2)_3$-NH-(phen-1,4-ylene)-$(CH_2)_3-$.

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

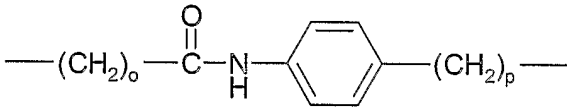
$$-(R^{4a})_d-(A^1)_e-(R^{4b})_f-Q-(R^{4c})_g-(A^2)_h-(R^{4d})_i-$$

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



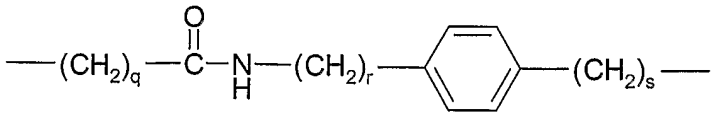
where m is an integer from 2 to 10; and n is an integer from 2 to 10; provided that m + n is an integer from 4 to 12. In this formula for R^4, d and g are 1 and e, f, h and i are 0; and R^{4a} is $-(CH_2)_m-$, R^{4c} is $-(CH_2)_n-$ and Q is –C(O)NH-. Particular values for m are 2 or 3; and for n, 4, 5 or 6.

Another particular value for R^4 is the formula:



where o is an integer from 2 to 7; and p is an integer from 1 to 6; provided that o + p 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 $-(CH_2)_o-$, A^2 is phen-1,4-ylene, R^{4d} is $-(CH_2)_p-$ and Q is –C(O)NH-. Particular values for o are 2 or 3; and for p, 1 or 2. In this embodiment, the phen-1,4-ylene group may be optionally substituted as defined herein for A^2.

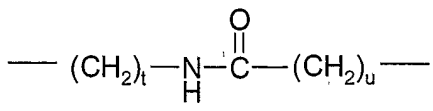
Another particular value for R^4 is the formula:



where q is an integer from 2 to 6; r is an integer from 1 to 5; and s is an integer from 1 to 5; provided that q + r + s 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 $-(CH_2)_q-$, R^{4c} is $-(CH_2)_r-$, A^2 is 1,4-phenylene, R^{4d} is $-(CH_2)_s-$ and Q is –C(O)NH-. Particular values for q are 2 or 3; for r, 1 or 2; and for s, 1 or

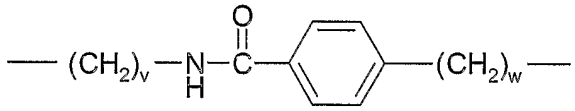
2. In this embodiment, the phen-1,4-ylene group may be optionally substituted as defined herein for A^2.

Another particular value for R^4 is the formula:



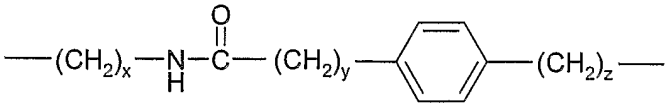
where t is an integer from 2 to 10; and u is an integer from 2 to 10; provided that t + u is an integer from 4 to 12. In this formula for R^4, d and g are 1 and e, f, h and i are 0; and R^{4a} is $-(CH_2)_t-$, R^{4c} is $-(CH_2)_u-$ and Q is –NHC(O)-. Particular values for t are 2 or 3; and for u, 4, 5 or 6.

Another particular value for R^4 is the formula:



where v is an integer from 2 to 7; and w is an integer from 1 to 6; provided that v + w 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 $-(CH_2)_v-$, A^2 is 1,4-phenylene, R^{4d} is $-(CH_2)_w-$ and Q is –NHC(O)-. Particular values for v are 2 or 3; and for w, 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 x is an integer from 2 to 6; y is an integer from 1 to 5; and z is an integer from 1 to 5; provided that x + y + z 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 $-(CH_2)_x-$, R^{4c} is $-(CH_2)_y-$, A^2 is 1,4-phenylene, R^{4d} is $-(CH_2)_z-$ and Q is –NHC(O)-. Particular values for x are 2 or 3; for y, 1 or 2; and for z, 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:

$-(CH_2)_7-$;

$-(CH_2)_8-$;

$-(CH_2)_9-$;

$-(CH_2)_{10}-$;

$-(CH_2)_{11}-$;

$-(CH_2)_2C(O)NH(CH_2)_5-$;

$-(CH_2)_2N(CH_3)C(O)(CH_2)_5-$;

$-(CH_2)_2C(O)NH$(phen-1,4-ylene)CH_2-;

$-(CH_2)_2NHC(O)$(phen-1,4-ylene)CH_2-;

$-(CH_2)_2NHC(O)NH(CH_2)_5-$;

$-(CH_2)_3NHC(O)NH(CH_2)_5-$;

$-(CH_2)_2C(O)NHCH_2$(cyclohex-1,3-ylene)CH_2-;

$-(CH_2)_2NHC(O)$(cyclopent-1,3-ylene)-;

$-(CH_2)_2NHC(O)NH$(phen-1,4-ylene)$(CH_2)_2-$;

1-[$-(CH_2)_2C(O)$](piperidin-4-yl)$(CH_2)_2-$;

$-(CH_2)_2NHC(O)$(*trans*-cyclohex-1,4-ylene)CH_2-;

$-(CH_2)_2NHC(O)$(*cis*-cyclopent-1,3-ylene)-;

$-(CH_2)_2NH$(phen-1,4-ylene)$(CH_2)_2-$;

1-[$-(CH_2)_2NHC(O)$](piperidin-4-yl)$(CH_2)_2-$;

$-CH_2$(phen-1,4-ylene)NH(phen-1,4-ylene)CH_2-;

$-(CH_2)_2C(O)NHCH_2$(phen-1,3-ylene)CH_2-;

$-(CH_2)_2C(O)NHCH_2$(pyrid-2,6-ylene)CH_2-;

$-(CH_2)_2C(O)NH$(*cis*-cyclohex-1,4-ylene)CH_2-;

$-(CH_2)_2C(O)NH$(*trans*-cyclohex-1,4-ylene)CH_2-;

$-(CH_2)_2NHC(O)$(*cis*-cyclopent-1,3-ylene)CH_2-;

$-(CH_2)_2N(CH_3)C(O)$(phen-1,3-ylene)CH_2-;

$-(CH_2)_2N(CH_3)C(O)$(*trans*-cyclohex-1,4-ylene)CH_2-;

$-(CH_2)_2C(O)NH$(phen-1,4-ylene)CH_2-;

$-(CH_2)_2C(O)NH$(phen-1,4-ylene)$C^*H(CH_3)-$ ((*S*)-isomer);

$-(CH_2)_2C(O)NH$(phen-1,4-ylene)$C^*H(CH_3)-$ ((*R*)-isomer);

2-[(S)-$(-CH_2-]$(pyrrolidin-1-yl)$C(O)(CH_2)_4-$;

2-[(S)-$(-CH_2-]$(pyrrolidin-1-yl)$C(O)$(phen-1,4-ylene)CH_2-;

-$(CH_2)_2C(O)NH$(4-chlorophen-1,3-ylene)CH_2-;
-CH_2(2-fluorophen-1,3-ylene)CH_2-;
-$(CH_2)_2C(O)NH$(4-methylphen-1,3-ylene)CH_2-;
-$(CH_2)_2C(O)NH$(6-chlorophen-1,3-ylene)CH_2-;
-$(CH_2)_2C(O)NH$(2-chlorophen-1,4-ylene)CH_2-;
-$(CH_2)_2C(O)NH$(2,6-dichlorophen-1,4-ylene)CH_2-;
-$(CH_2)_2NHC(O)NHCH_2$(phen-1,3-ylene)CH_2-;
4-[-CH_2-](piperidin-1-yl)C(O)(phen-1,4-ylene)CH_2-;
-$(CH_2)_2C(O)N(CH_2CH_3)$(phen-1,4-ylene)CH_2-;
1-[-$(CH_2)_2NHC(O)$](piperidin-4-yl)-;
-$(CH_2)_2C(O)NH$(phen-1,4-ylene)$(CH_2)_2$-;
-$(CH_2)_2NHC(O)$(thien-2,5-ylene)CH_2-;
-$(CH_2)_2N(CH_3)C(O)$(3-nitrophen-1,4-ylene)CH_2-;
-$(CH_2)_2N(CH_3)C(O)$(*trans*-cyclohex-1,4-ylene)-;
1-[-CH_2(2-fluorophen-1,3-ylene)CH_2](piperidin-4-yl)-;
5-[-$(CH_2)_2NHC(O)$](pyrid-2-yl)CH_2-;
-$(CH_2)_2$(phen-1,4-ylene)$(CH_2)_2$-;
-$(CH_2)_3$(thien-2,5-ylene)$(CH_2)_3$-;
-$(CH_2)_2$(phen-1,4-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-;
-CH_2(phen-1,2-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-;
1-[-CH_2(2-fluorophen-1,3-ylene)CH_2](piperidin-4-yl)$(CH_2)_2$-;
1-[-CH_2(2-fluorophen-1,3-ylene)CH_2](piperidin-4-yl)CH_2-;
-$(CH_2)_2C(O)NH$(3-chlorophen-1,4-ylene)CH_2-;
-$(CH_2)_2C(O)NH$(2-(CF_3O-)phen-1,4-ylene)CH_2-;
-$(CH_2)_3$(phen-1,3-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-;
-$(CH_2)_2S(O)_2NH(CH_2)_5$-;
-CH_2(phen-1,3-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-;
-$(CH_2)_2C(O)NH$(2-iodophen-1,4-ylene)CH_2-;
-$(CH_2)_2C(O)NH$(2-chloro-5-methoxyphen-1,4-ylene)CH_2-;
-$(CH_2)_2C(O)NH$(2-chloro-6-methylphen-1,4-ylene)CH_2-;
-$(CH_2)_2C(O)NH(CH_2)_5$-;
-$(CH_2)_2N(CH_3)S(O)_2$(phen-1,4-ylene)CH_2-;
-$(CH_2)_2C(O)NH$(2-bromophen-1,4-ylene)CH_2-;

-$(CH_2)_3$(phen-1,4-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_3$(phen-1,2-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-;

1-[-CH_2(2-fluorophen-1,3-ylene)CH_2](piperidin-4-yl)$(CH_2)_3$-;

-$(CH_2)_2$C(O)NH(2-methoxyphen-1,4-ylene)CH_2-;

-$(CH_2)_5$NH(phen-1,4-ylene)$(CH_2)_2$-;

4-[-$(CH_2)_2$-](piperidin-1-yl)(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_2$C(O)NH(phen-1,4-ylene)CH(CH_3)CH_2-;

-$(CH_2)_2$-(*trans*-cyclohex-1,4-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_2$C(O)NH(2-fluorophen-1,4-ylene)CH_2-;

-$(CH_2)_2$(phen-1,3-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_2$C(O)NH(2,5-difluorophen-1,4-ylene)CH_2-;

-$(CH_2)_2$NHC(O)(phen-1,4-ylene)$(CH_2)_2$-;

1-[-CH_2(pyrid-2,6-ylene)CH_2](piperidin-4-yl)CH_2-;

-$(CH_2)_3$NH(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_2$NH(naphth-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_3$O(phen-1,4-ylene)CH_2-;

1-[-$(CH_2)_3$](piperidin-4-yl)CH_2-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)(phen-1,4-ylene)CH_2-;

-$(CH_2)_3$(phen-1,4-ylene)NHC(O)$(CH_2)_2$-;

-$(CH_2)_3$O(phen-1,4-ylene)$(CH_2)_2$-;

2-[-$(CH_2)_2$](benzimidazol-5-yl)CH_2-;

-$(CH_2)_2$-(*trans*-cyclohex-1,4-ylene)NHC(O)$(CH_2)_2$-;

-$(CH_2)_2$-(*trans*-cyclohex-1,4-ylene)NHC(O)$(CH_2)_4$-;

-$(CH_2)_2$-(*trans*-cyclohex-1,4-ylene)NHC(O)$(CH_2)_5$-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)$(CH_2)_2$-;

-$(CH_2)_2$NHC(O)NH(phen-1,4-ylene)CH_2-;

-$(CH_2)_2$N(CH_3)$(CH_2)_2$(*cis*-cyclohex-1,4-ylene)-;

-$(CH_2)_2$C(O)NH(2,3,5,6-tetrafluorophen-1,4-ylene)CH_2-;

-$(CH_2)_2$C(O)NH(2,6-diiodophen-1,4-ylene)CH_2-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)$(CH_2)_3$-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)$(CH_2)_4$-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)$(CH_2)_5$-;

-$(CH_2)_2$C(O)NHCH$_2$(phen-1,4-ylene)CH_2-;

-$(CH_2)_2$NHC(O)NHCH$_2$(phen-1,4-ylene)CH$_2$-;

-$(CH_2)_2$C(O)NH(2-methylphen-1,4-ylene)CH$_2$-;

1-[-$(CH_2)_3$O(phen-1,4-ylene)$(CH_2)_2$](piperidin-4-yl)CH$_2$-;

-$(CH_2)_2$C(O)NHCH$_2$(phen-1,3-ylene)$(CH_2)_2$-;

-$(CH_2)_2$O(phen-1,3-ylene)CH$_2$-;

-$(CH_2)_2$N(CH_3)C(O)CH$_2$O(phen-1,4-ylene)CH$_2$-;

-$(CH_2)_2$N(CH_3)C(O)CH$_2$O(phen-1,3-ylene)CH$_2$-;

-$(CH_2)_2$N(CH_3)C(O)(fur-2,5-ylene)CH$_2$-;

-$(CH_2)_2$N(CH_3)C(O)(thien-2,5-ylene)CH$_2$-;

-$(CH_2)_2$O(phen-1,4-ylene)O$(CH_2)_2$-;

-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)(phen-1,4-ylene)CH$_2$-;

-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)CH$_2$O(phen-1,2-ylene)CH$_2$-;

-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)CH$_2$O(phen-1,3-ylene)CH$_2$-;

-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)CH$_2$O(phen-1,4-ylene)CH$_2$-;

-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)(fur-2,5-ylene)CH$_2$-;

-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)(thien-2,5-ylene)CH$_2$-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)CH$_2$O(phen-1,2-ylene)CH$_2$-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)CH$_2$O(phen-1,3-ylene)CH$_2$-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)CH$_2$O(phen-1,4-ylene)CH$_2$-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)(fur-2,5-ylene)CH$_2$-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)(thien-2,5-ylene)CH$_2$-;

-$(CH_2)_2$(phen-1,4-ylene)NHC(O)(phen-1,3-ylene)CH$_2$-;

-$(CH_2)_2$(phen-1,4-ylene)NHC(O)(phen-1,4-ylene)CH$_2$-;

-$(CH_2)_2$(phen-1,4-ylene)NHC(O)CH$_2$O(phen-1,2-ylene)CH$_2$-;

-$(CH_2)_2$(phen-1,4-ylene)NHC(O)CH$_2$O(phen-1,3-ylene)CH$_2$-;

-$(CH_2)_2$(phen-1,4-ylene)NHC(O)CH$_2$O(phen-1,4-ylene)CH$_2$-;

-$(CH_2)_2$(phen-1,4-ylene)NHC(O)(fur-2,5-ylene)CH$_2$-;

-$(CH_2)_2$(phen-1,4-ylene)NHC(O)(thien-2,5-ylene)CH$_2$-;

-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)(phen-1,3-ylene)CH$_2$-;

-$(CH_2)_3$O(phen-1,3-ylene)CH$_2$-;

-CH_2CH(OH)CH_2NH(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_4$NH(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_2$C(O)NH(phen-1,4-ylene)CH_2NHC(O)CH_2-;

-$(CH_2)_2C(O)NH$(phen-1,4-ylene)$(CH_2)_2NHC(O)CH_2$-;

-$(CH_2)_2C(O)NHCH_2$(*trans*-cyclohex-1,4-ylene)CH_2-;

-$(CH_2)_2NHC(O)(CH_2)_5$-;

-$(CH_2)_2O$(phen-1,3-ylene)$O(CH_2)_2$-;

-$(CH_2)_2O$(phen-1,2-ylene)$O(CH_2)_2$-;

-CH_2(phen-1,2-ylene)O(phen-1,2-ylene)CH_2-;

-$(CH_2)_2C(O)NH(CH_2)_6$-;

-$(CH_2)_3$(phen-1,4-ylene)$(CH_2)_3$-;

-$(CH_2)_3$(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_4$(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_3$(furan-2,5-ylene)$(CH_2)_3$-;

-$(CH_2)_2N(CH_3)C(O)NH$(phen-1,4-ylene)$(CH_2)_2$-;

4-[-$(CH_2)_2$](piperidin-1-yl)C(O)NH(phen-1,4-ylene)$(CH_2)_2$-;

-$(CH_2)_3$(phen-1,3-ylene)$(CH_2)_3$-;

-$(CH_2)_3$(tetrahydrofuran-2,5-ylene)$(CH_2)_3$-; and

-$(CH_2)_2O$(phen-1,4-ylene)$C(O)(CH_2)_2$-.

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. In particular, these subgeneric formulae and groupings provide representative examples of compounds of formula I that may be found in particular libraries of this invention.

A particular group of compounds of formula I are those disclosed in U.S. Provisional Application No. 60/447,843, filed on February 14, 2003. This group includes compounds of formula I; wherein:

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

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

each of R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f} and R^{1g} is independently hydrogen or (1-4C)alkyl;

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

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

each of R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f} and R^{2g} is independently hydrogen or (1-4C)alkyl;

W is attached to the 3- or 4-position with respect to the nitrogen atom in the piperidine ring, and represents O or NW^a;

W^a is hydrogen or (1-4C)alkyl;

c is 0 or an integer of from 1 to 4;

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

each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^{3e}, R^{3f} and R^{3g} is independently hydrogen or (1-4C)alkyl;

R^4 is a divalent group of the formula:

$$-(R^{4a})_d-(A^1)_e-(R^{4b})_f-Q-(R^{4c})_g-(A^2)_h-(R^{4d})_i-$$

wherein

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

R^{4a}, R^{4b}, R^{4c} and R^{4d} 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;

A^1 and A^2 are each independently selected from (3-7C)cycloalkylene, (6-10C)arylene, (2-9C)heteroarylene and (3-6C)heterocyclene; wherein each cycloalkylene is unsubstituted or substituted with from 1 to 4 substitutents 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 and (1-4C)alkoxy;

Q is selected from a bond, -O-, -C(O)O-, -OC(O)-, -S-, -S(O)-, $-S(O)_2-$, $-N(Q^a)C(O)-$, $-C(O)N(Q^b)-$, $-N(Q^c)S(O)_2-$, $-S(O)_2N(Q^d)-$, $-N(Q^e)C(O)N(Q^f)-$, $-N(Q^g)S(O)_2N(Q^h)-$, $-OC(O)N(Q^i)-$ and $-N(Q^j)C(O)O-$;

Q^a, Q^b, Q^c, Q^d, Q^e, Q^f, Q^g, Q^h, Q^i and Q^j are each independently selected from hydrogen, (1-6C)alkyl, A^3 and (1-4C)alkylene-A^4; 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^{4b} or R^{4c} to which they are attached, form a 4-6 membered azacycloalkylene group;

A^3 and A^4 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 substitutents 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;

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 8 to 14;

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

R^6 is $-NR^{6a}CR^{6b}(O)$ and R^7 is hydrogen, or R^6 and R^7 together form $-NR^{7a}C(O)-CR^{7b}=CR^{7c}-$, $-CR^{7d}=CR^{7e}-C(O)-NR^{7f}-$, $-NR^{7g}C(O)-CR^{7h}R^{7i}-CR^{7j}R^{7k}-$ or $-CR^{7l}R^{7m}-CR^{7n}R^{7o}-C(O)-NR^{7p}-$;

each of R^{6a} and R^{6b} is independently hydrogen or (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 hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

Another particular group of compounds of formula I are those disclosed in U.S. Provisional Application No. 60/467,035, filed on May 1, 2003. This group of compounds includes compounds of formula I; wherein:

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

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

each of R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f} and R^{1g} is independently hydrogen or (1-4C)alkyl;

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

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

each of R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f} and R^{2g} is independently hydrogen or (1-4C)alkyl;

W is attached to the 3- or 4-position with respect to the nitrogen atom in the piperidine ring, and represents O or NW^a;

W^a is hydrogen or (1-4C)alkyl;

c is 0 or an integer of from 1 to 4;

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

each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^{3e}, R^{3f} and R^{3g} is independently hydrogen or (1-4C)alkyl;

R^4 is a divalent group of the formula:

$$-(R^{4a})_d-(A^1)_e-(R^{4b})_f-Q-(R^{4c})_g-(A^2)_h-(R^{4d})_i-$$

wherein

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

R^{4a}, R^{4b}, R^{4c} and R^{4d} 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;

A^1 and A^2 are each independently selected from (3-7C)cycloalkylene, (6-10C)arylene, (2-9C)heteroarylene and (3-6C)heterocyclene; wherein each cycloalkylene is unsubstituted or substituted with from 1 to 4 substitutents 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 and (1-4C)alkoxy;

Q is selected from a bond, -O-, -C(O)O-, -OC(O)-, -S-, -S(O)-, $-S(O)_2-$, $-N(Q^a)C(O)-$, $-C(O)N(Q^b)-$, $-N(Q^c)S(O)_2-$, $-S(O)_2N(Q^d)-$, $-N(Q^e)C(O)N(Q^f)-$, $-N(Q^g)S(O)_2N(Q^h)-$, $-OC(O)N(Q^i)-$ and $-N(Q^j)C(O)O-$;

Q^a, Q^b, Q^c, Q^d, Q^e, Q^f, Q^g, Q^h, Q^i and Q^j are each independently selected from hydrogen, (1-6C)alkyl, A^3 and (1-4C)alkylene-A^4; 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^{4b} or R^{4c} to which they are attached, form a 4-6 membered azacycloalkylene group;

A^3 and A^4 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 substitutents 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;

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 14;

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

R^6 is $-NR^{6a}CR^{6b}(O)$ or $CR^{6c}R^{6d}OR^{6e}$ and R^7 is hydrogen, or R^6 and R^7 together form $-NR^{7a}C(O)-CR^{7b}=CR^{7c}-$, $-CR^{7d}=CR^{7e}-C(O)-NR^{7f}-$, $-NR^{7g}C(O)-CR^{7h}R^{7i}-CR^{7j}R^{7k}-$ or $-CR^{7l}R^{7m}-CR^{7n}R^{7o}-C(O)-NR^{7p}-$;

each of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} is independently hydrogen or (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 hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt or solvate or stereoisomer thereof.

Another particular group of compounds of formula I are those where: a is 0; b is 0; c is 0; W is O; W is attached at the 4-position of the piperidinyl ring; R^5 is hydrogen; and R^4, R^6 and R^7 are as defined herein; or a salt or stereoisomer thereof.

Still another particular group of compounds of formula I are those wherein: a is 0; b is 0; c is 0; W is NH; W is attached at the 4-position of the piperidinyl ring; R^5 is hydrogen; and R^4, R^6 and R^7 are as defined herein; or a salt or stereoisomer thereof.

Yet another particular group of compounds of formula I are those wherein: a is 0; b is 0; c is 0; W is O; W is attached at the 4-position of the piperidinyl ring; R^4 is $-(CH_2)_j-$ where j is 8, 9 or 10; R^5 is hydrogen; and R^6 and R^7 are as defined herein; or a salt or stereoisomer thereof.

Another particular group of compounds of formula I are those wherein: a is 0; b is 0; c is 0; W is NH; W is attached at the 4-position of the piperidinyl ring; R^4 is $-(CH_2)_j-$ where j is 8, 9 or 10; R^5 is hydrogen; and R^6 and R^7 are as defined herein; or a salt or stereoisomer thereof.

Yet another particular group of compounds of formula I are those wherein: a is 0; b is 0; c is 0; W is O; W is attached at the 4-position of the piperidinyl ring; R^4 is $-(CH_2)_2-$

C(O)NH-$(CH_2)_5$-; R^5 is hydrogen; and R^6 and R^7 are as defined herein; or a salt or stereoisomer thereof.

Another particular group of compounds of formula I are those wherein: a is 0; b is 0; c is 0; W is NH; W is attached at the 4-position of the piperidinyl ring; R^4 is $-(CH_2)_2$-C(O)NH-$(CH_2)_5$-; R^5 is hydrogen; and R^6 and R^7 are as defined herein; or a salt or stereoisomer thereof.

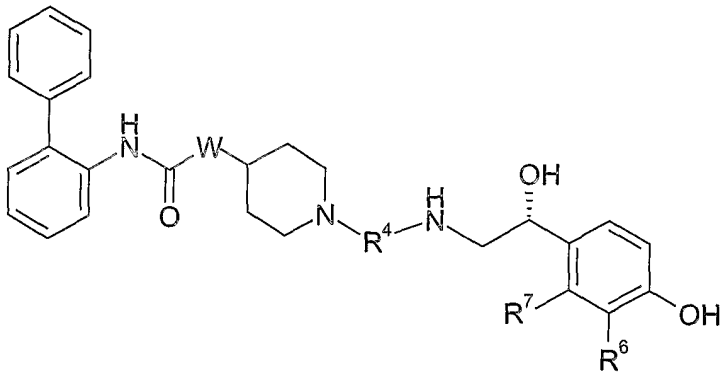
Another particular group of compounds of formula I are those of formula II as defined herein; or a salt or stereoisomer thereof.

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

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

Another particular group of compounds of formula I are those of formula II, III or IV as defined herein, wherein the piperidinyl ring is substitued at the 4-position with a methyl group; or a salt or stereoisomer thereof.

Representative compounds of formula I include compounds of formula V:



V

wherein W, R^4, R^6 and R^7 are as defined in Table I; or a pharmaceutically acceptable salt or solvate thereof.

Table I

Ex.	W	R^4	R^6	R^7
1	NH	$-(CH_2)_9-$ (racemic)[1]	-NHC(O)CH=CH-[2]	
2	O	$-(CH_2)_9-$ (racemic)	-NHC(O)CH=CH-	
3	O	$-(CH_2)_9-$	-NHC(O)CH=CH-	
4	O	$-(CH_2)_9-$	H	-NHC(O)H
5	O	$-(CH_2)_9-$	$-NHC(O)CH_2CH_2-$	
6	O	$-(CH_2)_2C(O)NH(CH_2)_5-$	-NHC(O)CH=CH-	
7	O	$-(CH_2)_2N(CH_3)C(O)(CH_2)_5-$	-NHC(O)CH=CH-	
8	O	$-(CH_2)_2C(O)NH$(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
9	O	$-(CH_2)_2NHC(O)$(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
10	O	$-(CH_2)_2NHC(O)NH(CH_2)_5-$	-NHC(O)CH=CH-	
11	O	$-(CH_2)_3NHC(O)NH(CH_2)_5-$	-NHC(O)CH=CH-	
12	O	$-(CH_2)_9-$	H	$-CH_2OH$
13	NH	$-(CH_2)_9-$	H	$-CH_2OH$
14	O	$-(CH_2)_2C(O)NHCH_2$(cyclohex-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
15	O	$-(CH_2)_2NHC(O)$(*cis*-cyclopent-1,3-ylene)-	$-NHC(O)CH_2CH_2-$	
16	O	$-(CH_2)_2C(O)NH$(2-chlorophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
17	O	$-(CH_2)_2S(O)_2NH(CH_2)_5-$	-NHC(O)CH=CH-	
18	O	$-(CH_2)_2N(CH_3)S(O)_2$(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
19	O	$-(CH_2)_2NHC(O)NHCH_2$(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
20	O	$-(CH_2)_3$(phen-1,4-ylene)NH(phen-1,4-ylene)$(CH_2)_2-$	-NHC(O)CH=CH-	
21	O	1-[$-CH_2$(2-fluorophen-1,3-ylene)CH_2](piperidin-4-yl)CH_2-	-NHC(O)CH=CH-	
22	O	$-(CH_2)_3O$(phen-1,4-ylene)$(CH_2)_2-$	-NHC(O)CH=CH-	
23	O	$-(CH_2)_2$(phen-1,4-ylene)$(CH_2)_2-$	-NHC(O)CH=CH-	
24	O	$-(CH_2)_3$(thien-2,5-ylene)$(CH_2)_3-$	-NHC(O)CH=CH-	
25	O	$-(CH_2)_2C(O)NH$(2-chloro-5-methoxyphen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
26	O	$-(CH_2)_7-$	-NHC(O)CH=CH-	
27	O	$-(CH_2)_8-$	-NHC(O)CH=CH-	

Ex.	W	R^4	R^6	R^7
28	O	-$(CH_2)_2$NHC(O)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
29	O	1-[-$(CH_2)_2$C(O)](piperidin-4-yl)$(CH_2)_2$-	-NHC(O)CH=CH-	
30	O	-$(CH_2)_2$NHC(O)(*trans*-cyclohex-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
31	O	-$(CH_2)_2$NHC(O)(*cis*-cyclopent-1,3-ylene)-	-NHC(O)CH=CH-	
32	O	-$(CH_2)_2$NHC(O)NH$(CH_2)_5$-	H	-NHC(O)H
33	O	-$(CH_2)_2$NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
34	O	-$(CH_2)_3$NHC(O)NH$(CH_2)_5$-	H	-NHC(O)H
35	O	1-[-$(CH_2)_2$NHC(O)](piperidin-4-yl)$(CH_2)_2$-	-NHC(O)CH=CH-	
36	O	-CH_2(phen-1,4-ylene)NH(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
37	O	-$(CH_2)_2$C(O)NHCH_2(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
38	NH	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
39	O	-$(CH_2)_2$C(O)NHCH_2(pyrid-2,6-ylene)CH_2-	-NHC(O)CH=CH-	
40	O	-$(CH_2)_2$C(O)NH(*cis*-cyclohex-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
41	O	-$(CH_2)_2$C(O)NH(*trans*-cyclohex-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
42	O	-$(CH_2)_2$NHC(O)(*cis*-cyclopent-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
43	O	-$(CH_2)_2$N(CH_3)C(O)(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
44	O	-$(CH_2)_2$N(CH_3)C(O)(*trans*-cyclohex-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
45	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)CH_2- (racemic)	-NHC(O)CH=CH-	
46	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)C*H(CH_3)-((*S*)-isomer)	-NHC(O)CH=CH-	
47	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)C*H(CH_3)-((*R*)-isomer)	-NHC(O)CH=CH-	
48	O	2-[(S)-(-CH_2-](pyrrolidin-1-yl)C(O)$(CH_2)_4$-	-NHC(O)CH=CH-	
49	O	2-[(S)-(-CH_2-](pyrrolidin-1-yl)C(O)(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
50	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)CH_2-	H	-NHC(O)H
51	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)C*H(CH_3)-((*R*)-isomer)	H	-NHC(O)H
52	O	-$(CH_2)_2$C(O)NH(4-chlorophen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
53	NH	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
54	NH	1-[-$(CH_2)_2$C(O)](piperidin-4-yl)$(CH_2)_2$-	-NHC(O)CH=CH-	

Ex.	W	R^4	R^6	R^7
55	NH	-$(CH_2)_2$C(O)NHCH_2(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
56	O	-CH_2(2-fluorophen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
57	O	-$(CH_2)_2$C(O)NH(4-methylphen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
58	O	-$(CH_2)_2$C(O)NH(6-chlorophen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
59	O	-$(CH_2)_2$C(O)NH(2,6-dichlorophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
60	O	4-[-CH_2-](piperidin-1-yl)C(O)(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
61	O	-$(CH_2)_2$NHC(O)(phen-1,4-ylene)CH_2-	H	-NHC(O)H
62	O	-$(CH_2)_2$C(O)N(CH_2CH_3)(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
63	O	1-[-$(CH_2)_2$NHC(O)](piperidin-4-yl)-	-NHC(O)CH=CH-	
64	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
65	O	-$(CH_2)_2$NHC(O)(thien-2,5-ylene)CH_2-	-NHC(O)CH=CH-	
66	O	-$(CH_2)_2$N(CH_3)C(O)(3-nitrophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
67	O	-$(CH_2)_2$C(O)NH(*trans*-cyclohex-1,4-ylene)CH_2-	H	-NHC(O)H
68	O	-$(CH_2)_2$N(CH_3)C(O)(*trans*-cyclohex-1,4-ylene)-	-NHC(O)CH=CH-	
69	O	1-[-CH_2(2-fluorophen-1,3-ylene)CH_2](piperidin-4-yl)-	-NHC(O)CH=CH-	
70	O	5-[-$(CH_2)_2$NHC(O)](pyrid-2-yl)CH_2-	-NHC(O)CH=CH-	
71	O	1-[-$(CH_2)_3$](piperidin-4-yl)CH_2-	-NHC(O)CH=CH-	
72	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)$(CH_2)_2$-	H	-NHC(O)H
73	O	-CH_2(phen-1,2-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
74	O	1-[-CH_2(2-fluorophen-1,3-ylene)CH_2](piperidin-4-yl)$(CH_2)_2$-	-NHC(O)CH=CH-	
75	O	-$(CH_2)_3$NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
76	O	-$(CH_2)_2$C(O)NH(3-chlorophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
77	O	-$(CH_2)_2$C(O)NH(2-(CF_3O-)phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
78	O	-$(CH_2)_3$(phen-1,3-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
79	O	-CH_2(phen-1,3-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
80	O	-$(CH_2)_2$C(O)NH(2-iodophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
81	O	-$(CH_2)_2$C(O)NH(2-chloro-6-methylphen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
82	O	-$(CH_2)_2$C(O)NH$(CH_2)_5$- (racemic)	-NHC(O)CH=CH-	

Ex.	W	R^4	R^6 R^7
83	O	-$(CH_2)_2$C(O)NH(2-bromophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-
84	O	-$(CH_2)_3$(phen-1,2-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-
85	O	1-[-CH_2(2-fluorophen-1,3-ylene)CH_2](piperidin-4-yl)$(CH_2)_3$-	-NHC(O)CH=CH-
86	O	-$(CH_2)_2$C(O)NH(2-methoxyphen-1,4-ylene)CH_2-	-NHC(O)CH=CH-
87	O	-$(CH_2)_5$NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-
88	O	4-[-$(CH_2)_2$-](piperidin-1-yl)(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-
89	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)CH$(CH_3)CH_2$-	-NHC(O)CH=CH-
90	O	-$(CH_2)_2$-(*trans*-cyclohex-1,4-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-
91	O	-$(CH_2)_2$C(O)NH(2-fluorophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-
92	O	-$(CH_2)_2$(phen-1,3-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-
93	O	-$(CH_2)_2$C(O)NH(2,5-difluorophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-
94	O	-$(CH_2)_2$NHC(O)(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-
95	O	1-[-CH_2(pyrid-2,6-ylene)CH_2](piperidin-4-yl)CH_2-	-NHC(O)CH=CH-
96	O	-$(CH_2)_2$NH(naphth-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-
97	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-
98	O	-$(CH_2)_3$(phen-1,4-ylene)NHC(O)$(CH_2)_2$-	-NHC(O)CH=CH-
99	O	-$(CH_2)_3$O(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-
100	O	2-[-$(CH_2)_2$](benzimidazol-5-yl)CH_2-	-NHC(O)CH=CH-
101	O	-$(CH_2)_2$-(*trans*-cyclohex-1,4-ylene)NHC(O)$(CH_2)_2$-	-NHC(O)CH=CH-
102	O	-$(CH_2)_2$-(*trans*-cyclohex-1,4-ylene)NHC(O)$(CH_2)_4$-	-NHC(O)CH=CH-
103	O	-$(CH_2)_2$-(*trans*-cyclohex-1,4-ylene)NHC(O)$(CH_2)_5$-	-NHC(O)CH=CH-
104	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)$(CH_2)_2$-	-NHC(O)CH=CH-
105	O	-$(CH_2)_2$NHC(O)NH(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-
106	O	-$(CH_2)_2$N$(CH_3)(CH_2)_2$(*cis*-cyclohex-1,4-ylene)-	-NHC(O)CH=CH-
107	O	-$(CH_2)_2$C(O)NH(2,3,5,6-tetrafluorophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-
108	O	-$(CH_2)_2$C(O)NH(2,6-diiodophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-
109	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)$(CH_2)_3$-	-NHC(O)CH=CH-

Ex.	W	R^4	R^6	R^7
110	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)$(CH_2)_4$-	-NHC(O)CH=CH-	
111	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)$(CH_2)_5$-	-NHC(O)CH=CH-	
112	O	-$(CH_2)_2$C(O)NHCH_2(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
113	O	-$(CH_2)_2$C(O)NHCH_2(phen-1,4-ylene)CH_2-	H	-NHC(O)H
114	O	-$(CH_2)_2$NHC(O)NHCH_2(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
115	O	-$(CH_2)_2$NHC(O)NHCH_2(phen-1,4-ylene)CH_2-	H	-NHC(O)H
116	O	-$(CH_2)_2$C(O)NH(2-methylphen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
117	O	1-[-$(CH_2)_3$O(phen-1,4-ylene)$(CH_2)_2$](piperidin-4-yl)CH_2-	-NHC(O)CH=CH-	
118	O	-$(CH_2)_2$C(O)NHCH_2(phen-1,3-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
119	O	-$(CH_2)_2$O(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
120	O	-$(CH_2)_2$N(CH_3)C(O)CH_2O(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
121	O	-$(CH_2)_2$N(CH_3)C(O)CH_2O(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
122	O	-$(CH_2)_2$N(CH_3)C(O)(fur-2,5-ylene)CH_2-	-NHC(O)CH=CH-	
123	O	-$(CH_2)_2$N(CH_3)C(O)(thien-2,5-ylene)CH_2-	-NHC(O)CH=CH-	
124	O	-$(CH_2)_2$O(phen-1,4-ylene)O$(CH_2)_2$-	-NHC(O)CH=CH-	
125	O	-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
126	O	-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)CH_2O(phen-1,2-ylene)CH_2-	-NHC(O)CH=CH-	
127	O	-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)CH_2O(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
128	O	-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)CH_2O(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
129	O	-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)(fur-2,5-ylene)CH_2-	-NHC(O)CH=CH-	
130	O	-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)(thien-2,5-ylene)CH_2-	-NHC(O)CH=CH-	
131	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)CH_2O(phen-1,2-ylene)CH_2-	-NHC(O)CH=CH-	

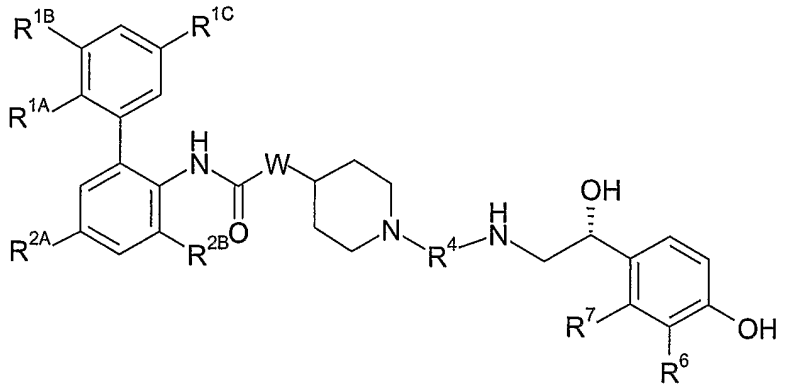
Ex.	W	R^4	R^6	R^7
132	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)CH_2O(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
133	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)CH_2O(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
134	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)(fur-2,5-ylene)CH_2-	-NHC(O)CH=CH-	
135	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)(thien-2,5-ylene)CH_2-	-NHC(O)CH=CH-	
136	O	-$(CH_2)_2$(phen-1,4-ylene)NHC(O)(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
137	O	-$(CH_2)_2$(phen-1,4-ylene)NHC(O)(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
138	O	-$(CH_2)_2$(phen-1,4-ylene)NHC(O)CH_2O(phen-1,2-ylene)CH_2-	-NHC(O)CH=CH-	
139	O	-$(CH_2)_2$(phen-1,4-ylene)NHC(O)CH_2O(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
140	O	-$(CH_2)_2$(phen-1,4-ylene)NHC(O)CH_2O(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
141	O	-$(CH_2)_2$(phen-1,4-ylene)NHC(O)(fur-2,5-ylene)CH_2-	-NHC(O)CH=CH-	
142	O	-$(CH_2)_2$(phen-1,4-ylene)NHC(O)(thien-2,5-ylene)CH_2-	-NHC(O)CH=CH-	
143	O	-$(CH_2)_2$(*trans*-cyclohex-1,4-ylene)NHC(O)(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
144	O	-$(CH_2)_3O$(phen-1,3-ylene)CH_2-	-NHC(O)CH=CH-	
145	O	-$CH_2CH(OH)CH_2NH$(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
146	O	-$(CH_2)_4NH$(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
147	O	-$(CH_2)_2C(O)NH$(phen-1,4-ylene)$CH_2NHC(O)CH_2$-	-NHC(O)CH=CH-	
148	O	-$(CH_2)_2C(O)NH$(phen-1,4-ylene)$(CH_2)_2NHC(O)CH_2$-	-NHC(O)CH=CH-	
149	O	-$(CH_2)_2C(O)NHCH_2$(*trans*-cyclohex-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
150	O	-$(CH_2)_2NHC(O)(CH_2)_5$-	-NHC(O)CH=CH-	
151	O	-$(CH_2)_2O$(phen-1,3-ylene)$O(CH_2)_2$-	-NHC(O)CH=CH-	
152	O	-$(CH_2)_2O$(phen-1,2-ylene)$O(CH_2)_2$-	-NHC(O)CH=CH-	

Ex.	W	R^4	R^6	R^7
153	O	-CH_2(phen-1,2-ylene)O(phen-1,2-ylene)CH_2-	-NHC(O)CH=CH-	
154	O	-$(CH_2)_2C(O)NH(CH_2)_6$-	-NHC(O)CH=CH-	
155	O	-$(CH_2)_2$NHC(O)(*cis*-cyclopent-1,3-ylene)-	-NHC(O)CH=CH-	
156	O	-$(CH_2)_3$(phen-1,4-ylene)$(CH_2)_3$-	-NHC(O)CH=CH-	
157	O	-$(CH_2)_3$(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
158	O	-$(CH_2)_4$(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
159	O	-$(CH_2)_3$(furan-2,5-ylene)$(CH_2)_3$-	-NHC(O)CH=CH-	
160	O	-$(CH_2)_2N(CH_3)C(O)NH$(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
161	O	4-[-$(CH_2)_2$](piperidin-1-yl)C(O)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
162	O	-$(CH_2)_3$(phen-1,3-ylene)$(CH_2)_3$-	-NHC(O)CH=CH-	
163	O	-$(CH_2)_3$(tetrahydrofuran-2,5-ylene)$(CH_2)_3$-	-NHC(O)CH=CH-	
164	O	-$(CH_2)_2O$(phen-1,4-ylene)$C(O)(CH_2)_2$-	-NHC(O)CH=CH-	

[1] In Tables I-III,"(racemic)" means the compound is racemic at the chiral carbon bearing the hydroxyl group in formula V, VI or VII.

[2] For this group, the nitrogen atom is attached at R^6 and carbon atom is attached at R^7.

Another particular group of compounds of formula I are compounds of formula VI:



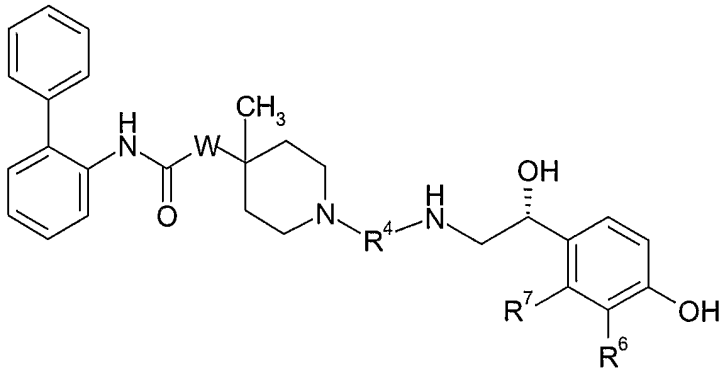
VI

wherein W, R^{1A}, R^{1B}, R^{1C}, R^{2A}, R^{2B}, R^4, R^6 and R^7 are as defined in Table II; or a pharmaceutically acceptable salt or solvate thereof.

Table II

Ex.	W	R^{1A}	R^{1B}	R^{1C}	R^{2A}	R^{2B}	R^4	R^6	R^7
165	O	H	H	H	Br	H	$-(CH_2)_9-$ (racemic)	-NHC(O)CH=CH-	
166	O	F	H	H	H	H	$-(CH_2)_9-$	-NHC(O)CH=CH-	
167	O	H	Cl	H	F	F	$-(CH_2)_9-$	-NHC(O)CH=CH-	
168	O	H	Cl	Cl	F	F	$-(CH_2)_9-$	-NHC(O)CH=CH-	
169	O	H	H	H	F	F	$-(CH_2)_9-$	-NHC(O)CH=CH-	

Another particular group of compounds of formula I are compounds of formula VII:



VII

wherein W, R^4, R^6 and R^7 are as defined in Table III; or a pharmaceutically acceptable salt or solvate thereof.

Table III

Ex.	W	R^4	R^6	R^7
170	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
171	O	-$(CH_2)_2$C(O)NH(phen-1,4-ylene)CH_2-	H	-NHC(O)H
172	O	-$(CH_2)_9$-	-NHC(O)CH=CH-	
173	O	-$(CH_2)_9$-	H	-NHC(O)H
174	O	-$(CH_2)_2$C(O)NH$(CH_2)_5$-	-NHC(O)CH_2CH_2-	
175	O	-$(CH_2)_2$C(O)NH$(CH_2)_5$-	H	-NHC(O)H
176	O	-$(CH_2)_2$NHC(O)$(CH_2)_5$-	-NHC(O)CH=CH-	
177	O	-$(CH_2)_2$NHC(O)$(CH_2)_5$-	H	-NHC(O)H
178	O	-$(CH_2)_2$NHC(O)(phen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
179	O	-$(CH_2)_2$NHC(O)(phen-1,4-ylene)CH_2-	H	-NHC(O)H
180	O	-$(CH_2)_3$(phen-1,4-ylene)NH(phen-1,4-ylene)$(CH_2)_2$-	-NHC(O)CH=CH-	
181	O	-$(CH_2)_2$NHC(O)(2-chlorophen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	
182	O	-$(CH_2)_2$NHC(O)(2-chloro-5-methoxyphen-1,4-ylene)CH_2-	-NHC(O)CH=CH-	

Definitions

When describing the libraries, 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 azacycloakyl group. Representative examples of an azacycloalkylene group are pyrrolidinylene and piperidinylene groups.

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.

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.

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.

The term "divalent hydrocarbon group" means a divalent hydrocarbon group which is composed primarily of carbon and hydrogen atoms and which optionally contains one or more heteroatoms. Such divalent hydrocarbon groups may be branched or unbranched, saturated or unsaturated, acyclic or cyclic, aliphatic or aromatic, or combinations thereof. The divalent hydrocarbon group can optionally contain heteroatoms incorporated into the hydrocarbon chain or as substituents attached to the hydrocarbon chain.

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 example, the term "(1-4C)alkyl" means an alkyl group having from 1 to 4 carbon atoms.

The term "library" means a collection of more than one compound, i.e., at least two compounds.

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 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. Particularly preferred are ammonium, calcium, magnesium, potassium and sodium salts. 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, 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. Salts derived from pharmaceutically acceptable acids include acetic, ascorbic, benzenesulfonic, benzoic, camphosulfonic, citric, ethanesulfonic, edisylic, fumaric, gentisic, gluconic, glucoronic, 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,

pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, xinafoic and the like. Particularly preferred are citric, hydrobromic, hydrochloric, isethionic, maleic, naphthalene-1,5-disulfonic, phosphoric, sulfuric and tartaric acids.

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 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 salt or stereoisomer thereof" is intended to include all permutations of salts and stereoisomers, such as a 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-fluroenylmethyl (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-ylidine, formed, for example, by reaction with a ketone, such as acetone.

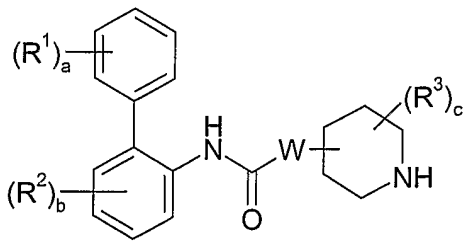
General Synthetic Procedures for Preparing Library

The biphenyl derivatives found in the libraries 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.

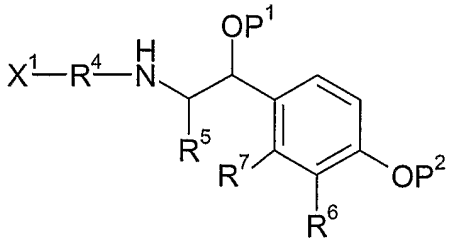
By way of illustration, the biphenyl derivatives employed in this invention can be prepared by a process comprising:

(a) reacting a compound of formula **1**:



1

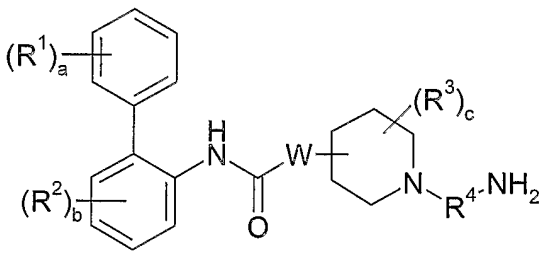
or a salt thereof; with a compound of formula **2**:



2

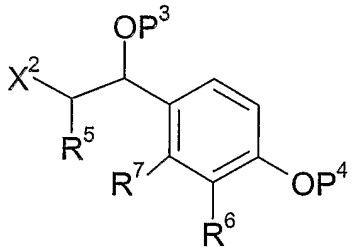
wherein X^1 represents a leaving group, and P^1 and P^2 each independently represent a hydrogen atom or a hydroxyl-protecting group;

(b) reacting a compound of formula **3**:



3

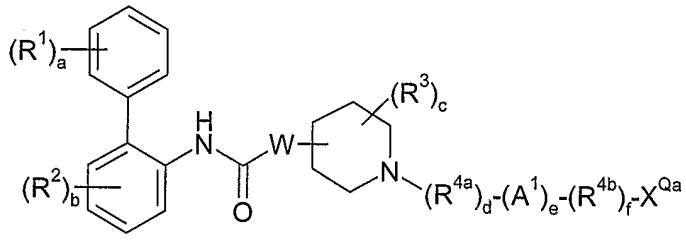
or salt thereof; with a compound of formula **4**:



4

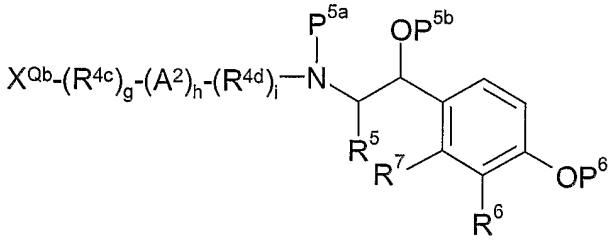
wherein X^2 represents a leaving group, and P^3 and P^4 each independently represent a hydrogen atom or a hydroxyl-protecting group;

(c) coupling a compound of formula **5**:



5

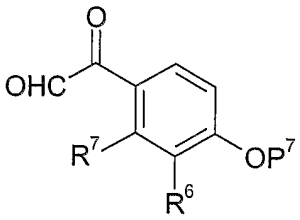
with a compound of formula 6:



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;

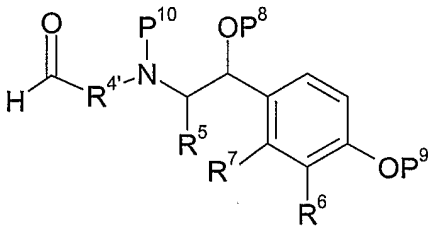
(d) for a compound of formula I wherein R^5 represents a hydrogen atom, reacting a compound of formula 3 with a compound of formula 7:



7

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;

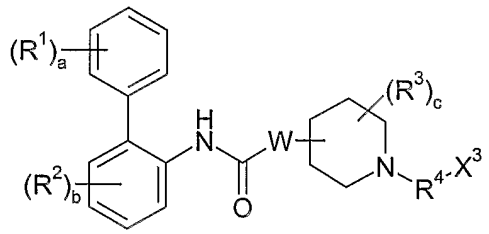
(e) reacting a compound of formula **1** with a compound of formula **8**:



8

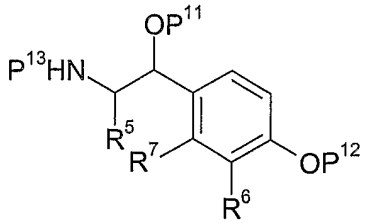
or a hydrate thereof, in the presence of a reducing agent, wherein P^8 and P^9 each independently represent a hydrogen atom or a hydroxyl-protecting group, P^{10} represents a hydrogen atom or an amino-protecting group, and $R^{4'}$ represents a residue that, together with the carbon to which it is attached,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

(f) reacting a compound of formula **9**:



9

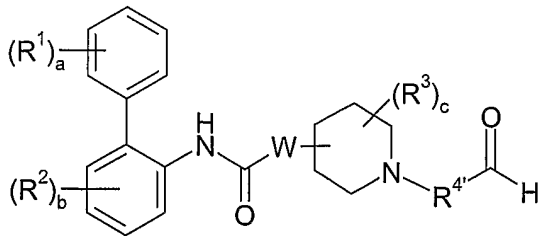
wherein X^3 represents a leaving group, with a compound of formula **10**:



10

wherein P^{11} and P^{12} each independently represent a hydrogen atom or a hydroxyl-protecting group, and P^{13} represents a hydrogen atom or an amino-protecting group; or

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



11

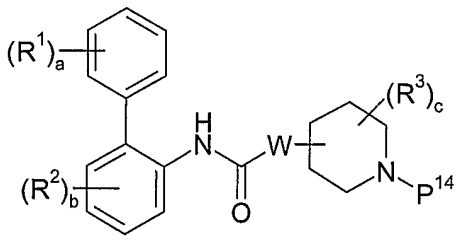
or a hydrate thereof; wherein $R^{4'}$ represents a residue that, together with the carbon to which it is attached, affords a group R^4 upon completion of the reaction; with a compound of formula **10** in the presence of a reducing agent; and then

(h) 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} or P^{13} to provide a compound of formula I. A library of compounds of formula I is prepared by repeating steps (a), (b), (c), (d), (e), (f) or (g) and step (h) to prepare each member of the library.

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 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 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 °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.

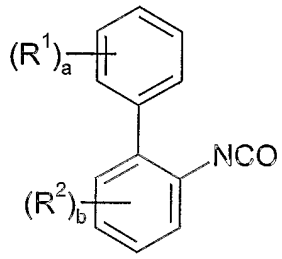
Compounds of formula **1** are generally known in the art or can be prepared from commercially available starting materials and reagents using well-known procedures. For example, compounds of formula **1** can be prepared by deprotecting a compound of formula **12**:



12

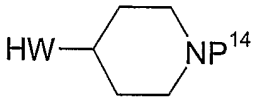
wherein P^{14} represents an amino-protecting group, such as a benzyl group. By way of illustration, a benzyl group can be readily removed by reduction using, for example, hydrogen or ammonium formate and a group VIII metal catalyst, such as palladium on carbon. When W represents NW^a, the hydrogenation reaction is conveniently performed using Pearlman's catalyst (i.e., $Pd(OH)_2$).

Compounds of formula **12** can be prepared by reacting an isocyanate compound of formula **13**:



13

with a compound of formula **14**:



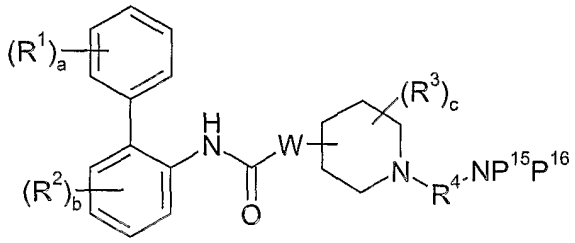
14

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 **23** 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^2 can be, for example, halo, such as chloro, bromo or iodo, or a sulfonic ester group, such as mesylate or tosylate. The groups P^3 and P^4 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 deprotecting a compound of formula **15**:



15

wherein one or both of P^{15} and P^{16} independently represents a protecting group, such as *tert*-butoxycarbonyl, and any remainder represents a hydrogen atom. For example, a *tert*-butoxycarbonyl group can be removed by treating the protected compound with trifluoroacetic acid.

Compounds of formula **15** can be prepared by reacting a compound of formula **1** with a compound of formula **16**:

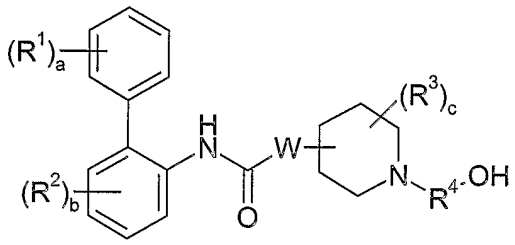
$$X^3\text{-}R^4\text{-}NP^{15}P^{16}$$

16

wherein X^3 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 **16** 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.

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 **17**:



17

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 temperature ranging from about -20 °C to about 25 °C.

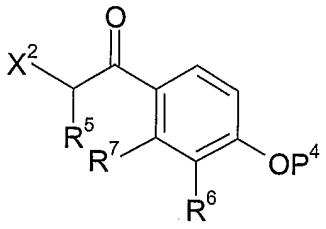
Compounds of formula **17** can be prepared by reacting a compound of formula **1** with a compound of formula **18**:

$$X^4\text{-}R^4\text{-}OH$$

18

wherein X^4 represents a leaving group such as halo, such as chloro, bromo or iodo, or a sulfonic ester group, such as mesylate or tosylate.

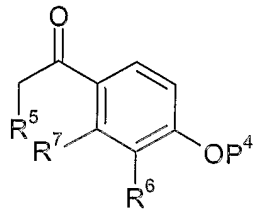
Compounds of formula **4** can be prepared by reacting a compound of formula **19**:



19

with a reducing agent, such as borane. If desired, such a reduction can be performed in the presence of a chiral catalyst to provide compounds of formula 4 in chiral form. For example, compounds of formula 19 can be reduced in the presence of a chiral catalyst formed from (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol and trimethylboroxine; or alternatively, from (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol and trimethylboroxine. The resulting hydroxyl group can then be protected with a hydroxyl-protecting group, P^3, by reaction with, for example, *tert*-butyldimethylsilyl trifluoromethanesulfonate.

Compounds of formula 19 in which X^2 represents a bromine atom can be prepared by reacting a compound of formula 20:



20

with bromine in the presence of a Lewis acid, such as boron trifluoride diethyl etherate. Compounds of formula 20 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, 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 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** with a compound of formula **21**:

$$X^5\text{-}(R^{4a})_d\text{-}(A^1)_e\text{-}(R_{4b})_f\text{-}X^{Qa'}$$

21

wherein X^5 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 **3**, followed by removing any protecting group in $X^{Qa'}$.

Compounds of formula **6** can be prepared by reacting a compound of formula **4** with a compound of formula **22**:

$$X^{Qb'}\text{-}(R^{4c})_g\text{-}(A^2)_h\text{-}(R^{4d})_i\text{-}X^6$$

22

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 $X^{Qb'}$ represents X^{Qb}, such as a carboxyl group or an amino group NHQ^b, or a protected derivative thereof, such as a (1-6C)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 $X^{Qb'}$.

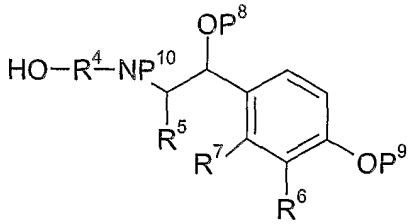
Referring to process (d), i.e., the reaction of a compound of formula **3** with a compound of formula **7**, any suitable reducing agent may be used in this reaction. For example, the reducing agent can be hydrogen in the presence of a Group VIII metal catalyst, such as palladium on carbon; or a metal 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 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** (where X^2 in this case can also be hydrogen), 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 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 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 **23**:



23

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 °C to about 25 °C until the oxidation is substantially complete.

Compounds of formula **23** can be prepared by reacting a compound of formula **10** with a compound of formula **24**:

$HO\text{-}R^4\text{-}X^7$

24

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.

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 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 °C to 100 °C until the reaction is substantially complete.

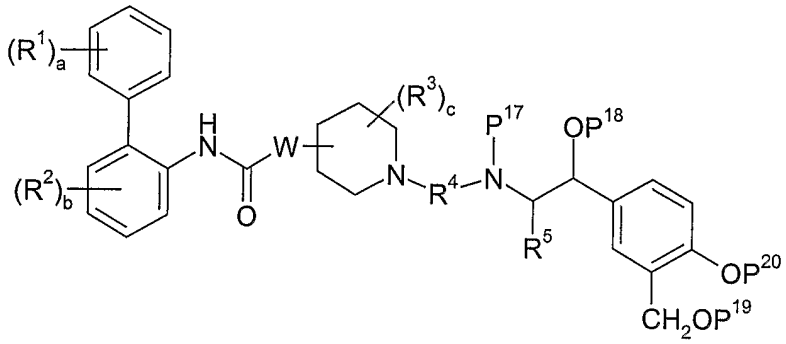
Compounds of formula **9** can be prepared by steps analogous to those of methods (a) to (e) herein, starting from a compound of formula **1**. Additionally, compounds of formula **10** can be prepared from compounds of formula **4** by reaction with an amine of formula $P^{13}NH_2$.

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^{11}, P^{12} and P^{13} 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.

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.

In a particular embodiment, certain compounds of formula I are prepared by a process comprising:

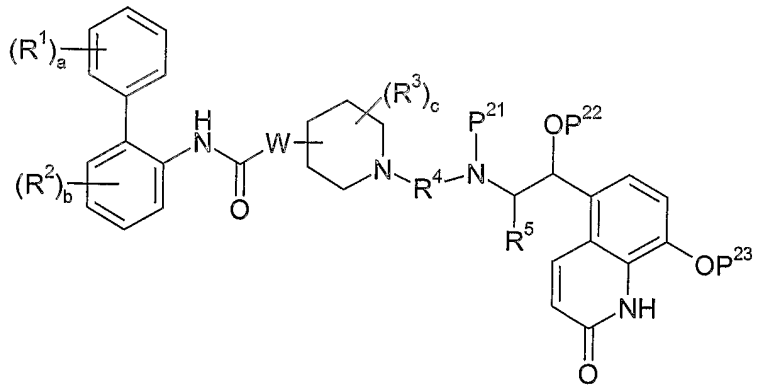
(h) deprotecting a compound of formula **25**:



25

wherein P^{17} represents a hydrogen atom or an amino-protecting group; and each of P^{18}, P^{19} and P^{20} independently represent a hydrogen atom or a hydroxyl-protecting group; provided that at least one of P^{17}, P^{18}, P^{19} or P^{20} is a protecting group;

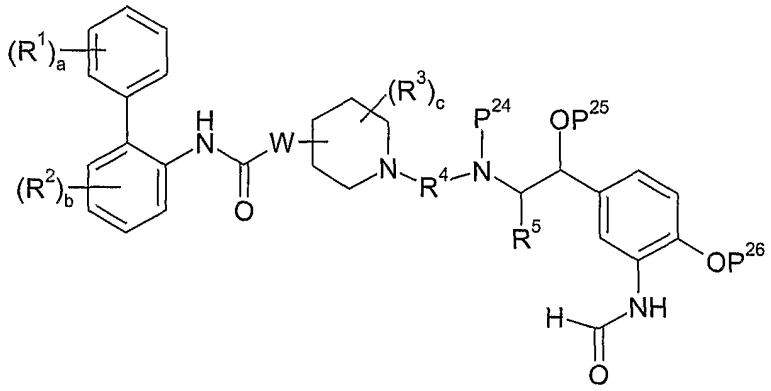
(i) deprotecting a compound of formula **26**:



26

wherein P^{21} represents a hydrogen atom or an amino-protecting group; and each of P^{22} and P^{23} independently represent a hydrogen atom or a hydroxyl-protecting group; provided that at least one of P^{21}, P^{22} or P^{23} is a protecting group; or

(j) deprotecting a compound of formula **27**:



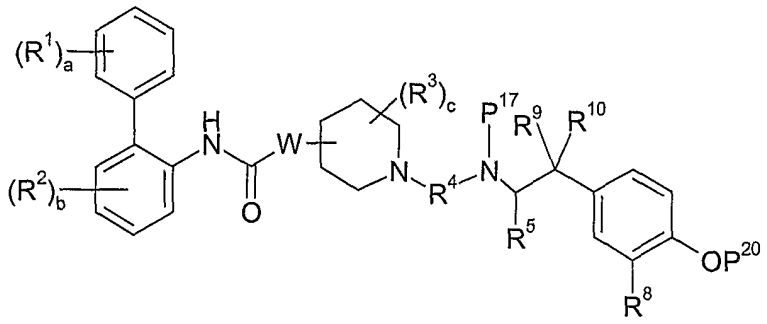
27

wherein P^{24} represents a hydrogen atom or an amino-protecting group; and each of P^{25} and P^{26} independently represent a hydrogen atom or a hydroxyl-protecting group; provided that at least one of P^{24}, P^{25} or P^{26} is a protecting group.

to provide a compound of formula I.

Referring to process (h), examples of particular values for P^{17}, P^{18}, P^{19} and P^{20} are: for P^{17}, hydrogen or benzyl; for P^{18} hydrogen or *tert*-butyldimethylsilyl; and for P^{19} and P^{20} hydrogen or benzyl, or together propylidine. In this process, benzyl protecting groups are conveniently removed by catalytic hydrogenation in the presence of a Group VIII metal catalyst, such as palladium on carbon; a *tert*-butyldimethylsilyl group is conveniently removed by treatment with hydrogen fluoride, such as triethylamine trihydrofluoride; and a propylidine group is conveniently removed by treatment with an acid, such as trifluoroacetic acid.

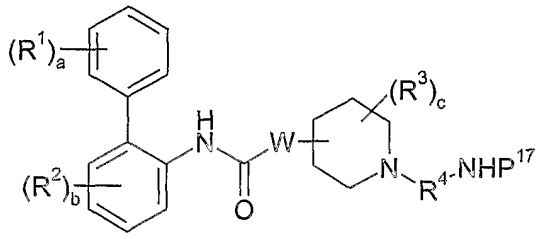
Compounds of formula **25** can be prepared by the methods described herein, such as by processes (a) to (g). Alternatively, compounds of formula **25** can be prepared by reacting a compound of formula **28**:



28

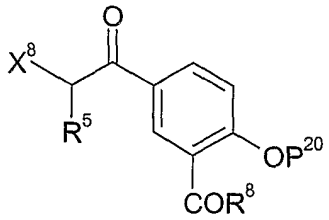
wherein R^8 represents $-CH_2OP^{19}$, -CHO, -COOH or –C(O)O(1-6C)alkoxy, such as carbomethoxy, R^9 represents $-OP^{18}$ and R^{10} represents a hydrogen atom, or R^9 and R^{10} together represent =O, with a reducing agent. Any suitable reducing agent may be used in this reaction including, by way of example, metal hydride reducing agents, such as sodium borohydride, lithium aluminum hydride and the like.

Compounds of formula **28** in which R^9 and R^{10} together represent a =O group can be readily prepared by reacting a compound of formula **29**:



29

or a salt thereof, with a compound of formula **30**:



30

wherein X^8 represents a leaving group, such as a bromo.

Referring to process (i), examples of particular values for P^{21}, P^{22} and P^{23} are: for P^{21}, hydrogen or benzyl; for P^{22} hydrogen or *tert*-butyldimethylsilyl; and for P^{23} hydrogen or benzyl. In this process, benzyl protecting groups are conveniently removed by catalytic hydrogenation in the presence of a Group VIII metal catalyst, such as palladium on carbon; and a *tert*-butyldimethylsilyl group is conveniently removed by treatment with hydrogen fluoride, such as triethylamine trihydrofluoride. Compounds of formula **26** can be prepared by the methods described herein, such as by processes (a) to (g).

Referring to process (j), examples of particular values for P^{24}, P^{25} and P^{26} are: for P^{24}, hydrogen or benzyl; for P^{25} hydrogen or *tert*-butyldimethylsilyl; and for P^{26} hydrogen or benzyl. In this process, benzyl protecting groups are conveniently removed by catalytic hydrogenation in the presence of a Group VIII metal catalyst, such as palladium on carbon; and a *tert*-butyldimethylsilyl group is conveniently removed by treatment with hydrogen fluoride, such as triethylamine trihydrofluoride. Compounds of formula **27** can be prepared by the methods described herein, such as by processes (a) to (g).

Additionally, 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 by catalytic hydrogenation as described in Example 6 hereinafter.

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

Libraries of Biphenyl Derivatives

The libraries of this invention typcially contain at least two compounds of formula I. For example, in one embodiment, the library contains from 2 to 1,000 compounds; including, by way of illustration from 2 to 500 compounds; or from 2 to 200 compounds; or from 2 to 100 compounds; or from 2 to 50 compounds. If desired, the library can contain more than 1000 compounds, such as up to 5,000 or 10,000 compounds or more.

The members of the library can be synthesized individually, or in arrays or as mixtures. Typically, each compound of the library will be prepared individually in a separate reaction vessel or as a member of an array, i.e. in a separate well of a multi-well

plate. Methods for preparing compounds of formula I are described in further detail in the Examples hereinbelow.

Once a library of compounds of formula I has been prepared, the members of the library are evaluated or screened to determine whether a compound in the library has both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity. Any suitable test, assay or procedure may be used to evaluate the members of the library, including numerous *in vitro* and *in vivo* assays which are well-known to those skilled in the art. Generally, all members of the library will be evaluated, however, if desired, the evaluation process may be terminated at any point once a compound having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity has been found.

By way of illustration, suitable *in vitro* and *in vivo* assays can include radioligand binding assays, functional assays, bronchoprotection animal models and the like. For example, suitable functional assays include ligand-mediated changes in intracellular cyclic adenosine monophosphate (cAMP), ligand-mediated changes in activity of the enzyme adenylyl cyclase (which synthesizes cAMP), ligand-mediated changes in incorporation of guanosine 5'-O-(-thio)triphosphate ([^{35}S]GTP S) into isolated membranes via receptor catalyzed exchange of [^{35}S]GTP S for GDP, ligand-mediated changes in free intracellular calcium ions (measured, for example, with a fluorescence-linked imaging plate reader or FLIPR® from Molecular Devices, Inc.). By way of further example, assays suitable for evaluating compounds of formula I are described in detail in the Examples hereinbelow.

Utility

The libraries and methods of this invention are useful for identifying compounds having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity. Compounds having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity are useful for treating medical conditions mediated by β_2 adrenergic receptors or muscarinic receptors, i.e., medical conditions that are ameliorated by treatment with a β_2 adrenergic receptor agonist or a muscarinic receptor antagonist. 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 which may be treated 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.

Among other properties, compounds of particular interest that can be identified using the libraries and methods of this invention are those that demonstrate a K_i value of less than about 300 nM for a β_2 adrenergic receptor and a K_i value less than 300 nM for a muscarinic receptor.

Another group of compounds of particular interest that can be identified using the libraries and methods of this invention are those that demonstrate an inhibitory constant K_i value for binding at a muscarinic receptor, such as a M_3 muscarinic receptor, of less than about 100 nM; particularly less than 10 nM; and an EC_{50} value for β_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 β_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 β_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.

Additionally, those skilled in the art will recognize that, even if a particular library does not contain any compound having both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity, such information is useful for designing new libraries to be screened for bifunctional activity.

Representative examples of the libraries and methods of this invention are demonstrated by the following synthetic procedures and *in vitro* and *in vivo* assays.

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.

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

AC	adenylyl cyclase
Ach	acetylcholine
ATCC	American Type Culture Collection
BSA	bovine serum albumin
cAMP	3'-5' cyclic adenosine monophosphate
CHO	Chinese hamster ovary
cM_5	cloned chimpanzee M_5 receptor
DCM	dichloromethane (i.e., methylene chloride)
DIPEA	*N,N*-diisopropylethylamine
dPBS	Dulbecco's phosphate buffered saline
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	dimethyl sulfoxide
EDTA	ethylenediaminetetraacetic acid
Emax	maximal efficacy
EtOAc	ethyl acetate
EtOH	ethanol
FBS	fetal bovine serum
FLIPR	fluorometric imaging plate reader
Gly	glycine
HATU	*O*-(7-azabenzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBSS	Hank's buffered salt solution
HEK	human embryonic kidney cells
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
hM_1	cloned human M_1 receptor
hM_2	cloned human M_2 receptor
hM_3	cloned human M_3 receptor
hM_4	cloned human M_4 receptor
hM_5	cloned human M_5 receptor
HPLC	high-performance liquid chromatography
IBMX	3-isobutyl-1-methylxanthine
%Eff	% efficacy
PBS	phosphate buffered saline
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
rpm	rotations per minute
TFA	trifluoroacetic acid
THF	tetrahydrofuran
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_2O-TFA; and mobile phase B was 90 % - 10 % - 0.1 % ACN-H_2O-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).

The specific rotation for chiral compounds (indicated as $[\alpha]^{20}_D$) 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.

A library of compounds of formula I (i.e., Examples 1-170 and 180-186) was prepared as follows:

Preparation 1

***N*-1,1'-Biphenyl-2-yl-*N*'-4-(1-benzyl)piperidinylurea**

Biphenyl-2-isocyanate (50 g, 256 mmol) was dissolved in acetonitrile (400 mL) at ambient temperature. After cooling to 0 °C, a solution of 4-amino-*N*-benzylpiperidine (48.8 g, 256 mmol) in acetonitrile (400 mL) was added over 5 min. A precipitate was observed immediately. After 15 min, acetonitrile (600 mL) was added, and the resultant viscous mixture was stirred for 12 h at 35°C. The solids were then filtered off and washed

with cold acetonitrile, then dried under vacuum, yielding the title compound (100 g, 98% yield). MS *m/z*: [M + H^+] calcd for $C_{25}H_{27}N_3O$ 386.22; found 386.3.

Preparation 2

***N*-1,1'-Biphenyl-2-yl-*N*'-4-piperidinylurea**

The product of Preparation 1 (20 g, 52 mmol) was dissolved in a mixture of anhydrous methanol and anhydrous DMF (3:1, 800 mL). Aqueous hydrochloric acid (0.75 mL of 37% conc. solution, 7.6 mmol) was added and nitrogen gas was bubbled through the solution vigorously for 20 min. Pearlman's catalyst ($Pd(OH)_2$, 5 g) was added under a stream of nitrogen, before placing the reaction mixture under a hydrogen atmosphere (balloon). The reaction mixture was allowed to stir for 4 days and was then passed twice through pads of Celite to remove the catalyst. The solvent was then removed under reduced pressure to yield the title compound (13 g, 85% yield). MS *m/z*: [M + H^+] calcd for $C_{18}H_{21}N_3O$ 296.17; found 296.0.

Alternatively, *N*-1,1'-biphenyl-2-yl-*N*'-4-piperidinylurea was synthesized by heating together biphenyl-2-isocyanate (50 g, 256 mmol) and 4-amino-*N*-benzylpiperidine (51.1 g, 269 mmol) at 70 °C for 12 h (the reaction was monitored by LCMS). The reaction mixture was cooled to 50 °C and ethanol (500 mL) added, followed by slow addition of 6M hydrochloric acid (95 mL). The reaction mixture was cooled to room temperature. Ammonium formate (48.4 g, 768 mmol) was added to the reaction mixture and nitrogen gas bubbled through the solution vigorously for 20 min, before adding palladium (10 wt. % (dry basis) on activated carbon) (10 g). The reaction mixture was heated at 40 °C for 12 h, and then filtered through a pad of Celite and the solvent was removed under reduced pressure. To the crude residue was added 1M hydrochloric acid (20 mL) and 10N sodium hydroxide was added to adjust the pH to 12. The aqueous layer was extracted with ethyl acetate (2 x 80 mL), dried (magnesium sulfate) and solvent removed under reduced pressure to give the title compound as a solid (71.7 g, 95% yield). MS *m/z*: [M + H^+] calcd for $C_{18}H_{21}N_3O$ 296.17; found 296.0.

Preparation 3

***N*-1,1'-Biphenyl-2-yl-*N*'-4-[1-(9-hydroxynonyl)]piperidinylurea**

9-Bromo-1-nonanol (4.84 g, 21.7 mmol) was added to a stirred solution of the product of Preparation 2 (5.8 g, 19.7 mmol) and diisopropylethylamine (10.29 mL, 59.1

mmol) in acetonitrile (99 mL) at 50°C. The reaction mixture was heated at 50 °C for 8 h. The reaction mixture was then allowed to cool and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (100 mL), washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and dried (magnesium sulfate). The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (dichloromethane:methanol:ammonia system) to yield the title compound (7.1 g, 16.2 mmol, 82% yield).

Preparation 4

***N*-1,1'-Biphenyl-2-yl-*N*'-4-[1-(9-oxononyl)]piperidinylurea**

Dimethyl sulfoxide (490 μL, 6.9 mmol), followed by diisopropylethylamine (324 μL, 3.45 mmol) was added to a solution of the product of Preparation 3 (500 mg, 1.15 mmol) in dichloromethane (11.5 mL) at –10 °C under an atmosphere of nitrogen. The reaction mixture was stirred at –15 °C for 15 min, and then sulfur trioxide pyridine complex was added portionwise (549 mg, 3.45 mmol). The reaction mixture was stirred at –15 °C for 1 h, and then water (10 mL) was added. The organic phase was then separated, washed with water (10 mL), and dried (sodium sulfate). The solvent was removed under reduced pressure to give the title compound (475 mg, 1.09 mmol, 95% yield). HPLC (10-70) R_t = 3.39.

Preparation 5

***N*-1,1'-Biphenyl-2-yl-*N*'-4-[1-(9-aminononyl)]piperidinylurea**

Palladium (10 wt. % (dry basis) on activated carbon) (1.5 g) was added to a stirred solution of the product of Preparation 4 (1.58 g, 3.63 mmol) and benzylamine (516 μL, 4.72 mmol) in methanol (36.3 mL). The reaction mixture was placed under an atmosphere of hydrogen. After stirring for 12 h, the reaction mixture was filtered through a pad of Celite and washed with methanol (10 mL). The solvent was removed under reduced pressure to give the title compound (1.50 g, 3.45 mmol, 95% yield). HPLC (10-70) R_t = 2.35; MS *m/z*: [M + H^+] calcd for $C_{27}H_{40}N_4O_1$ 437.06; found 437.5.

Preparation 6

8-Benzyloxy-5-(2,2-dihydroxyacetyl)-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 with acetic anhydride (2x100mL) 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) was cooled in ice, and the product of 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 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 product was collected on a Buchner funnel and dried under reduced pressure to give 5-acetyl-8-hydroxy-2(1*H*)-quinolinone (121 g).

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

To the product of step (b) (37.7 g, 186 mmol) was added *N*,*N*-dimethylformamide (200 mL) and potassium carbonate (34.5 g, 250 mmol) followed by 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 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 5-acetyl-8-benzyloxy-1*H*-quinolin-2-one (44 g) as a powder.

(d) 8-Benzyloxy-5-(2,2-dihydroxyacetyl)-1*H*-quinolin-2-one

To a slurry of the product of step (c) (10.0 g, 34.1 mmol) in DMSO (60 mL) was added a 48% w/w hydrobromic acid solution (11.8 mL, 102.3 mmol). The mixture was warmed to 60 °C for 16 h then allowed to cool to room temperature. Water (100 mL) was added and the resulting slurry stirred at room temperature for 0.5 h before being cooled to 0°C. The product was collected on a Buchner funnel then dried under reduced pressure to give 8-benzyloxy-5-(2,2-dihydroxyacetyl)-1*H*-quinolin-2-one (12.2 g) as a solid.

Preparation 7

1-(1-{9-[2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]nonyl}piperidin-4-yl)-3-biphenyl-2-ylurea

The products of Preparation 5 (183 mg, 0.42 mmol) and Preparation 6 (149 mg, 0.46 mmol) were stirred in dichloroethane (4.2 mL) at ambient temperature for 2 h. Sodium triacetoxyborohydride (267 mg, 1.26 mmol) was then added and the reaction mixture was stirred for a further 12 h. The reaction mixture was then diluted with dichloromethane (10 mL), washed with saturated aqueous sodium bicarbonate (10 mL), dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (5-10% methanol in dichloromethane, 0.5% ammonium hydroxide) to give the title compound (144 mg, 0.20 mmol, 48% yield). HPLC (10-70) R_t = 3.48; MS *m/z*: [M + H^+] calcd for $C_{45}H_{55}N_5O_4$ 730.4; found 730.7.

Example 1

1-Biphenyl-2-yl-3-(1-{9-[2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}piperidin-4-yl)urea

Palladium (10 wt. % (dry basis) on activated carbon) (63 mg) was added to a stirred solution of the product of Preparation 7 (144 mg, 0.20 mmol) in methanol (2 mL) and the reaction mixture was placed under an atmosphere of hydrogen. After 12 h stirring, the reaction mixture was filtered through a pad of Celite, washed with methanol (2 mL) and then the solvent was removed under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound (10 mg). HPLC (10-70) R_t = 2.8; MS *m/z*: [M + H^+] calcd for $C_{38}H_{49}N_5O_4$ 640.3; found 640.5.

Preparation 8

Biphenyl-2-ylcarbamic Acid Piperidin-4-yl Ester

Biphenyl-2-isocyanate (97.5 g, 521 mmol) and 4-hydroxy-1-benzylpiperidine (105 g, 549 mmol), both commercially-available from Aldrich, Milwaukee, WI, were heated together at 70 °C for 12 h, during which time the formation of biphenyl-2-ylcarbamic acid 1-benzylpiperidin-4-yl ester was monitored by LCMS. The reaction mixture was then cooled to 50 °C and ethanol (1 L) was added, and then 6M hydrochloric acid (191 mL) was added slowly. The reaction mixture was then cooled to ambient temperature and ammonium formate (98.5 g, 1.56 mol) was added and nitrogen gas was bubbled through the solution vigorously for 20 min. Palladium (10 wt. % (dry basis) on activated carbon) (20 g) was then added. The reaction mixture was heated at 40 °C for 12 h and then filtered through a pad of Celite. The solvent was then removed under reduced pressure and 1M hydrochloric acid (40 mL) was added to the crude residue. Sodium hydroxide (10N) was then added to adjust the pH to 12. The aqueous layer was extracted with ethyl acetate (2 x 150 mL) and dried (magnesium sulfate), and then the solvent was removed under reduced pressure to give the title compound (155 g, 100%). HPLC (10-70) $R_t = 2.52$; MS *m/z*: [M + H^+] calc'd for $C_{18}H_{20}N_2O_2$ 297.15; found 297.3.

Preparation 9

***N,N*-(Di-*tert*-butoxycarbonyl)-9-bromononylamine**

A solution of di-*tert*-butoxycarbonylamine (3.15 g, 14.5 mmol) in *N,N*-dimethylformamide (0.28 mL) was cooled to 0 °C for about 10 min. Sodium hydride, 60% in mineral oil (0.58 g, 14.5 mmol) was added and the reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was removed from the ice bath and allowed to warm to room temperature for about 30 min. The reaction mixture was then cooled back down to 0 °C and a solution of 1,9-dibromononane (2.46 mL, 12.1 mmol) in dimethylformamide (100 mL) was added. The reaction mixture was stirred overnight at room temperature. After 24 h, MS analysis showed that the reaction was completed. The reaction mixture was concentrated to dryness and diluted with ethyl acetate (100 mL). The organic layer was washed with saturated sodium bicarbonate (2 x 100 mL), brine (100 mL), dried (magnesium sulfate) and concentrated under reduced pressure to yield the crude product,

which was purified by chromatography on silica gel using 5% ethyl acetate in hexanes to afford the title compound. MS *m/z*: [M + H^+] calcd for $C_{19}H_{36}N_1O_4Br$ 423.18; found 423.

Preparation 10

Biphenyl-2-ylcarbamic Acid 1-(9-Di-*tert*-butoxycarbonylamino)nonyl]piperidin-4-yl Ester

A mixture of 1:1 acetonitrile and *N,N*-dimethylformamide (50 mL) was added to the products of Preparation 8 (3.0 g, 10.1 mmol) and Preparation 9 (5.1 g, 12.2 mmol) and triethylamine (1.42 mL, 10.1 mmol). The reaction mixture was stirred at ambient temperature for 24 h and was monitored by LCMS analysis. The reaction mixture was then concentrated and diluted with ethyl acetate (50 mL). The organic layer was washed with saturated sodium bicarbonate (2 x 50 mL) and brine (50 mL). The organic phase was then dried over magnesium sulfate and concentrated to yield 6.5 g of crude oil. The oil was purified by chromatography on silica gel using 1:1 hexanes/ethyl acetate to provide the title compound (3 g). MS *m/z*: [M + H^+] calcd for $C_{37}H_{55}N_3O_6$ 638.41; found 639.

Preparation 11

Biphenyl-2-ylcarbamic Acid 1-(9-Aminononyl)piperidin-4-yl Ester

Trifluoroacetic acid (11 mL) was added to a solution of the product of Preparation 10 (7.2 g, 11.3 mmol) in dichloromethane (56 mL). After 2 h, LCMS analysis showed that the reaction was completed. The reaction mixture was then concentrated to dryness and diluted with ethyl acetate (75 mL). Sodium hydroxide (1N) was then added until the pH of the mixture reached 14. The organic phase was then collected and washed with saturated sodium bicarbonate (2 x 50 mL) and brine (50 mL). The organic phase was then dried over magnesium sulfate and concentrated to provide the title compound (5.5 g). MS *m/z*: [M + H^+] calcd for $C_{27}H_{39}N_3O_2$ 438.30; found 439.

Preparation 12

Biphenyl-2-ylcarbamic Acid 1-{9-[2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]nonyl}piperidin-4-yl Ester

The product of Preparation 11 (196 mg, 0.43 mmol) was dissolved in dichloroethane (4 mL) and sodium triacetoxyborohydride (101 mg, 0.48 mmol) was added. The reaction mixture was stirred at ambient temperature for about 10 min. and then 8-

benzyloxy-5-(2,2-dihydroxyacetyl)-1*H*-quinolin-2-one (Preparation 6) (141 mg, 0.43 mmol) was added. LCMS analysis showed that the reaction was completed after 2 h. Methanol (1 mL) was added to the reaction mixture and then sodium borohydride (18 mg, 0.48 mmol) was added slowly. After 1 hour, LCMS analysis showed that the reaction was completed. The reaction mixture was then quenched with aqueous ammonium chloride and this mixture was extracted with dichloromethane. The organic phase was washed with saturated sodium bicarbonate (2 x 50 mL) and brine (10 mL). The organic phase was then dried over magnesium sulfate and concentrated to provide 315 mg of a yellow solid. The solid was purified by silica gel chromatography using 10% methanol in dichloromethane to afford the title compound (64 mg). MS *m/z*: $[M + H^+]$ calcd for $C_{43}H_{55}N_4O_5$ 730.40; found 731.

Example 2

Biphenyl-2-ylcarbamic Acid 1-{9-[2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}piperidin-4-yl Ester Ditrifluoroacetate

A solution of the product of Preparation 12 (64 mg, 0.09 mmol) in methanol (450 mL) was flushed with nitrogen. Palladium on carbon (10%, 10 mg) was then added and the reaction mixture was placed under a balloon containing hydrogen and stirred. LCMS analysis showed that the reaction was completed after 9 h. The reaction mixture was then filtered and the filtrate was concentrated to provide a yellow crispy solid. The solid was purified by preparative HPLC (5-35 over 60 min) to afford the title compound (19 mg). MS *m/z*: $[M + H^+]$ calcd for $C_{38}H_{48}N_4O_5$ 641.36; found 641.

Preparation 13

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

(a) 8-Benzyloxy-5-(2-Bromoacetyl)-1*H*-quinolin-2-one

5-Acetyl-8-benzyloxy-1*H*-quinolin-2-one (Preparation 6) (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 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 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.

(b) 8-Benzyloxy-5-((R)-2-bromo-1-hydroxyethyl)-1H-quinolin-2-one

(R)-(+)-α,α-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 µL 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±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).

(c) 8-Benzyloxy-5-[(*R*)-2-bromo-1-(*tert*-butyldimethylsilanyloxy)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 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).

Preparation 14

Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-(8-benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]nonyl}piperidin-4-yl Ester

The product of Preparation 13 (3.9 g, 8.17 mmol) was added to a solution of the product of Preparation 11 (5.0 g, 11.4 mmol) in THF (20 mL), followed by sodium bicarbonate (2.0 g, 24.5 mmol) and sodium iodide (1.8 g, 12.2 mmol). The reaction mixture was heated to 80 °C for 72 h. The reaction mixture was then cooled, diluted with dichloromethane (20 mL) and the organic phase was washed with saturated sodium bicarbonate (2 x 50 mL) and brine (50 mL). The organic phase was then dried (magnesium sulfate) and concentrated to give 6.5 g of a crude product. The crude product was purified by chromatography on silica gel eluting with 3% methanol in dichloromethane to provide the title compound (1.4 g, 21% yield).

Preparation 15

Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-(8-benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]nonyl}piperidin-4-yl Ester

Triethylamine hydrogen fluoride (376 μL, 2.3 mmol) was added to a solution of the product of Preparation 14 (1.3 g, 1.5 mmol) in THF (8 mL) and the reaction mixture was stirred at ambient temperature. After 5 h, the reaction was complete as determined by LCMS analysis. The reaction mixture was then quenched with 1N NaOH until the pH was 14 and then diluted with ethyl acetate (20 mL) and washed with 1N NaOH (20 mL) and brine (20 mL). The organic phase was then separated, dried over magnesium sulfate, and concentrated to yield the title compound (1.1 g).

Example 3

Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydro-quinolin-5-yl)ethylamino]nonyl}piperidin-4-yl Ester Ditrifluoroacetate

A solution of the product of Preparation 15 (1.1 g, 1.5 mmol) was flushed with nitrogen and palladium on carbon (10%, 110 mg) was added. The reaction mixture was stirred under hydrogen at balloon pressure. Analysis by LCMS showed that the reaction was completed after 9 h. The reaction mixture was then filtered and concentrated to yield a yellow solid. The solid was purified by preparative HPLC (5-30 over 60 min) to afford the title compound (510 mg). MS *m/z*: $[M + H^+]$ calcd for $C_{38}H_{48}N_4O_5$ 641.36; found 641. HPLC method 10-70: 3.207. $[\alpha]^{20}_D$ = -23.6 (c = 1.0 mg/mL, water).

Example 3A

Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydro-quinolin-5-yl)ethylamino]nonyl}piperidin-4-yl Ester Ditrifluoroacetate

Alternatively, the title compound was prepared as follows:

(a) 9-Bromononanal

To a 100-mL round-bottomed flask equipped with a magnetic stirrer, addition funnel and temperature controller, under nitrogen, was added 9-bromononanol (8.92 g, 40 mmol) and dichloromethane (30 mL). The resulting mixture was cooled to 5 °C and a solution of sodium bicarbonate (0.47 g, 5.6 mmol) and potassium bromide (0.48 g, 4 mmol) in water (10 mL) was added. 2,2,6,6-Tetramethyl-1-piperidinyloxy free radical (TEMPO) (63 mg, 0.4 mmol) was added and then a 10 to 13% bleach solution (27 mL) was added dropwise through the addition funnel at a rate such that the temperature was maintained at about 8 °C (+/- 2 °C) with an ice cold bath (over about 40 min.). After addition of the bleach was complete, the mixture was stirred for 30 min. while maintaining the temperature at about 0°C. A solution of sodium bisulfite (1.54 g) in water (10 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The layers of the mixture were then separated, and the milky aqueous layer was extracted with dichloromethane (1 x 20 mL). The combined dichloromethane layers were then washed with water (1 x 30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title intermediate (8.3 g, 94% yield), which was used without further purification in the next step.

(b) 9-Bromo-1,1-dimethoxynonane

To a 100 mL round-bottomed flask was added 9-bromononanal (7.2 g, 32.5 mmol), methanol (30 mL) and trimethylorthoformate (4 mL, 36.5 mmol). A solution of 4 N hydrochloric acid in dioxane (0.2 mL, 0.8 mmol) was added and the resulting mixture was refluxed for 3 h. The reaction mixture was then cooled to room temperature and solid sodium bicarbonate (100 mg, 1.2 mmol) was added. The resulting mixture was concentrated to one-fourth its original volume under reduced pressure and then ethyl acetate (50 mL) was added. The organic layer was washed with water (2 x 40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title intermediate (8.44 g, (97 % yield)) as a liquid, which as used in the next step without further purification.

(c) Biphenyl-2-ylcarbamic Acid 1-(9,9-Dimethoxynonyl)piperidin-4-yl Ester

To a 50 mL three-necked, round-bottomed flask was added biphenyl-2-ylcarbamic acid piperidin-4-yl ester (1 g, 3.38 mmol) and acetonitrile (10 mL) to form a slurry. To this slurry was added 9-bromo-1,1-dimethoxynonane (1.1g, 1.3 mmol) and triethylamine (0.57 g, 4.1 mmol) and the resulting mixture was heated at 65 °C for 6 h (the reaction was monitored by HPLC until starting material is < 5 %). The reaction mixture was then cooled to room temperature at which time the mixture formed a thick slurry. Water (5 mL) was added and the mixture was filtered to collect the solid on a coarse fritted glass filer. The solid was washed with pre-mixed solution of acetonitrile (10 mL) and water (5 mL) and then with another pre-mixed solution of acetonitrile (10 mL) and water (2 mL). The resulting solid was air dried to afford the title intermediate (1.37 g, 84 %, purity >96 % by LC, 1H NMR) as a white solid.

(d) Biphenyl-2-ylcarbamic Acid 1-(9-Oxononyl)piperidin-4-yl Ester

To a 500 mL round-bottomed flask with a magnetic stirrer was added biphenyl-2-ylcarbamic acid 1-(9,9-dimethoxynonyl)piperidin-4-yl ester (7.7 g, 15.9 mmol) and then acetonitrile (70 mL) and aqueous 1M hydrochloric acid (70 mL). The resulting mixture was stirred at room temperature for 1 h and then dichloromethane (200 mL) was added. This mixture was stirred for 15 min. and then the layers were separated. The organic layer

was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title intermediate (6.8 g), which was used in the next step without further purification.

(e) Biphenyl-2-ylcarbamic Acid 1-(9-{Benzyl-[(*R*)-2-(8-benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethyl]amino}nonyl)-piperidin-4-yl Ester

To a 300 mL round-bottomed flask was added 5-[(*R*)-2-benzylamino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-benzyloxy-1H-quinolin-2-one (5 g, 9.73 mmol), dichloromethane (100 mL) and glacial acetic acid (0.6 mL, 10 mmol). This mixture was cooled to 0 °C using an ice bath and biphenyl-2-ylcarbamic acid 1-(9-oxononyl)piperidin-4-yl ester (4.6 g, 9.73 mmol) was added with stirring. This mixture was stirred at 0 °C for 30 minutes and then sodium triacetoxyborohydride (6.15 g, 29 mmol) was added in portions over 15 minutes. The reaction mixture was stirred at 0 °C to 10 °C for 2 hours and then aqueous saturated sodium bicarbonate solution (50 mL) was added and this mixture was stirred for 15 minutes. The layers were then separated and the organic layer was washed with 5% aqueous sodium chloride solution (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title intermediate (8.5 g, 80% purity by HPLC), which was used without further purification.

(f) Biphenyl-2-ylcarbamic Acid 1-{9-[(R)-2-(tert-Butyldimethylsilanyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}piperidin-4-yl Ester

To a 200 mL round-bottomed flask was added the intermediate from Step E (8.5 g, 9 mmol), ethanol (100 mL) and glacial acetic acid (0.54 mL, 18 mmol) and this mixture was stirred until the solid dissolved. The reaction mixture was purged with hydrogen for 5 min. and then 10% palladium on carbon (1.7 g) was added. This mixture was stirred at room temperature while hydrogen was slowly bubbling through the reaction mixture until >95% conversion was observed by HPLC (about 8-9 h). The mixture was then filtered through a Celite pad and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (15g silica/1g crude) using 5% MeOH in DCM/0.5% NH_4OH (10 x 150 mL), 8% MeOH in DCM/0.5% NH_4OH (10 x 150 mL) and 10% MeOH in DCM/0.5% NH_4OH (10 x 150 mL). The appropriate fractions were

combined and the solvent was removed under reduced pressure while maintaining the temperature <35 °C to give the title intermediate (4.05 g , 97% purity).

(g) Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}piperidin-4-yl Ester

To a 200 mL round-bottomed flask was added the intermediate from Step F (4.05 g, 5.36 mmol) and dichloromethane (80 mL) and the resulting mixture was stirred until the solid dissolved. Triethylamine trihydrofluoride (2.6 mL, 16 mmol) was added and stirring was continued under nitrogen for 18 to 20 h. Methanol (20 mL) was added and then saturated aqueous sodium bicarbonate (50 mL) was added slowly and the mixture was stirred for 15 min. The layers were then separated and the organic layer was washed with saturated aqueous sodium chloride solution (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title compound (3.5g, 98% purity by HPLC) as a yellow solid.

Example 3B

Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-Hydroxy-2-(8-Hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}piperidin-4-yl Ester Naphthalene-1,5-disulfonic Acid Salt

Biphenyl-2-ylcarbamic acid 1-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}piperidin-4-yl ester (1.0 g, 1.56 mmol, free base) was dissolved in methanol (10 mL; low water content). A solution of naphthalene-1,5-disulfonic acid (0.45 g, 1.56 mmol) in methanol (5 mL; low water content) was added and the reaction mixture was stirred at 30 °C for two hours and then at room temperature overnight (18 h). The resulting thick slurry was filtered and the filtrate cake was washed with methanol (5 mL) and then dried to give the title compound (1.16 g, 80% yield) as off-white crystalline solid.

Preparation 16

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

(*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 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 (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*: $[M + H^+]$ calcd for $C_{22}H_{30}NO_3SiBr$ 464.1; found 464.2.

The starting material, (*R*)-2-bromo-1-(3-formamido-4-benzyloxyphenyl)ethanol, 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.

Preparation 17

Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-(4-Benzyloxy-3-formylaminophenyl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]nonyl}piperidin-4-yl Ester

The product of Preparation 16 (500 mg, 1.008 mmol) and sodium iodide (243 mg, 1.62 mmol) were stirred in tetrahydrofuran (0.5 mL) for 15 min at ambient temperature. The product of Preparation 11, (564 mg, 1.29 mmol) and sodium bicarbonate (272 mg, 3.24 mmol) were then added and the reaction mixture was heated at 80 °C for 24 h. The reaction mixture was then allowed to cool. Water (2 mL) was then added and the mixture was extracted with dichloromethane (2 x 2 mL). The combined organic extracts were washed with 1M hydrochloric acid (2 x 1 mL), dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography (5-10% methanol/dichloromethane) to give the title compound (360 mg, 0.44 mmol, 41% yield). HPLC (10-70) R_t = 4.96; MS *m/z*: $[M + H^+]$ calcd for $C_{49}H_{68}N_4O_5$ 821.51; found 821.9.

Preparation 18

Biphenyl-2-ylcarbamic Acid 1-{9-[(R)-2-(4-Benzyloxy-3-formylaminophenyl)-2-hydroxyethylamino]nonyl}piperidin-4-yl Ester

To a stirred solution of the product of Preparation 17 (360 mg, 0.44 mmol) in tetrahydrofuran (2.2 mL) at ambient temperature was added triethylamine trihydrofluoride (108 μL, 0.66 mmol). The reaction mixture was stirred for 24 h and then diluted with dichloromethane (5 mL) and washed with 1M hydrochloric acid (2 mL) and saturated aqueous sodium bicarbonate (2 mL). The organic phase was dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude title compound was used directly in the next step without further purification. HPLC (10-70) R_t = 4.6; MS *m/z*: [M + H^+] calcd for $C_{43}H_{54}N_4O_5$ 707.43; found 707.8.

Example 4

Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-(3-Formylamino-4-hydroxyphenyl)-2-hydroxyethylamino]nonyl}piperidin-4-yl Ester Ditrifluoroacetate

Palladium (10 wt. % (dry basis) on activated carbon) (124 mg) was added to a stirred solution of the product of Preparation 18 (311 mg, 0.44 mmol) in ethanol (4 mL) and the reaction mixture was placed under an atmosphere of hydrogen. After stirring for 12 h, the reaction mixture was filtered through a pad of Celite, washed with methanol (2 mL) and the solvent was removed under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound (41 mg). HPLC (10-70) R_t = 3.0; MS *m/z*: [M + H^+] calcd for $C_{36}H_{48}N_4O_5$ 617.39; found 617.5.

Example 5

Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)ethylamino]nonyl}piperidin-4-yl Ester Ditrifluoroacetate

Palladium (10 wt. % (dry basis) on activated carbon) (80 mg) was added to a stirred solution of the product of Example 3 (80 mg, 0.11 mmol) in ethanol (1.1 mL) and the reaction mixture was placed under an atmosphere of hydrogen. The reaction mixture was stirred for 12 h, and then filtered through a pad of Celite, washed with methanol (2 mL) and the solvent removed under reduced pressure. The crude material was resubjected to the above conditions to ensure complete reaction. The resulting residue was purified by

preparative HPLC to yield the title compound (6 mg). HPLC (10-70) $R_t = 3.23$; MS *m/z*: $[M + H^+]$ calcd for $C_{38}H_{50}N_4O_5$ 643.39; found 643.7.

Preparation 19

3-[4-(Biphenyl-2-ylcarbamoyloxy)piperidin-1-yl]propionic Acid Methyl Ester

Methyl 3-bromopropionate (553 μL, 5.07 mmol) was added to a stirred solution of the product of Preparation 8 (1.00 g, 3.38 mmol) and DIPEA (1.76 mL, 10.1 mmol) in acetonitrile (34 mL) at 50 °C and the reaction mixture was heated at 50 °C overnight. The solvent was then removed under reduced pressure and the residue was dissolved in dichloromethane (30 mL). The resulting solution was washed with saturated aqueous sodium bicarbonate solution (10 mL), dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (5-10% MeOH/DCM) to give the title compound (905 mg, 70%).

Preparation 20

3-[4-(Biphenyl-2-ylcarbamoyloxy)piperidin-1-yl]propionic Acid

A stirred solution of the product of Preparation 19 (902 mg, 2.37 mmol) and lithium hydroxide (171 mg, 7.11 mmol) in 50% THF/H_2O (24 mL) was heated at 30 °C overnight, and then acidified with concentrated hydrochloric acid and lyophilized to give the title compound (~ 100% yield, also contains LiCl salts).

Preparation 21

{5-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]pentyl}carbamic Acid *tert*-Butyl Ester

The product of Preparation 13 (600 mg, 1.23 mmol) and *N*-*tert*-butoxycarbonyl-1,5-diaminopentane (622 mg, 3.07 mmol) were dissolved in dimethyl sulfoxide (1.23 mL) and heated to 105 °C for 6 h. The reaction mixture was then cooled and diluted with ethyl acetate (10 mL) and washed with saturated aqueous sodium bicarbonate solution (4 mL). The organic phase was dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (5-10% methanol/dichloromethane) to give the title compound (~100% yield).

Preparation 22

5-[(*R*)-2-(5-Aminopentylamino)-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-benzyloxy-1H-quinolin-2-one

A solution of the product of Preparation 21 (800 mg, 1.31 mmol) in trifluoroacetic acid/dichloromethane (25%, 12 mL) was stirred at ambient temperature for 1 hour. The solvent was then removed under reduced pressure and the crude residue was dissolved in dichloromethane (15 mL) and washed with 1N sodium hydroxide (8 mL). The organic phase was separated, dried (magnesium sulfate) and the solvent was removed under reduced pressure to give the title compound (509 mg, 81% yield over 2 steps).

Preparation 23

Biphenyl-2-ylcarbamic Acid 1-(2-{5-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]pentylcarbamoyl}ethyl)piperidin-4-yl Ester

To the product of Preparation 20 (417 mg, 1.13 mmol) and HATU (430 mg, 1.13 mmol) was added the product of Preparation 22 (458 mg, 0.90 mmol) in DMF (1.8 mL), followed by DIPEA (204 μL, 1.17 mmol). The reaction mixture was stirred at 50 °C for 12 h, and then the solvent was removed under reduced pressure. The crude residue was dissolved in dichloromethane (10 mL). The resulting solution was washed with saturated aqueous sodium bicarbonate solution (4 mL), dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (5-10% methanol/dichloromethane and 0.5% NH_4OH) to give the title compound (240 mg, 31% yield).

Preparation 24

Biphenyl-2-ylcarbamic Acid 1-(2-{5-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]pentylcarbamoyl}ethyl)piperidin-4-yl Ester

To a stirred solution of the product of Preparation 23 (240 mg, 0.28 mmol) in dichloromethane (2.8 mL) was added triethylamine trihydrofluoride (91 μL, 0.56 mmol). The reaction mixture was stirred for 10 h, and then diluted with dichloromethane (10 mL). The resulting solution was then washed with saturated aqueous sodium bicarbonate solution (5 mL), and then the organic phase was dried (magnesium sulfate) and the solvent was removed under reduced pressure to give the title compound (209 mg, 100% yield).

Example 6

Biphenyl-2-ylcarbamic Acid 1-(2-{5-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentylcarbamoyl}ethyl)piperidin-4-yl Ester, Ditrifluoroacetate

To a stirred solution of the product of Preparation 24 (209 mg, 0.28 mmol) in ethanol (2.8 mL) was added palladium (10 wt. % (dry basis) on activated carbon) (81 mg) and the reaction mixture was placed under an atmosphere of hydrogen and stirred overnight. The reaction mixture was then filtered and solvent was removed under reduced pressure. The crude residue was purified by preparative HPLC to give the title compound (58 mg). HPLC (10-70) $R_t = 2.30$; MS *m/z*: $[M + H^+]$ calcd for $C_{37}H_{45}N_5O_6$ 656.34; found 656.6; $[\alpha]^{20}_D = -6.5$ (c=1.0mg/mL, water).

Example 6A

Biphenyl-2-ylcarbamic Acid 1-(2-{5-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentylcarbamoyl}ethyl)piperidin-4-yl Ester

Alternatively, the title compound can be prepared as follows:

(a) 5-Chloropentanal

To a 2 L three-necked round-bottomed flask, equipped with a magnetic stirrer, addition funnel and temperature controller under nitrogen, was added 5-chloropentanol (53 g, 0.433 mol) and dichloromethane (300 mL). This mixture was cooled to 5 °C and a solution of sodium bicarbonate (5 g, 0.059 mol) and potassium bromide (5.1 g, 0.043 mol) in water (225 mL) was added. 2,2,6,6-Tetramethyl-1-piperidinyloxy free radical (TEMPO) (63 mg, 0.4 mmol) was added and then a 10 to 13% bleach solution (275 mL) was added dropwise through the addition funnel at a rate such that the temperature was maintained at about 8 °C (+/- 2 °C) with an ice cold bath (over about 45 min.). After addition of the bleach was complete, the mixture was stirred for 30 min. while maintaining the temperature at about 5°C. A solution of sodium bisulfite (4 g) in water (30 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The layers of the mixture were then separated, and the aqueous layer was extracted with dichloromethane (1 x 50 mL). The combined dichloromethane layers were then washed with water (1 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title compound (53 g). The product was distilled at 65°C/8 torr to afford the title compound (31.16 g) as an orange oil (GC purity was 70 to 80 %).

The product was further purified by adding the crude material (4 g) to a mixture of ethanol (920 mL), ethyl acetate (12 mL) and water (4 mL). Sodium bisulfite (4g) was added and the mixture was heated to reflux for 4 h and then cooled to room temperature and stirred for 14 h at room temperature to form a very thick slurry. The solids were filtered on a coarse fritted filter, washed with the solvent mixture (5 mL) and the solids were dried on the filter to afford 8.4 g of the bisulfite adduct. This material was then added to MTBE (20 mL) and aqueous 1 N sodium hydroxide (45 mL) was added with vigorous stirring. The resulting biphasic mixture was stirred vigorously until all the solids had dissolved (about 15 min) and then the layers were separated. The aqueous layer was extracted with MTBE (20 mL) and the combined MTBE layers were dried ($MgSO_4$), filtered and concentrated to afford 3.46 g of the title compound as a colorless liquid (GC purity >90 %).

(b) 5-[(*R*)-2-[Benzyl-(5-chloropentyl)amino]-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-benzyloxy-1H-quinolin-2-one

To a 1 L three-necked round-bottomed flask was added the product of Preparation 28 (48.4 g, 94 mmol), dichloromethane (400 mL) and glacial acetic acid (11.3 mL). This mixture was stirred at 0 °C (ice bath) and the product from step (a) (12.5 g, 103.6 mmol) was added and stirring was continued for 15 min. Sodium triacetoxyborohydride (59.8 g, 282 mmol) was then added in portions over a 15 min. period and the resulting mixture was stirred at 0 °C to 10 °C for 2 h. Aqueous saturated sodium bicarbonate solution (200 mL) was then added slowly (gas evolution) and stirring was continued for 15 min. The pH of the solution was then adjusted with solid sodium carbonate to a pH of about 9 and the layers were separated. The organic layer was washed with aqueous 5% sodium chloride solution (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title compound (53 g).

(c) 5-[(*R*)-2-[(5-*N*,*N*-Diformylaminopentyl)benzylamino]-1-(*tert*-butyldimethyl-silanyloxy)ethyl]-8-benzyloxy-1H-quinolin-2-one

To a stirred solution of the product of step (b) (26.5 g, 42.8 mmol) in 1-methyl-2-pyrrolidinone (175 mL) was added sodium diformylamide (6.1 g, 64.2 mmol) and sodium iodide (2.13 g, 14.3 mmol). The reaction flask was flushed with nitrogen and then the mixture was heated at 65 °C for 8 h. The mixture was then cooled to room temperature

and water (300 mL) and ethyl acetate (100 mL) were added. This mixture was stirred for 10 min. and then the layers were separated. The aqueous layer was extracted with ethyl acetate (150 mL) and the combined organic layers were washed with water (300 mL), aqueous 50 % brine solution (300 mL), water (300 mL), dried ($MgSO_4$) filtered and concentrate to afford the title compound (23.3 g).

(d) 5-[(*R*)-2-[(5-Aminopentyl)benzylamino]-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-benzyloxy-1H-quinolin-2-one

To a stirred solution of the product from step (c) (10.5 g, 16 mmol) in methanol (75 mL) was added *p*-toluenesulfonic acid (7.42 g. 39 mmol). The resulting mixture was heated at 40 °C for 15 h and then concentrated under reduced pressure to about half its volume. Methanol (70 mL) was added and the mixture was heated at 50 °C for 2 h and then concentrated under reduced pressure. Water (100 mL), methanol (50 mL) and MTBE (100 mL) were added and this mixture was stirred for 15 min and then the layers were separated. To the aqueous layer was added aqueous 1 N sodium hydroxide (45 mL) and MTBE (100 mL), and this mixture was stirred for 15 min. The layers were then separated and the aqueous layer was extracted with MTBE (100 mL). The combined MTBE layers were dried ($MgSO_4$), filtered and concentrated to afford the title compound as a yellow oil (7.3 g). This material contained about 13 % (by HPLC) of the corresponding des-*tert*-butyldimethylsilyl compound.

(e) 3-[4-(Biphenyl-2-ylcarbamoyloxy)piperidin-1-yl]propionic Acid

To a solution of the product of Preparation 8 (50 g, 67.6 mmol) in dichloromethane (500 mL) was added acrylic acid (15.05 mL, 100 mmol). The resulting mixture was heated at 50 °C under reflux for 18 h and then the solvent was removed. Methanol (600 mL) was added and this mixture was heated at 75 °C for 2 h and then cooled to room temperature to form a thick slurry. The solid was collected by filtration, washed with methanol (50 mL) and air dried to afford the title compound (61g, >96% purity) as white powder.

(f) Biphenyl-2-ylcarbamic Acid 1-[2-(5-{Benzyl-[(*R*)-2-(8-benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethyl]amino}-pentylcarbamoyl)ethyl]piperidin-4-yl Ester

A mixture of the product of step (e) (3.68 g, 10 mmol) and *N,N*-dimethylformamide (50 mL) was heated at 60 °C until the solid completely dissolved and then cooled to room temperature. The product of step (d) (6 g, 10 mmol) and diisopropylethylamine (3.5 mL) was added and the reaction mixture was cooled to 0°C. PyBOP (6.25 g, 12 mmol) was added in one portion and the reaction mixture was stirred at 0 °C to room temperature for 2 hours. The reaction mixture was then poured into cold water (500 mL) with stirring and the pH of the resulting mixture was adjusted to about 2 using aqueous 1 M hydrochloric acid. This mixture was stirred for 15 min and then filtered to collect the solid, which was washed with water (100 mL) and dried to afford the title compound (8.7 g, HPLC purity >95%) as an off- white solid.

(g) Biphenyl-2-ylcarbamic Acid 1-(2-{5-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentylcarbamoyl}ethyl)piperidin-4-yl Ester

The product of step (f) can be deprotected using essentially the same procedures as those described in Preparation 24 and Example 6 to afford the title compound.

Preparation 25

2-(*N*-Benzyloxycarbonyl-*N*-methylamino)ethanal

(a) 2-(*N*-Benzyloxycarbonyl-*N*-methylamino)ethanol

Benzyl chloroformate (19 g, 111.1 mmol) in THF (20 mL) was added dropwise over 15 min to a stirred solution of 2-(methylamino)ethanol (10 g, 133.3 mmol) in THF (100 mL) and aqueous sodium carbonate (100 mL) at 0°C. The reaction mixture was stirred at 0 °C for 12 h and then extracted with EtOAc (2 x 200 mL). The organic layer was washed with aqueous sodium carbonate (200 mL) and dried (potassium carbonate) and solvent was removed under reduced pressure to give the title compound (22.5 g, 97% yield).

(b) 2-(*N*-Benzyloxycarbonyl-*N*-methylamino)ethanal

DMSO (71 mL,1 mol) and DIPEA (87.1 mL, 0.5 mol) were added to a stirred solution of the product of step (a) (20.9 g, 0.1 mol) in dichloromethane (200 mL) at -10°C.

The reaction mixture was stirred at –10 °C for 15 min and then sulfur trioxide pyridine complex (79.6 g, 0.5 mol) was added and the resulting mixture was stirred for 1 hour. The reaction mixture was quenched with addition of 1M hydrochloric acid (200 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried (potassium carbonate) and solvent removed under reduced pressure to give the title compound (20.7 g, ~100% yield).

Preparation 26

Biphenyl-2-ylcarbamic Acid 1-[2-(methylamino)ethyl]piperidin-4-yl Ester

To a stirred solution of the product of Preparation 25 (20.7 g, 100 mmol) and the product of Preparation 8 (25 g, 84.7 mmol) in MeOH (200 mL) was added sodium triacetoxyborohydride (21.2 g, 100 mmol). The reaction mixture was stirred for 12 h at ambient temperature and then it was quenched with 2M hydrochloric acid and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (50 mL), and then dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (50-90% EtOAc/hexanes) to give biphenyl-2-ylcarbamic acid 1-[2-(benzyloxycarbonyl-methylamino)ethyl]piperidin-4-yl ester as an oil.

The oil was dissolved in methanol (100 mL) and palladium (10 wt. % (dry basis) on activated carbon) (5 g) was added. The reaction mixture was stirred under hydrogen (30 psi) for 12 h and then filtered through Celite, which was washed with methanol, and solvent was evaporated to give the title compound (13.2 g, 44% yield).

Preparation 27

Biphenyl-2-ylcarbamic Acid 1-{2-[(6-Bromohexanoyl)methylamino]ethyl}piperidin-4-yl Ester

6-Bromohexanoyl chloride (3.23 mL, 21.1 mmol) was added to a stirred solution of the product of Preparation 26 (6.2 g, 17.6 mmol) and DIPEA (6.13 mL, 35.2 mmol) in dichloroethane (170 mL). The reaction mixture was stirred for 1 hour and it was then diluted with EtOAc (250 mL) and washed with saturated aqueous sodium bicarbonate solution (2 x 200 mL) and brine (200 mL), and then dried (magnesium sulfate). The solvent was removed under reduced pressure to give the title compound (6.6 g, 73% yield).

Preparation 28

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

A stirred solution of the product of Preparation 13 (1.00 g, 2.05 mmol) and benzylamine (493 μL, 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 ($MgSO_4$) 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^+] calcd for $C_{31}H_{38}N_2O_3Si$ 515.27; found 515.5.

Preparation 29

Biphenyl-2-ylcarbamic Acid 1-{2-[(6-{Benzyl-[(*R*)-2-(8-benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethyl]amino}hexanoyl)-methylamino]ethyl}piperidin-4-yl Ester

To a stirred solution of the product of Preparation 28 (807 mg, 1.57 mmol) and DIPEA (819 μL, 4.7 mmol) in acetonitrile (3.14 mL) was added the product of Preparation 27 (995 mg, 1.88 mmol). The reaction mixture was heated to 80 °C for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (10 mL) and then washed with saturated aqueous sodium bicarbonate solution (5 mL), dried (magnesium sulfate), and the solvent removed under reduced pressure. The crude material was purified by column chromatography (4-6% MeOH/DCM) to obtain the title compound (452 mg, 30% yield).

Preparation 30

Biphenyl-2-ylcarbamic Acid 1-{2-[(6-{Benzyl-[(*R*)-2-(8-benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethyl]amino}hexanoyl)methylamino]ethyl}piperidin-4-yl Ester

To a stirred solution of the product of Preparation 29 (452 mg, 0.47 mmol) in dichloromethane (4.7 mL) was added triethylamine trihydrofluoride (116 μL, 0.71 mmol). The reaction mixture was stirred for 10 h. and then it was diluted with dichloromethane (10 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL). The organic

phase was then dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the title compound (100% yield).

Example 7

Biphenyl-2-ylcarbamic Acid 1-[2-({6-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]hexanoyl}methylamino)ethyl]piperidin-4-yl Ester Ditrifluoroacetate

To a stirred solution of the product of Preparation 30 (400 mg, 0.47 mmol) in ethanol (4.7 mL) was added palladium (10 wt. % (dry basis) on activated carbon) (160 mg) and the reaction mixture was placed under an atmosphere of hydrogen and stirred overnight. The reaction mixture was then filtered and solvent was removed under reduced pressure. The crude residue was purified by preparative HPLC to give the title compound (73 mg). HPLC (10-70) $R_t = 2.33$; MS *m/z*: $[M + H^+]$ calcd for $C_{38}H_{47}N_5O_6$ 670.36; found 670. $[\alpha]^{20}_D = -9.4$ ($c = 1.0$ mg/mL, water).

Preparation 31

Biphenyl-2-ylcarbamic Acid 1-[2-(4-(Aminomethyl)phenylcarbamoyl)-ethyl]piperidin-4-yl Ester

To a stirred solution of 4-(*N-tert*-butoxycarbonylaminomethyl)aniline (756 mg, 3.4 mmol), the product of Preparation 20 (1.5 g, 4.08 mmol) and HATU (1.55 g, 4.08 mmol) in DMF (6.8 mL) was added DIPEA (770 µL, 4.42 mmol). The reaction mixture was stirred at 50 °C overnight and then the solvent was removed under reduced pressure. The resulting residue was dissolved in dichloromethane (20 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic phase was then dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (5-10% MeOH/DCM) to give a solid, which was dissolved in TFA/DCM (25%, 30 mL) and stirred at room temperature for 2 h. The solvent was then removed under reduced pressure and the crude residue was dissolved in dichloromethane (30 mL) and washed with 1N sodium hydroxide (15 mL). The organic phase was separated, dried (magnesium sulfate) and the solvent was removed under reduced pressure to give the title compound (1.5 g, 94% over 2 steps).

Preparation 32

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]methyl}phenylcarbamoyl)ethyl]-piperidin-4-yl Ester

A solution of the product of Preparation 31 (489 mg, 1.04 mmol), the product of Preparation 13 (610 mg, 1.25 mmol), sodium bicarbonate (262 mg, 3.12 mmol) and sodium iodide (203 mg, 1.35 mmol) in THF (0.52 mL) were heated at 80 °C for 12 h. The reaction mixture was diluted with dichloromethane (10 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography (10% MeOH/DCM) to give the title compound as a solid (687 mg, 77% yield).

Preparation 33

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl Ester

To a stirred solution of the product of Preparation 32 (687 mg, 0.8 mmol) in dichloromethane (8 mL) was added triethylamine trihydrofluoride (261 μL, 1.6 mmol). The reaction mixture was stirred for 10 h and then was diluted with dichloromethane (20 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic phase was then dried (magnesium sulfate) and the solvent was removed under reduced pressure to yield the title compound (500 mg, 81% yield).

Example 8

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl Ester Ditrifluoroacetate

To a stirred solution of the product of Preparation 33 (500 mg, 0.65 mmol) in ethanol (6.5 mL) was added palladium (10 wt. % (dry basis) on activated carbon) (200 mg) and the reaction mixture was placed under a hydrogen atmosphere and stirred overnight. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The crude residue was purified by preparative HPLC to give the title compound

(81 mg, 2 TFA salt). HPLC (10-70) R_t = 2.41; MS *m/z*: [M + H^+] calcd for $C_{39}H_{41}N_5O_6$ 676.32; found 676.5.

Preparation 34

Biphenyl-2-ylcarbamic Acid 1-(2-*tert*-Butoxycarbonylaminoethyl)piperidin-4-yl Ester

To a stirred solution of the product of Preparation 8 (2.00 g, 6.76 mmol) and DIPEA (3.54 mL, 20.3 mmol) in acetonitrile (67.6 mL) at 50 °C was added 2-*tert*-butoxycarbonylaminoethyl bromide (1.82 g, 8.11 mmol) and the reaction mixture was heated at 50 °C overnight. The solvent was then removed under reduced pressure and the residue was dissolved in dichloromethane (60 mL) and washed with saturated aqueous sodium bicarbonate solution (30 mL). The organic phase was dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (5 % MeOH/DCM) to yield the title compound as a solid (2.32 g, 78% yield).

Preparation 35

Biphenyl-2-ylcarbamic Acid 1-(2-Aminoethyl)piperidin-4-yl Ester

The product of Preparation 34 was dissolved in TFA/DCM (25%, 52 mL) and stirred at room temperature for 2 h. The solvent was then removed under reduced pressure and the crude residue dissolved in dichloromethane (30 mL) and washed with 1N sodium hydroxide (15 mL). The organic phase was separated, dried (magnesium sulfate) and the solvent was removed under reduced pressure to give the title compound (1.61 g, 90% yield).

Preparation 36

Biphenyl-2-ylcarbamic Acid 1-[2-(4-Aminomethylbenzoylamino)ethyl]piperidin-4-yl Ester

To a stirred solution of the product of Preparation 35 (339 mg, 1 mmol), 4-(*tert*-butoxycarbonylaminomethyl)benzoic acid (301 mg, 1.2 mmol) and HATU (456 mg, 1.2 mmol) in DMF (2 mL) was added DIPEA (226 µL, 1.3 mmol). The reaction mixture was stirred at room temperature overnight and then the solvent was removed under reduced pressure. The resulting residue was dissolved in dichloromethane (20 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic phase was dried

(magnesium sulfate) and the solvent was removed under reduced pressure. The crude product was dissolved in TFA/DCM (25%, 10 mL) and this mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the crude residue was dissolved in dichloromethane (15 mL) and washed with 1N sodium hydroxide (5 mL). The organic phase was separated, dried (magnesium sulfate) and the solvent was removed under reduced pressure to afford the title compound (472 mg, ~100% over 2 steps).

Preparation 37

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]methyl}benzoylamino)ethyl]-piperidin-4-yl Ester

A solution of the product of Preparation 36 (520 mg, 1.1 mmol), the product of Preparation 13 (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) was heated at 80 °C for 12 h. The reaction mixture was then diluted with dichloromethane (10 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL). The organic phase was then dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography (5-10% MeOH/DCM) to give the title compound as a solid (316 mg, 33% yield).

Preparation 38

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]methyl}benzoylamino)ethyl]piperidin-4-yl Ester

To a stirred solution of the product of Preparation 37 (316 mg, 0.36 mmol) in dichloromethane (3.6 mL) was added triethylamine trihydrofluoride (117 μL, 0.72 mmol). The reaction mixture was stirred for 10 h and was then diluted with dichloromethane (10 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the title compound, which was used directly in the next step (100 % yield).

Example 9

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}benzoylamino)ethyl]piperidin-4-yl Ester Ditrifluoroacetate

To a stirred solution of the product of Preparation 38 (275 mg, 0.36 mmol) in ethanol (3.6 mL) was added palladium (10 wt. % (dry basis) on activated carbon) (275 mg) and the reaction mixture was placed under a hydrogen atmosphere and stirred overnight. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The crude residue was purified by preparative HPLC to yield the title compound (6 mg, 2 TFA salt). HPLC (10-70) $R_t = 2.26$; MS *m/z*: $[M + H^+]$ calcd for $C_{39}H_{41}N_5O_6$ 676.32; found 676.5.

Preparation 39

Biphenyl-2-ylcarbamic Acid 1-(2-Aminoethyl)piperidin-4-yl Ester

2-*tert*-Butoxycarbonylaminoethyl bromide (1.22 g, 5.44 mmol) was added to a solution of the product of Preparation 8 (1.46 g, 4.95 mmol) and diisopropylethylamine (1.03 mL, 5.94 mmol) in acetonitrile (24 mL). The reaction mixture was stirred at 65 °C for 12 hours, at which time MS analysis showed that the reaction was completed. The reaction mixture was concentrated to dryness and then dichloromethane (10 mL) was added. Trifluoroacetic acid was added to this mixture and the mixture was stirred at room temperature for 4 hours, at which time MS analysis showed that the reaction was complete. The mixture was then concentrated to half its volume and 1N sodium hydroxide was added to the solution until the pH was adjusted to 14. The organic layer was washed with brine, then dried over magnesium sulfate and filtered. The filtrate was concentrated to give 1.6 g of the title compound as a solid. MS *m/z*: $[M + H^+]$ calcd for $C_{20}H_{25}N_3O_2$ 340.2; found 340.

Preparation 40

5-[(*R*)-2-(5-Aminopentylamino)-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-benzyloxy-1H-quinolin-2-one

N-*tert*-butoxycarbonyl-1,5-diaminopentane (1.04 g, 5.12 mmol) was added to a solution of the product of Preparation 13 (1.00 g, 2.05 mmol) in dimethyl sulfoxide (2 mL). The solution was stirred at 75 °C for 12 hours, at which time LCMS analysis

showed that the reaction was complete. The reaction mixture was then concentrated under vacuum to dryness. To the residue was added dichloromethane (2 mL) and trifluoroacetic acid (1 mL) was then added. The solution was stirred at room temperature for about 3 hours, at which time MS analysis showed that the reaction was complete. The solution was concentrated to half its volume and 1N sodium hydroxide was added until the pH was adjusted to 14. The organic layer was collected, washed with brine, dried over magnesium sulfate and then concentrated to yield 782 mg of the title compound as an oil. MS *m/z*: [M + H^+] calcd for $C_{29}H_{43}N_3O_3Si$ 510.8; found 510.

Preparation 41

Biphenyl-2-ylcarbamic Acid 1-[2-(3-{5-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]pentyl}-ureido)ethyl]piperidin-4-yl Ester

Carbonyl diimidazole (127 mg, 0.78 mmol) was added to a solution of the product of Preparation 39 (266 mg, 0.78 mmol) in dimethyl formamide (4 mL) and the resulting mixture was stirred at room temperature for 3 hours. After 3 hours, the product of Preparation 40 (399 mg, 0.78 mmol) was added to the reaction mixture and this mixture was stirred for 12 hours at room temperature, at which time LCMS analysis determined that the reaction was complete. The reaction mixture was concentrated *in vacuo* and the residue was diluted with ethyl acetate (5 mL). The organic layer was washed two times with saturated sodium bicarbonate (5 mL) and then brine (5 mL). The organic layer was dried over magnesium sulfate, filtered and then concentrated to afford 597 mg of the title compound as a solid which was used without further purification. MS *m/z*: [M + H^+] calcd for $C_{50}H_{66}N_6O_6Si$ 875.5; found 875.

Preparation 42

Biphenyl-2-ylcarbamic Acid 1-[2-(3-{5-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]pentyl}ureido)ethyl]piperidin-4-yl Ester

Triethylamine trihydrofluoride (0.16 mL, 1.02 mmol) was added to a solution of the product of Preparation 41 (597 mg, 0.68 mmol) in tetrahydrofuran (3.4 mL) and this mixture was stirred at room temperature for about 12 hours, at which time the reaction was determined to be completed by MS analysis. The reaction mixture was diluted with ethyl acetate (5 mL) and this mixture was washed with 1N sodium hydroxide (5 mL), brine,

dried over magnesium sulfate and concentrated to give 417 mg of the title compound as a solid. MS *m/z*: [M + H^+] calcd for $C_{44}H_{51}N_6O_6$ 760.4; found 760.

Example 10

Biphenyl-2-ylcarbamic Acid 1-[2-(3-{5-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentyl}ureido)ethyl]piperidin-4-yl Ester Ditrifluoroacetate

A solution of the product of Preparation 42 (417 mg, 0.55 mmol) in ethanol (3 mL) was purged with nitrogen for about 10 minutes. Palladium (10 wt. % (dry basis) on activated carbon) (200 mg) was added and the solution was flushed again with nitrogen for about 10 minutes. The flask was purged under vacuum and then filled with nitrogen three times and then a hydrogen-filled balloon was placed over the flask. The reaction mixture was stirred under hydrogen for 12 hours, at which time the reaction was determined to be complete by MS analysis. The reaction mixture was then filtered and the organic filtrate concentrated and purified by HPLC (10-35 % over 60 minute) to give 146 mg of the title compound as a powder. MS *m/z*: [M + H^+] calcd for $C_{37}H_{46}N_6O_6$ 671.4; found 670. HPLC (10-70) R_t = 2.6 minutes.

Example 11

Biphenyl-2-ylcarbamic Acid 1-[3-(3-{5-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentyl}ureido)propyl]piperidin-4-yl Ester Ditrifluoroacetate

Using the method described above in Preparations 39-42 and Example 10, and substituting 3-*tert*-Butoxycarbonylaminoprop-1-yl bromide for 2-*tert*-butoxycarbonylaminoethyl bromide in Preparation 39, the title compound was prepared. MS *m/z*: [M + H^+] calcd for $C_{38}H_{48}N_6O_6$ 685.4; found 684. HPLC (10 70) R_t = 2.6 minutes.

Preparation 43

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

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_2SO_4, filtered and concentrated under reduced pressure to give the title compound as an oil.

(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 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_2SO_4, 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.

(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, 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_2SO_3 premixed with 500 mL of 5% aqueous $NaHCO_3$. The phases were separated and the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as an oil that solidified upon storage in 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 between –20 °C and –10 °C and BH_3-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.

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

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 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 $MgSO_4$ 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 give the title compound as an oil.

Preparation 44

Biphenyl-2-ylcarbamic Acid 1-{9-[2-(*tert*-Butyldimethylsilanyloxy)-2-(2,2-dimethyl-4H-benzo[1,3]dioxin-6-yl)ethylamino]nonyl}piperidin-4-yl Ester

The product of Preparation 43 (802 mg, 2.00 mmol) and sodium iodide (300 mg, 2.00 mmol) were stirred in tetrahydrofuran (0.77 mL) for 15 min at ambient temperature. The product of Preparation 11 (675 mg, 1.54 mmol) and sodium bicarbonate (388 mg, 4.62 mmol) were added and the reaction mixture was heated at 80 °C for 24 h. The reaction mixture was then cooled and water (2 mL) was added. The mixture was then extracted with dichloromethane (2 x 2 mL). The combined organic extracts were dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography (5-10% methanol/dichloromethane) to give the title compound as a solid (798 mg, 1.05 mmol, 60% yield). MS *m/z*: [M + H^+] calcd for $C_{45}H_{67}N_3O_5Si$ 758.5; found 758.6.

Preparation 45

Biphenyl-2-ylcarbamic Acid 1-{9-[2-(2,2-Dimethyl-4H-benzo[1,3]dioxin-6-yl)-2-hydroxyethylamino]nonyl}piperidin-4-yl Ester

Triethylamine trihydrofluoride (342 μL, 2.10 mmol) was added to a stirred solution of the Product of Preparation 44 (798 mg, 1.05 mmol) in dichloromethane (10.5 mL) at ambient temperature. The reaction mixture was stirred for 24 h and it was then diluted with dichloromethane (20 mL) and washed with saturated aqueous sodium bicarbonate (15 mL). The organic layer was dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude title compound was isolated as an oil (659 mg, 1.02 mmol), which was used in the next step without further purification. MS *m/z*: $[M + H^+]$calcd for $C_{39}H_{53}N_3O_5$ 644.4; found 644.8.

Example 12

Biphenyl-2-ylcarbamic Acid 1-{9-[(*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethylamino]nonyl}piperidin-4-yl Ester Ditrifluoroacetate

Trifluoroacetic acid (2.80 mL) was added to a stirred solution of the product of Preparation 45 (600 mg, 0.93 mmol) in THF/H_2O (14 mL, 1:1) and the reaction mixture was stirred for 2 h at ambient temperature. The reaction mixture was concentrated under reduced pressure and dissolved in 20% MeCN/H_2O then purified by preparative HPLC to yield the title compound (200 mg, 2TFA salt). HPLC (10-70) $R_t = 2.76$; MS *m/z*: $[M + H^+]$calcd for $C_{36}H_{49}N_3O_5$ 604.4; found 604.8.

Preparation 46

1-[1-(9-Benzylaminononyl)piperidin-4-yl]-3-biphenyl-2-ylurea

N-Benzylamine (0.903 ml, 8.30 mmol) was added to a solution of the product of Preparation 4 (2.40 g, 5.52 mmol) in methanol (25 mL) and the resulting mixture was stirred at ambient temperature. After 10 min, sodium triacetoxyborohydride (1.75 g, 8.30 mmol) was added to the reaction mixture. The progress of the reaction was followed by HPLC analysis. After 2 h at ambient temperature, the reaction was quenched with water (5 mL) and then concentrated to half its volume under vacuum. The reaction mixture was diluted with dichloromethane (15 mL) and washed with 1N sodium hydroxide (2 x 10 mL) and then brine (5 mL). The organic layer was dried over magnesium sulfate and concentrated to yield the title compound.

Preparation 47

2-Benzyloxy-5-(2-bromoacetyl)benzoic Acid Methyl Ester

(a) 2-Benzyloxy-5-acetylbenzoic Acid Methyl Ester

Methyl 5-acetylsalicylate (100 g, 0.515 mol) was dissolved in acetonitrile (1 L) in a 2 L flask under reflux conditions and a nitrogen atmosphere. Potassium carbonate (213.5 g, 1.545 mol) was added portion-wise over 15 min. Benzyl bromide (67.4 mL, 0.566 mol) was added using a dropping funnel over 15 min. The reaction was heated to 85 °C for 9 h, and then filtered and rinsed with acetonitrile (100 mL). The solution was concentrated to about 300 mL volume under reduced pressure and partitioned between water (1 L) and ethyl acetate (1 L). The organic layer was washed with saturated sodium chloride (250 mL), dried using magnesium sulfate (75 g), and then filtered and rinsed with ethyl acetate (100 mL). The organic layer was concentrated to give 2-benzyloxy-5-acetylbenzoic acid methyl ester as a solid (100% yield).

(b) 2-Benzyloxy-5-(2-bromoacetyl)benzoic Acid Methyl Ester

The product of step (a) (10.0 g, 35.2 mmol) was dissolved in chloroform (250 mL) in a 500 mL flask under a nitrogen atmosphere. Bromine (1.63 mL, 31.7 mmol) dissolved in chloroform (50 mL) was added using a dropping funnel over 30 min. The reaction mixture was stirred for 2.5 h and then concentrated to give a solid. The solid was dissolved in toluene (150 mL) with some gentle heat, followed by the addition of ethyl ether (150 mL) to yield the title compound as a crystalline solid (55% yield).

Preparation 48

5-[2-(Benzyl-{9-[4-(3-biphenyl-2-ylureido)piperidin-1-yl]nonyl}amino)acetyl]-2-benzyloxybenzoic Acid Methyl Ester

The product of Preparation 47 (371 mg, 1.00 mmol) was added to a solution of the product of Preparation 46 (448 mg, 0.85 mmol) in dimethyl sulfoxide (4.5 mL) followed by the addition of potassium carbonate (234 mg, 1.7 mmol). The reaction mixture was stirred at 40 °C for 6 h, at which time the product of Preparation 46 was no longer observed by HPLC analysis. The reaction mixture was cooled to ambient temperature and filtered, and then diluted with ethanol (4 mL). Sodium borohydride (63 mg, 1.7 mmol)

was added to the reaction mixture and the reaction was stirred at ambient temperature for 24 h. The reaction mixture was quenched with 0.5 M ammonium chloride (5 mL) and extracted into ethyl acetate (2 x 10 mL). The combined organic layers were washed with saturated sodium bicarbonate (10 mL) and then with brine (5 mL). The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (3% methanol in chloroform) to give the title compound.

Preparation 49

1-[1-(9-{Benzyl-[2-(4-benzyloxy-3-hydroxymethylphenyl)-2-hydroxyethyl]amino}nonyl)piperidin-4-yl]-3-biphenyl-2-ylurea

A solution of the product of Preparation 48 (163mg, 0.20 mmol) in tetrahydrofuran (1.00 mL) was cooled to 0°C. Lithium aluminium hydride (1.0 M in THF; 0.50 mL, 0.50 mmol) was added dropwise to the mixture. After 1 h, the reaction mixture was quenched with water (1 mL) and diluted with ethyl acetate (2 mL). The organic layer was washed with brine, dried over magnesium sulfate, and the organic extracts were combined and concentrated to give the title compound.

Example 13

1-Biphenyl-2-yl-3-(1-{9-[2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethylamino]nonyl}piperidin-4-yl)urea Dihydrochloride

A solution of the product of Preparation 49 (130 mg, 0.16 mmol) in isopropanol (0.80 ml) was flushed with nitrogen for ten minutes and then palladium (10 wt. % (dry basis) on activated carbon (60 mg) was added. The reaction flask was purged with nitrogen and then a balloon filled with hydrogen was attached to the flask and the reaction mixture was stirred under an atmosphere of hydrogen. After 72 h, the reaction mixture was filtered and concentrated and the residue was purified by preparative HPLC. The resulting ditrifluoroacetic acid salt of the title compound was dissolved in 1N hydrochloric acid (5 mL) and lyophilized to yield the title compound as its dihydrochloride salt.

Preparation 50

5-[(*R*)-2-[(3-Aminomethylcyclohexylmethyl)amino]-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-benzyloxy-1H-quinolin-2-one

A stirred solution of the product of Preparation 13 (1.46 g, 3 mmol) and 1,3-cyclohexanebis(methylamine) (426 mg, 3 mmol) in DMSO (3 mL) was heated at 100 °C for 6 h. The reaction mixture was allowed to cool and it was then diluted with dichloromethane (20 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography (10% MeOH/DCM and 0.5% NH_4OH) to give the title compound as a solid (775 mg, 50% yield). MS *m/z*: $[M + H^+]$ calcd for $C_{32}H_{47}N_3O_3Si$ 550.3; found 550.6.

Preparation 51

Biphenyl-2-ylcarbamic Acid 1-{2-[(3-{[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydro-quinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]methyl}-cyclohexylmethyl)carbamoyl]ethyl}piperidin-4-yl Ester

To a stirred solution of the product of Preparation 50 (552 mg, 1.01 mmol), the product of Preparation 20 (309 mg, 0.84 mmol) and HATU (384 mg, 1.01 mmol) in DMF (1.68 mL) was added DIPEA (190 μL, 1.09 mmol). The reaction mixture was stirred at 50 °C overnight and then the solvent was removed under reduced pressure. The resulting residue was dissolved in dichloromethane (20 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic phase was dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (5-10% MeOH/DCM) to give the title compound as a solid (267 mg, 36% yield). LCMS (10-70) R_t = 5.04. MS *m/z*: $[M + H^+]$ calcd for $C_{53}H_{69}N_5O_6Si$ 900.5; found 900.6.

Preparation 52

Biphenyl-2-ylcarbamic Acid 1-{2-[(3-{[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]methyl}cyclohexylmethyl)carbamoyl]ethyl}piperidin-4-yl Ester

To a stirred solution of the product of Preparation 51 (267 mg, 0.30 mmol) in dichloromethane (3 mL) was added triethylamine trihydrofluoride (98 μL, 0.6 mmol). The

reaction mixture was stirred for 10 h and then it was diluted with dichloromethane (10 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL). The organic phase was dried (magensium sulfate) and the solvent was removed under reduced pressure to give the title compound as a solid (236 mg, 100% yield). MS *m/z*: $[M + H^+]$ calcd for $C_{47}H_{55}N_5O_6$ 786.4; found 786.5.

Example 14

Biphenyl-2-ylcarbamic Acid 1-{2-[(3-{[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-cyclohexylmethyl)carbamoyl]ethyl}-piperidin-4-yl Ester

Palladium (10 wt. % (dry basis) on activated carbon) (120 mg) was added to a stirred solution of the product of Preparation 52 (236 mg, 0.30 mmol) in ethanol (3 mL). The reaction mixture was placed under a hydrogen atmosphere and stirred overnight. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The crude residue was purified by preparative HPLC to give the title compound (27 mg, 2 TFA salt). HPLC (10-70) $R_t = 2.76$. MS *m/z*: $[M + H^+]$ calcd for $C_{40}H_{49}N_5O_6$ 696.4; found 696.6.

Preparation 53

Biphenyl-2-ylcarbamic Acid 1-{2-[((1*R*,3*S*)-3-Aminocyclopentanecarbonyl)amino]-ethyl}piperidin-4-yl Ester

To a stirred solution of the product of Preparation 39 (318 mg, 0.94 mmol), (1*R*,3*S*)-3-*tert*-butoxycarbonylaminocyclopentanecarboxylic acid (258 mg, 1.1 mmol) and HATU (428 mg, 1.1 mmol) in DMF (5 mL) was added DIPEA (245 μL, 1.09 mmol). The reaction mixture was stirred at room temperature overnight and then the solvent was removed under reduced pressure. The resulting residue was dissolved in dichloromethane (20 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (5-10% MeOH/DCM) and then dissolved in a trifluoroacetic acid/DCM mixture (1 mL/5 mL) and stirred at room temperature for 1h. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (20 mL) and washed with 1M sodium hydroxide (10 mL),

dried (magnesium sulfate) and the solvent reduced to yield the title compound (167 mg, 39% yield).

Preparation 54

Biphenyl-2-ylcarbamic Acid 1-[2-({(1*R*,3*S*)-3-[(*R*)-2-(8-benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]-cyclopentanecarbonyl}amino)ethyl]piperidin-4-yl Ester

A stirred solution of the product of Preparation 53 (167 mg, 0.38 mmol) and the product of Preparation 13 (92 mg, 0.19 mmol) in DMSO (0.38 mL) was heated at 90 °C for 5 h. The solution was cooled and diluted with ethyl acetate (10 mL) and then washed with saturated aqueous sodium bicarbonate (5 mL). The organic phase was dried (magnesium sulfate) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (5-10% MeOH/DCM) to yield the title compound (343 mg, 100% yield). LCMS (10-70) $R_t = 4.97$. MS *m/z*: $[M + H^+]$ calcd for $C_{50}H_{63}N_5O_6Si$ 858.5; found 858.8.

Preparation 55

Biphenyl-2-ylcarbamic Acid 1-[2-({(1*R*,3*S*)-3-[(*R*)-2-(8-benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]cyclopentanecarbonyl}amino)ethyl]-piperidin-4-yl Ester

To a stirred solution of the product of Preparation 54 (343 mg, 0.4 mmol) in THF (2 mL) was added triethylamine trihydrofluoride (130 μL, 0.8 mmol). The reaction mixture was stirred for 10 h and was then diluted with EtOAc (10 mL). The reaction mixture was washed with saturated aqueous sodium bicarbonate solution (5 mL) and then the organic phase was dried (magnesium sulfate) and the solvent was removed under reduced pressure to give the title compound as a solid (298 mg, 100% yield). HPLC (10-70) $R_t = 2.8$. MS *m/z*: $[M + H^+]$ calcd for $C_{44}H_{49}N_5O_6$ 744.4 ; found 744.4.

Example 15

Biphenyl-2-ylcarbamic Acid 1-[2-({(1*R*,3*S*)-3-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)ethylamino]-cyclopentanecarbonyl}amino)ethyl]-piperidin-4-yl Ester Ditrifluoroacetate

To a stirred solution of the product of Preparation 55 (236 mg, 0.40 mmol) in ethanol (3 mL) was added palladium (10 wt. % (dry basis) on activated carbon (120 mg). The reaction mixture was placed under a hydrogen atmosphere and stirred overnight. The reaction mixture was filtered and the solvent was removed under reduced pressure. The crude residue was purified by preparative HPLC to give the title compound (3 mg, 2 TFA salt). HPLC (5-75) $R_t = 2.18$. MS *m/z*: $[M + H^+]$ calcd for $C_{37}H_{45}N_5O_6$ 656.3; found 656.2.

Preparation 56

4-(*tert*-Butoxycarbonylaminomethyl)-2-chlorophenylamine

A stirred solution of 4-aminomethyl-2-chlorophenylamine (940 mg, 6 mmol) and di-*tert*-butyl dicarbonate (1.44 g, 6.6 mmol) in dichloromethane (30 mL) was stirred at room temperature for 4 h, at which time the reaction was determined to be complete by LCMS. The reaction mixture was then washed with saturated aqueous sodium bicarbonate (15 mL) and the organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The resulting orange solid was recrystallized from ethyl acetate to give the title intermediate as a white solid (~100% yield).

Preparation 57

***N*-[4-(*tert*-Butoxycarbonylaminomethyl)-2-chlorophenyl]acrylamide**

To a stirred solution of the product of Preparation 56 (1.54 g, 6.0 mmol) in a mixture of diethyl ether (35 mL) and 1 M sodium hydroxide (35 mL) was added dropwise acryloyl chloride (687 μL, 8.45 mmol). After 1 h, the organic layer was separated, dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the title intermediate as a white solid (1.8 g, 96% yield).

Preparation 58

Biphenyl-2-ylcarbamic Acid 1-[2-(4-(*tert*-Butoxycarbonylaminomethyl)-2-chlorophenylcarbamoyl)ethyl]piperidin-4-yl Ester

A solution of the product of Preparation 8 (1.04 g, 3.5 mmol) and the product of Preparation 57 (1.19 g, 3.85 mmol) in a mixture of dichloromethane and methanol (12 mL, 1:1) was heated at 60 °C for 12 h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (5-10% MeOH/DCM) to give the title intermediate as a white solid (2.00 g, 94% yield).

Preparation 59

Biphenyl-2-ylcarbamic Acid 1-[2-(4-Aminomethyl-2-chlorophenylcarbamoyl)ethyl]-piperidin-4-yl Ester

A solution of the product of Preparation 58 (2.00 g, 3.3 mmol) was stirred in dichloromethane (24 mL) and TFA (8 mL) for 1 h and then the solvent was removed under reduced pressure. The crude reaction mixture was dissolved in dichloromethane (30 mL) and washed with 1 M sodium hydroxide (2 x 30 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the title intermediate as an oily white solid (1.46 g, 88% yield).

Preparation 60

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]methyl}-2-chlorophenylcarbamoyl)-ethyl]piperidin-4-yl Ester

A stirred solution of the product of Preparation 59 (1.41 g, 2.79 mmol) and the product of Preparation 13 (680 mg, 1.39 mmol) in DMSO (1.39 mL) was heated at 90 °C for 8 h and then cooled to room temperature. The reaction mixture was diluted with ethyl acetate/chloroform (20 mL, 1/1) and the organic layer was washed with saturated aqueous sodium bicarbonate (10 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting crude residue was purified by column chromatography (5-10% MeOH/DCM) to give the title intermediate as a white solid (1.12 g, 88% yield). MS *m/z* $M+H^+ = 914.9$.

Preparation 61

Biphenyl-2-yl-Carbamic Acid 1-[2-(4-{[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]methyl}-2-chloro-phenylcarbamoyl)ethyl]piperidin-4-yl Ester

To a stirred solution of the product of Preparation 60 (1.12 g, 1.23 mmol) in dichloromethane (12 mL) was added $Et_3N.3HF$ (401 μL, 0.6 mmol). The reaction mixture was stirred for 10 h and then diluted with dichloromethane (10 mL). This mixture was washed with saturated aqueous sodium bicarbonate solution (5 mL) and the organic layer dried (Na_2SO_4) and the solvent removed under reduced pressure to give the title intermediate as a white solid (959 mg, 100% yield). MS *m/z* $M+H^+$ =800.5.

Example 16

Biphenyl-2-ylcarbamic Acid 1-[2-(2-Chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl Ester Ditrifluoroacetate

To a stirred solution of the product of Preparation 61 (959 mg, 1.2 mmol) in ethanol (12 mL) was added Pd/C (290 mg) and the reaction mixture was placed under a hydrogen atmosphere and stirred overnight. The reaction mixture was then filtered and the solvent removed under reduced pressure. The crude residue was purified by preparative HPLC to give the title compound (67 mg, 2 TFA salt). HPLC (10-70) R_t = 2.76; MS *m/z* $M+H^+$ = 710.6.

Preparation 62

2-Chloroethanesulfonic Acid (5-*tert*-Butoxycarbonylaminopentyl)amide

To a stirred solution of 5-(*tert*-butoxycarbonylamino)pentylamine (1.00 g, 4.94 mmol) and triethylamine (689 μL g, 4.94 mmol) in dichloromethane (22 mL) at 0 °C was added 2-chloro-1-ethanesulfonyl chloride (470 μL, 4.50 mmol). The reaction mixture was stirred for 2 h at room temperature and then washed with saturated aqueous sodium bicarbonate solution (15 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the title compound (100% yield), which was used in the next step without further purification.

Preparation 63

Biphenyl-2-ylcarbamic Acid 1-[2-(5-*tert*-Butoxycarbonylaminopentylsulfamoyl)-ethyl]piperidin-4-yl Ester

A solution of the product of Preparation 8 (1.33 g, 3.5 mmol) and the product of Preparation 62 (1.62 g, 4.94 mmol) in dichloromethane and methanol (22 mL, 1:1) was heated at 60 °C for 5 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude residue was dissolved in dichloromethane (20 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was then dried (Na_2SO_4) and solvent removed under reduced pressure. The crude residue was purified by column chromatography (5-10% MeOH/DCM) to give the title intermediate as a white solid (1.6 g, 55%). MS *m/z* $M+H^+$ = 589.6.

Preparation 64

Biphenyl-2-ylcarbamic Acid 1-[2-(5-Aminopentylsulfamoyl)ethyl]piperidin-4-yl Ester

A solution of the product of Preparation 63 (1.6 g, 2.72 mmol) was stirred in dichloromethane (21 mL) and TFA (7 mL) for 1 h and then the solvent was removed under reduced pressure. The crude reaction mixture was dissolved in dichloromethane (30 mL) and washed with 1 M sodium hydroxide (2 x 30 mL). The organic layer was dried (Na_2SO_4) and the solvent was then removed under reduced pressure to give the title intermediate as an oily white solid (1.19 g, 90% yield).

Preparation 65

Biphenyl-2-ylcarbamic Acid 1-(2-{5-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]pentylsulfamoyl}ethyl)piperidin-4-yl Ester

A stirred solution of the product of Preparation 64 (917 mg, 1.88 mmol) and the product of Preparation 13 (460 mg, 0.94 mmol) in DMSO (0.92 mL) was heated at 90 °C for 8 h and then cooled to room temperature. The reaction mixture was diluted with ethyl acetate/chloroform (20 mL,1/1) and the organic layer was washed with saturated aqueous sodium bicarbonate solution (10 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting crude residue was purified by column chromatography (3-

6% MeOH/DCM) to give the title intermediate as a white solid (500 mg, 60% yield). MS *m/z* $M+H^+$ = 896.9.

Preparation 66

Biphenyl-2-ylcarbamic Acid 1-(2-{5-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]pentylsulfamoyl}ethyl)piperidin-4-yl Ester

To a stirred solution of the product of Preparation 65 (500 mg, 0.56 mmol) in dichloromethane (5.6 mL) was added triethylamine trihydrofluoride (183 μL, 1.12 mmol). The reaction mixture was stirred for 10 h and dichloromethane (10 mL) was added. The resulting mixture was washed with saturated aqueous sodium bicarbonate solution (5 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the title intermediate as a yellow solid (437 mg, 100% yield. MS *m/z* $M+H^+$ = 782.8.

Example 17

Biphenyl-2-ylcarbamic Acid 1-(2-{5-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentylsulfamoyl}ethyl)piperidin-4-yl Ester Ditrifluoroacetate

To a stirred solution of the product of Preparation 66 (437 mg, 0.56 mmol) in ethanol/methanol (5.6 mL, 1/1) was added Pd/C (131 mg) and the reaction mixture placed under a hydrogen atmosphere and stirred overnight. The reaction mixture was then filtered and the solvent was removed under reduced pressure. The crude residue was purified by preparative HPLC to give the title compound as the ditrifluoroacetic acid salt (71 mg). HPLC (10-70) R_t = 2.59; MS *m/z* $M+H^+$ = 692.6.

Preparation 67

Biphenyl-2-ylcarbamic Acid 1-{2-[(4-Formylbenzenesulfonyl)methylamino]-ethyl}piperidin-4-yl Ester

To a stirred solution of the product of Preparation 26 (350 mg, 1 mmol) and triethylamine (167 μL, 1.2 mmol) in dichloromethane (5 mL) was added 4-formylbenzenesulfonyl chloride (225 mg, 1.1 mmol). After 1 h at room temperature, the reaction was complete by MS and the reaction mixture was then washed with saturated aqueous sodium bicarbonate solution (5 mL). The organic layer was then dried (Na_2SO_4)

and solvent removed under reduced pressure to give the title intermediate (323 mg, 62% yield). MS *m/z* $M+H^+ = 522.4$.

Preparation 68

Biphenyl-2-ylcarbamic Acid 1-{2-[(4-{[(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}benzenesulfonyl)-methylamino]ethyl}piperidin-4-yl Ester

A solution of 5-[(*R*)-2-amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one (293 mg, 0.74 mmol) and the product of Preparation 67 in dichloromethane and methanol (6.2 mL, 1/1) was stirred at room temperature for 1h and then sodium triacetoxyborohydride (394 mg, 1.86 mmol) was added. The reaction mixture was stirred for 4 h at which time the reaction was determined to be complete by MS. The reaction mixture was then acidified with concentrated hydrochloric acid and the solvent was removed under reduced pressure to provide the title compound, which was used in the next step without further purification. MS *m/z* $M+H^+ = 840.8$.

Example 18

Biphenyl-2-ylcarbamic Acid 1-{2-[(4-{[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}benzenesulfonyl)methylamino]ethyl}-piperidin-4-yl Ester Ditrifluoroacetate

A stirred solution of the product of Preparation 68 (520 mg, 0.62 mmol) in 1M hydrochloric acid (5 mL) and acetonitrile (5 mL) was heated at 60 °C for 8 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude residue was purified by preparative HPLC to give the title compound as the ditrifluoroacetic acid salt (220 mg). HPLC (10-70) $R_t = 2.77$; MS *m/z* $M+H^+ = 726.7$.

Preparation 69

(3-Aminomethylphenyl)methanol Hydrochloride

(a) (3-*tert*-Butoxycarbonylmethylphenyl)methanol

Borane dimethyl sulfide (2.05 mL, 21.6 mmol) was added to a solution of 3-(*tert*-butoxycarbonylaminomethyl)benzoic acid (1.81 g, 7.20 mmol) in tetrahydrofuran (24 mL). and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate (20 mL) and the layers were separated. The

organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried over magnesium sulfate and concentrated to give the title compound as a yellow oil (1.71 g).

(b) (3-Aminomethylphenyl)methanol Hydrochloride

To the product of step (a) (1.71 g, 7.2 mmol) was added a solution of 4 M hydrochloric acid in dioxane (9 mL, 36 mmol) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then concentrated and the residue was diluted with diethyl ether (50 mL) and filtered to provide the title compound as a white solid (1.09 g).

Preparation 70

Biphenyl-2-ylcarbamic Acid 1-{2-[3-(3-Hydroxymethylbenzyl)ureido]ethyl}piperidin-4-yl Ester

A 0.2 M solution of the product of Preparation 35 (760 mg, 2.24 mmol) in *N,N*-dimethylformamide was added dropwise to a solution of 1,1'-carbonyldiimidazole (364 mg, 2.24 mmol) and diisopropylethylamine (0.31 mL, 2.24 mmol) in *N,N*-dimethylformamide (11 mL) and the resulting mixture was stirred at room temperature for 2 h. Diisopropylethylamine (0.31 mL, 2.24 mmol) and the product of Preparation 69 (578 mg, 3.4 mmol) were added and this mixture was stirred at 50 °C for 12 hours. The reaction mixture was then concentrated to dryness and the residue was diluted with dichloromethane (20 mL) and this solution was washed with saturated sodium bicarbonate (2 x), saturated sodium chloride, dried over magnesium sulfate, and concentrated to provide the title compound (1.12 g). LCMS (2-90) R_t = 4.01 min.; MS *m/z* M+H = 503.5.

Preparation 71

Biphenyl-2-ylcarbamic Acid 1-{2-[3-(3-Formylbenzyl)ureido]ethyl}piperidin-4-yl Ester

A solution of the product of Preparation 70 (1.12 g, 2.23 mmol) in dichloromethane (11.1 mL) was cooled to 0 °C and diisopropylethylamine (1.17 mL, 6.70 mmol) and dimethyl sulfoxide (0.949 mL, 13.4 mmol) were added. After about 10 minutes, pyridine sulfur trioxide complex (1.06 g, 6.70 mmol) was added and the resulting mixture was stirred at 0 °C for 2 h. The reaction was then quenched with water (15 mL) and the organic

layer was washed with cold water (3 x), dried over magnesium sulfate and concentrated to provide the title compound as a yellow crisp (609 mg). LCMS (2-90) R_t = 4.13 min; MS *m/z* M+H = 501.3.

Preparation 72

Biphenyl-2-ylcarbamic Acid 1-{2-[3-(3-{[(*R*)-2-(*tert*-butyldimethylsilanyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}benzyl)ureido]ethyl}-piperidin-4-yl Ester

5-[(*R*)-2-Amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one (575 mg, 1.40 mmol) was added to a solution of the product of Preparation 71 (609 mg, 1.2 mmol) and diisopropylamine (0.25 mL, 1.40 mmol) in dichloromethane (6 mL) and the resulting mixture was stirred at room temperature for 45 min. Sodium triactetoxyborohydride (385 mg, 1.80 mmol) was then added and this mixture was stirred at room temperature for 12 h. The reaction was then quenched with 10% aqueous hydrochloric acid (5 mL) and the layers were separated. The organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried over magnesium sulfate and concentrated to give the title compound (1.1 g). HPLC (10-70) R_t = 3.55 min; MS *m/z* M+H = 819.7.

Example 19

Biphenyl-2-ylcarbamic Acid 1-{2-[3-(3-{[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}benzyl)ureido]ethyl}piperidin-4-yl Ester Ditrifluoroacetate

Triethylamine trihydrofluoride (2.4 mL, 13.6 mmol) was added to a solution of the product of Preparation 72 (1.1 g, 1.36 mmol) in dichloromethane (2 mL) and the resulting mixture was stirred at room temperature for 15 h. The reaction mixture was then concentrated under vacuum to dryness and the residue was dissolved in a 1:1 mixture of water and acetonitrile with 0.1% TFA and this mixture was purified by HPLC (5-35 over 60 min) to provide the title compound as the ditrifluroacetate salt (296 mg, 99% purity). MS *m/z* M+H = 705.6.

Preparation 73

Biphenyl-2-ylcarbamic Acid 1-[(*E*)-3-(4-Nitrophenyl)allyl]piperidin-4-yl Ester

The product of Preparation 8 (2.96 g, 0.01 mol) and *p*-nitrocinnamaldehyde (1.77 g, 0.01 mol) were stirred in 50 mL of dichloromethane for 2 h. Sodium triacetoxyborohydride (6.33 g, 0.03 mol) was added and the resulting mixture was stirred for 2 h. The reaction was then quenched with 10 mL of water and this mixture was diluted with dichloromethane (100 mL). The organic layer was washed with saturated sodium bicarbonate (2 x), brine, dried over Na_2SO_4, filtered and concentrated to provide the title compound as a yellow foam (3.8 g, 80% yield).

Preparation 74

Biphenyl-2-ylcarbamic Acid 1-[3-(4-Aminophenyl)propyl]piperidin-4-yl Ester

The product of Preparation 73 (2.5 g, 5.4 mmol) was dissolved in 100 mL of ethanol and the resulting solution was purged with nitrogen for 30 min. Palladium on carbon (2.5g; 50% w/w water; 10% Pd; 1.1mmol Pd) was then added while degassing with nitrogen. This mixture was then placed under hydrogen (50 psi) until hydrogen was no longer consumed (~30 minutes). The mixture was then purged with nitrogen, filtered through Celite and concentrated. The residue was dissolved in ethyl acetate and this mixture was washed with saturated sodium bicarbonate (2 x), brine, dried (Na_2SO_4), filtered and concentrated to provide the title compound (2.08 g, 90% yield). MS *m/z* M+H = 430.5.

Preparation 75

Biphenyl-2-ylcarbamic Acid 1-{3-[4-(4-{2-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydro-quinolin-5-yl)-2-(*tert*-butyldimethylsilanyloxy)ethylamino]ethyl}phenylamino)-phenyl]propyl}piperidin-4-yl Ester

To a 25 mL round-bottomed flask was added the product of Preparation 74 (400 mg, 0.8 mmol); 8-benzyloxy-5-[(*R*)-2-[2-(4-bromophenyl)ethylamino]-1-(*tert*-butyldimethylsilanyloxy)ethyl]-1H-quinolin-2-one (769 mg, 1.2 mmol); tris(dibenzylideneacetone)dipalladium(0) (73 mg, 0.08 mmol, 20% Pd); and 2-(dicyclohexylphosphino)biphenyl (84 mg, 0.24 mmol). This mixture was purged with nitrogen and then dry, degassed toluene (8 mL, 0.1 M) was added and the resulting mixture was heated at 70 °C for 30 min. Sodium *tert*-butoxide (382 mg, 4.0 mmol) was then

added, and the temperature was raised to 95 °C for 4 h, at which time LCMS showed complete consumption of the product of Preparation 74 and a large product peak (M+H = 956.7). The reaction mixture was then cooled to room temperature and diluted with ethyl acetate. This mixture was washed with saturated sodium bicarbonate (2 x), brine, dried (Na_2SO_4), filtered and concentrated to provide the title compound (1.5g), which was used without further purification.

Preparation 76

Biphenyl-2-ylcarbamic Acid 1-{3-[4-(4-{2-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydro-quinolin-5-yl)-2-hydroxyethylamino]ethyl}phenylamino)phenyl]propyl}piperidin-4-yl Ester

The product of Preparation 75 was dissolved in dichloromethane (10 mL) and triethylamine trihydrofluoride (10 eq.) was added. The reaction mixture was stirred overnight and then diluted with dichloromethane and the organic layer was washed with saturated sodium bicarbonate (2 x), brine, dried (Na_2SO_4), filtered and concentrated to provide 1.3 g of crude product. This material was purified by silica gel chromatography (DCM, incrementally to 50% methanol) to provide the title compound (300 mg, about 75% purity), which was used without further purification.

Example 20

Biphenyl-2-ylcarbamic acid 1-{3-[4-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)phenyl]propyl}piperidin-4-yl ester Ditrifluoroacetate

The product of Preparation 76 (300 mg) was dissolved in 10 mL of ethanol and this mixture was purged with nitrogen for 15 minutes. Palladium on carbon (10% Pd, 50% w/w water, 0.2 eq. Pd) was added while degassing. The resulting mixture was then placed under 1 atm. of hydrogen for 2 h, at which time the reaction was complete by LCMS. The solution was then purged with nitrogen for 15 min and then filtered through Celite and concentrated. The resulting residue was purified by prep HPLC to afford the title compound as the ditrifluoroacetate salt (59 mg, >95% purity). MS *m/z* M+H = 752.8.

Preparation 77

Biphenyl-2-ylcarbamic Acid 1-[2-Fluoro-3-(4-hydroxymethylpiperidin-1-ylmethyl)-benzyl]piperidin-4-yl Ester

The product of Preparation 8 (500 mg, 1.69 mmol), 2,6-bis(bromomethyl)-1-fluorobenzene (476 mg, 1.69 mmol, piperidin-4-ylmethanol (195 mg, 1.69 mmol) and potassium carbonate (466 mg, 3.37 mmol) were suspended in acetonitrile (5 mL) and stirred at room temperature for 18 h. The reaction mixture was then concentrated and the residue was dissolved in dichloromethane/water. The layers were separated and the organic layer was washed with water (2 x), brine, dried ($MgSO_4$) and concentrated. The crude material was purified by silica gel column chromatography eluting with 3% methanol/chloroform to give the title compound as a white foam (282 mg). MS *m/z* M+H = 532.3.

Preparation 78

Biphenyl-2-ylcarbamic Acid 1-[2-Fluoro-3-(4-formylpiperidin-1-ylmethyl)benzyl]-piperidin-4-yl Ester

The product of Preparation 77 (282 mg, 0.53 mmol) was dissolved in dichloromethane and to this mixture was added diisopropylethylamine (280 μL, 1.6 mmol) and dimethyl sulfoxide (115 μL, 1.6 mmol). The reaction mixture was cooled to –15 °C under nitrogen and pyridine sulfur trioxide complex (255 mg, 1.6 mmol) was added and the resulting mixture was stirred for 40 min. The reaction was then quenched with water and the layers were separated. The organic layer was washed with aqueous NaH_2PO_4 (1M × 3), brine, dried ($MgSO_4$) and concentrated to provide the title compound as a foam (253 mg). MS *m/z* M+H = 530.4.

Example 21

Biphenyl-2-ylcarbamic Acid 1-[2-Fluoro-3-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}piperidin-1-ylmethyl)benzyl]piperidin-4-yl Ester Ditrifluoroacetate

The product of Preparation 78 (253 mg, 0.48 mmol) was dissolved in a 1:1 mixture of dichloromethane and methanol (6 mL) and to this mixture was added 5-[(*R*)-2-amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one acetate (228 mg, 0.58

mmol) and sodium triacetoxyborohydride (317 mg, 1.5 mmol). The reaction mixture was stirred under nitrogen at room temperature for 18 h and then concentrated. The residue was dissolved in a 2:3 mixture of acetonitrile and aqueous 6 N hydrochloric acid, and this mixture was heated at 55 °C for 4 hours. The reaction mixture was then concentrated and the residue was dissolved in water/acetonitrile/trifluoroacetic acid (1:1:0.005) and purified by reverse phase column chromatography to afford the title compound as a white solid (175 mg). MS *m/z* M+H = 734.5.

Preparation 79

2-[4-(3-Bromopropoxy)phenyl]ethanol

To a solution of 4-hydroxyphenethyl alcohol (4.37 g, 31.0 mmol) and potassium carbonate (6.55 g, 47.0 mmol) in acetonitrile (62.0 mL) was added 1,3 dibromopropane (31.0 mL, 316 mmol). The reaction mixture was heated to 70 °C for 12 hours and then cooled to room temperature, filtered and concentrated under vacuum. The resulting oil was purified by silica gel chromatography using a mixture of 4:1 hexanes and ethyl acetate to give the title compound (6.21 g) as a white solid.

Preparation 80

Biphenyl-2-ylcarbamic Acid 1-{3-[4-(2-Hydroxyethyl)phenoxy]propyl}piperidin-4-yl Ester

To a solution of the product of Preparation 79 (1.11 g, 4.30 mmol) and diisopropylethylamine (0.90 mL, 5.10 mmol) in acetonitrile (21.5 mL) was added the product of Preparation 8 (1.27 g, 4.30 mmol) and the resulting mixture was stirred at 60°C. for 12 h. The reaction mixture was then diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate (25 mL), saturated sodium chloride (25 mL), dried over magnesium sulfate and concentrated to provide the title compound (1.98 g, 85% purity). MS *m/z* M+H = 475.5.

Preparation 81

Biphenyl-2-ylcarbamic Acid 1-{3-[4-(2-Oxoethyl)phenoxy]propyl}piperidin-4-yl Ester

A solution of the product of Preparation 80 (723 mg, 1.53 mmol) and dichloromethane (75 mL) was cooled to about 5 °C and diisopropylethylamine (798 mL, 4.58 mmol) and dimethyl sulfoxide (649 mL, 9.15 mmol) were added. Pyridine sulfur

trioxide (728 mg, 4.58 mmol) was then added and the resulting mixture was stirred at 5 °C for 45 min. The reaction mixture was then diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate (25 mL), saturated sodium chloride (25 mL), dried over magnesium sulfate and concentrated to provide the title compound (604 mg). MS *m/z* M+H = 473.4.

Preparation 82

Biphenyl-2-ylcarbamic Acid 1-[3-(4-{2-[(*R*)-2-(*tert*-butyldimethylsilanyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}-phenoxy)propyl]piperidin-4-yl Ester

The product of Preparation 81 (604 mg, 1.28 mmol) was dissolved in methanol (6.4 mL) and 5-[(*R*)-2-amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one (605 mg, 1.53 mmol) and diisopropylethylamine (0.27 mL, 1.53 mmol) were added. Sodium triacetoxyborohydride (405 mg,1.91 mmol) was then added and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then concentrated to dryness and the residue was diluted with ethyl acetate (20 mL) and this solution was washed with saturated sodium bicarbonate (25 mL), saturated sodium chloride (25 mL), dried over magnesium sulfate and concentrated to give the title compound (704 mg). MS *m/z* M+H = 791.8.

Example 22

Biphenyl-2-ylcarbamic Acid 1-[3-(4-{2-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenoxy)propyl]piperidin-4-yl Ester Ditrifluoroacetate

Triethylamine trihydrofluoride (1.5 mL, 8.87 mmol) was added to a solution of the product of Preparation 82 (702 mg, 0.89 mmol) in dichloromethane (4.5 mL) and the resulting mixture was stirred at room temperature for 24 h. The mixture was then concentrated under vacuum and purified by HPLC (2-35 over 90 min) to give the title compound (92 mg) as a white powder. MS *m/z* M+H = 677.4.

Preparation 83

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.

Preparation 84

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

To a stirred solution of the product of Preparation 83 (4.5 g, 16.3 mmol) in diethylamine (100 mL) was added but-3-yn-1-ol (1.9 mL, 32.6 mmol), $Pd(PPh_3)_2Cl_2$ (500 mg, 1.63 mmol) and 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 85

Methyl [4-(4-Hydroxybutyl)phenyl]acetate

A stirred solution of the product of Preparation 84 (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 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 86

Methyl (4-{4-[4-(Biphenyl-2-ylcarbamoyloxy)piperidin-1-yl]butyl}phenyl)acetate

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

To a stirred solution of the product of Preparation 85 (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

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 ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the title compound, which was used without further purification.

(b) Methyl (4-{4-[4-(Biphenyl-2-ylcarbamoyloxy)piperidin-1-yl]butyl}phenyl)acetate

To the crude product from step (a) was added DMF (50 mL), diisopropylethylamine (3.0 mL, 17.3 mmol) and the product of Preparation 8 (2.4 g, 8.1 mmol). The reaction mixture was stirred at room temperature for 18 h and then the solvent was removed under reduced pressure to give the title compound (3.5 g, 86.3% yield). MS *m/z* 501.6 (MH^+), R_f 4.89 min (10-70% ACN: H_2O, reverse phase HPLC).

Preparation 87

Biphenyl-2-ylcarbamic Acid 1-{4-[4-(2-Hydroxyethyl)phenyl]butyl}piperidin-4-yl Ester

To a stirred solution of the product of Preparation 86 (2.0 g, 4.0 mmol) in THF (100 mL) was added dropwise DIBAL (24 mL, 24 mmol, 1.0 M in THF). After the addition was complete, the reaction mixture was stirred for 3 h and then quenched by slow addition of methanol (until gas evolution ceased). The mixture was then stirred for 30 min. and then ethyl acetate (200 mL) and aqueous 1N sodium hydroxide (200 mL) were added. The organic layer was separated and washed with aqueous saturated sodium chloride solution (100 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the title compound (1.3 g, 69% yield), which was used without further purification. MS *m/z* 473.4 (MH^+), R_f 4.53 min (10-70% ACN: H_2O, reverse phase HPLC).

Example 23

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{2-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenyl)ethyl]piperidin-4-yl Ester

To a stirred solution of the product of Preparation 87 (500 mg, 1.06 mmol) in dichloromethane (25 mL) was added dimethyl sulfoxide (0.60 mL, 10.6 mmol) and diisopropylethylamine (0.921 mL, 5.3 mmol). The reaction mixture was then cooled to -10 °C and pyridine sulfur trioxide (842 mg, 5.3 mmol) was added. The reaction mixture was stirred for 1 h and then quenched by adding water (100 mL). This mixture was stirred for 10 min and then the organic layer was removed and washed with aqueous saturated sodium chloride solution (100 mL), dried ($MgSO_4$) and then filtered.

To the filtrate was added methanol (25 mL), 5-[(*R*)-2-amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one acetate (419 mg, 1.06 mmol) and sodium triacetoxyborohydride (468 mg, 2.12 mmol). This mixture was stirred for 16 h and then condensed and, to the resulting mixture, was added a 1:1 mixture of acetonitrile and aqueous 4N hydrochloric acid (20 mL). This mixture was heated at 50 °C for 17 h and then the solvent was removed under reduced pressure. To the residue was added a 1:1 mixture of acetic acid and water (8.0 mL) and the mixture was chromatographed on reverse-phase silica gel (gradient elution, 10-50% ACN/H_2O) to afford the title compound (67 mg, 7% yield over 3 steps). MS *m/z* (MH^+) 675.5; R_f 3.07 (10-70% ACN: H_2O, reverse phase HPLC).

Preparation 88

Ethyl 3-[5-(2-Ethoxycarbonylvinyl)thiophen-2-yl]acrylate

To a stirred solution of sodium hydride (2.1 g, 53 mmol, 60% in mineral oil) in THF (200 mL) was slowly added triethylphosphonoacetate (10 mL, 50 mmol) Hydrogen gas evolution was observed and the reaction was stirred until gas evolution ceased (about 30 min). To this reaction mixture was added 2,5-thiophenedicarboxaldehyde (3 g, 21 mmol) and the reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (200 mL). The organic layer was washed with water (100 mL), aqueous 1N hydrochloric acid (100 mL), aqueous saturated sodium chloride solution (100 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the title compound (5.8 g, 98% yield), which was used without further purification.

Preparation 89

Ethyl 3-[5-(2-Ethoxycarbonylethyl)thiophen-2-yl]propionate

A stirred solution of the product of Preparation 88 (5.8 g, 21 mmol) in methanol (200 mL) was flushed with nitrogen and 10% palladium on carbon (576 mg, 10% wt/wt) was added. The reaction flask was alternately placed under vacuum and flushed with hydrogen for 3 cycles and then the reaction mixture was stirred under hydrogen for 1h. The mixture was then was flushed with nitrogen, filtered and the solvent removed under reduced pressure to give the title compound (5.8 g, 99% yield), which was used without further purification.

Preparation 90

3-[5-(3-Hydroxypropyl)thiophen-2-yl]propan-1-ol

To a stirred solution of DIBAL (88 mL, 88 mmol, 1.0M in cyclohexane) in THF (300 mL) at –78 °C was added dropwise the product of Preparation 89 (5.0 g, 17.6 mmol). After the addition was complete, the reaction mixture was warmed to room temperature over 30 min and then quenched by slow addition of aqueous 1N hydrochloric acid (200 mL). Dichloromethane (400 mL) was added and the layers were separated. The aqueous layer was washed with dichloromethane (4 x 100 mL) and the combined organic layers were washed with aqueous saturated sodium chloride solution (100 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the title compound (3.0 g, 85% yield), which was used without further purification.

Preparation 91

Biphenyl-2-ylcarbamic Acid 1-{3-[5-(3-Hydroxypropyl)thiophen-2-yl]propyl}piperidin-4-yl Ester

(a) Toluene-4-sulfonic Acid 3-[5-(3-Hydroxypropyl)thiophen-2-yl]propyl Ester

To a stirred solution of the product of Preparation 90 (423 mg, 2.1 mmol) in THF (20 mL) was added DABCO (420 mg, 4.2 mmol) and then *p*-toluenesulfonyl chloride (442 mg, 2.3 mmol). The reaction mixture was stirred at room temperature for 2 h and then the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (200 mL). The organic layer was washed with water (2 x 100 mL),

aqueous saturated sodium chloride solution (100 mL), dried $MgSO_4$), filtered and the solvent removed under reduced pressure to give the title compound, which was used without further purification.

(b) **Biphenyl-2-ylcarbamic Acid 1-{3-[5-(3-Hydroxypropyl)thiophen-2-yl]propyl}piperidin-4-yl Ester**

To the product from step (a) was added acetonitrile (20 mL), diisopropylethylamine (0.5 mL, 2.8 mmol) and the product of Preparation 8 (626 mg, 2.11 mmol). The reaction mixture was heated to 50 °C for 20 h and then cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (5% MeOH/DCM with 0.6% NH_3 (aq)) to afford the title compound (450 mg, 44% yield). MS *m/z* (MH^+) 479.6; R_f 4.15 min (10-70% ACN: H_2O, reverse phase HPLC).

Preparation 92

Biphenyl-2-ylcarbamic Acid 1-[3-(5-{3-[(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propyl}thiophen-2-yl)propyl]-piperidin-4-yl Ester

To a stirred solution of the product of Preparation 91 (450 mg, 0.94 mmol) in dichloromethane (20 mL) was added dimethyl sulfoxide (0.21 mL, 3.7 mmol) and diisopropylethylamine (0.65 mL, 3.7 mmol). This mixture was cooled to –10 °C and pyridine sulfur trioxide (444 mg, 2.8 mmol) was added. The reaction mixture was stirred for 3 h and then was quenched by adding water (100 mL). This mixture was stirred for 10 min and then the organic layer was removed and was washed with aqueous saturated sodium chloride solution (100 mL), dried ($MgSO_4$) and filtered.

To the filtrate was added methanol (20 mL), 5-[(*R*)-2-amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one acetate (368 mg, 0.93 mmol) and then sodium triacetoxyborohydride (412 mg, 1.86 mmol). This mixture was stirred for 19 h and then the mixture was condensed to give the title compound, which was used without further purification. MS *m/z* (MH^+) 795.8; R_f 4.93 min (10-70% ACN: H_2O, reverse phase HPLC).

Example 24

Biphenyl-2-ylcarbamic Acid 1-[3-(5-{3-[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propyl}thiophen-2-yl)propyl]piperidin-4-yl Ester

To the crude product from Preparation 92 was added a 1:1 mixture of acetonitrile and aqueous 4 N hydrochloric acid (25 mL). This mixture was heated at 50 °C for 17 h and then the solvent was then removed under reduced pressure. To the residue was added a 1:1 mixture of acetic acid and water (8.0 mL) and this mixture was chromatographed on reverse-phase silica gel (gradient elution, 10-50% ACN/H_2O) to afford the title compound (135 mg, 16 % yield for 3 steps). MS *m/z* (MH^+) 681.5; R_f 3.03 (10-70% ACN: H_2O, reverse phase HPLC).

Preparation 93

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 94

Methyl 4-Acryloylamino-5-chloro-2-methoxybenzoate

To crude product of Preparation 93 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_2SO_4), filtered and the solvent was removed *in vacuo* to give the title compound as a brown foamy solid, which was used without further purification.

Preparation 95

Methyl 4-{3-[4-(Biphenyl-2-ylcarbamoyloxy)piperidin-1-yl]propionylamino}-5-chloro-2-methoxybenzoate

To the crude product from Preparation 94 was added the product of Preparation 8 (1.33 g, 4.5 mmol) and a mixture of THF (22.5 mL) and methanol (2.5 mL). This mixture was heated at 50 °C with stirring for 16 h and then the solvent was removed *in vacuo*. The residue was chromatographed (silica gel; EtOAc) to give the title compound (0.82 g; R_f = 0.4, 29% yield over 3 steps) as an off-white foamy solid. MS *m/z* 566.4 (M+H, expected 565.20 for $C_{30}H_{32}ClN_3O_6$).

Preparation 96

Biphenyl-2-ylcarbamic Acid 1-[2-(2-Chloro-4-hydroxymethyl-5-methoxy-phenylcarbamoyl)ethyl]piperidin-4-yl Ester

To a solution of the product of Preparation 95(0.82 mg, 1.45 mmol) in a mixture of THF (4.5 mL) and methanol (0.5 mL) at 0 °C was added lithium borohydride (32 mg, 1.45 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 41 h. The reaction was then quenched by adding 1N aqueous hydrochloric acid at 0 °C until no more bubbling was observed and this mixture was stirred for 10 min. The solvent was removed *in vacuo* and the residue was dissolved in acetonitrile (about 2 mL). This solution was purified by prep-RP-HPLC (gradient: 2 to 50% acetonitrile in water with 0.05% TFA). The appropriate fractions were collected and combined and lyophilized to give the title compound as a trifluoroacetate salt. This salt was treated with isopropyl acetate (10 mL) and 1N aqueous sodium hydroxide (10 mL) and the organic layer was collected, dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to give the title compound (161 mg, 21% yield) as a white foamy solid. MS *m/z* 538.4 (M+H, expected 537.20 for $C_{29}H_{32}ClN_3O_5$).

Preparation 97

Biphenyl-2-ylcarbamic Acid 1-[2-(2-Chloro-4-formyl-5-methoxyphenylcarbamoyl)-ethyl]piperidin-4-yl Ester

To a solution of the product of Preparation 96 (161 mg, 0.3 mmol) in dichloromethane (3 mL) was added dimethyl sulfoxide (213 μL, 3.0 mmol) and diisopropylethylamine (261 μL, 1.5 mmol). This mixture was cooled to –20 °C and sulfur

trioxide pyridine complex (238 mg, 1.5 mmol) was added slowly. After 30 min, the reaction mixture was quenched by adding water (about 3 mL). The layers were separated and the organic layer was dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to give the title compound as a light yellow solid. MS *m/z* 536.3 (M+H, expected 535.19 for $C_{29}H_{30}ClN_3O_5$).

Preparation 98

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-(tert-Butyldimethylsilanyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-2-chloro-5-methoxy-phenylcarbamoyl)ethyl]piperidin-4-yl Ester

To the product from Preparation 97 in a mixture of dichloromethane (0.5 mL) and methanol (0.5 mL) was added 5-[(*R*)-2-amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one acetate (124.1 mg, 3.1 mmol) and the resulting mixture was stirred at room temperature for 1.5 h. Sodium triacetoxyborohydride (190.7 mg, 0.9 mmol) was added and the resulting mixture was stirred at room temperature for 15 h. The reaction was quenched by adding water (about 0.2 mL) and the mixture was concentrated *in vacuo* to give the title compound, which was used without further purification. MS *m/z* 854.5 (M+H, expected 853.36 for $C_{46}H_{56}ClN_5O_7Si$).

Example 25

Biphenyl-2-ylcarbamic Acid 1-[2-(2-Chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl Ester Ditrifluoroacetate

To a suspension of the product of Preparation 98 in dichloromethane (1.0 mL, 0.3 M) was added triethylamine trihydrofluoride (245 μL, 1.5 mmol). This mixture was stirred at room temperature for 45 h and then the mixture was concentrated *in vacuo*. The residue was dissolved in a mixture of DMF (0.5 mL), acetonitrile/water (1:1, with 0.1% TFA, 0.6 mL), TFA (0.3 mL) and acetonitrile (about 1 mL) and this mixture was purified by prep-RP-HPLC (gradient: 2 to 50% acetonitrile in water with 0.05% TFA). The appropriate fractions were collected and combined and lyophilized to give the title compound (100 mg, 34% yield, 98.7% pure by HPLC) as an off-white solid. MS *m/z* 740.5 (M+H, expected 739.28 for $C_{40}H_{42}ClN_5O_7$).

Using the methods described above and the appropriate starting materials, the following compounds were prepared.

Ex.	Compound	MS
26	Biphenyl-2-ylcarbamic acid 1-{7-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]heptyl}piperidin-4-yl ester	613.5
27	Biphenyl-2-ylcarbamic acid 1-{8-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]octyl}piperidin-4-yl ester	627.5
28	Biphenyl-2-ylcarbamic acid 1-{2-[3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenyl)ureido]ethyl}piperidin-4-yl ester	705.3
29	Biphenyl-2-ylcarbamic acid 1-[3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}piperidin-1-yl)-3-oxopropyl]piperidin-4-yl ester	682.4
30	Biphenyl-2-ylcarbamic acid 1-{2-[(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-cyclohexanecarbonyl)amino]ethyl}piperidin-4-yl ester	682.7
31	Biphenyl-2-ylcarbamic acid 1-[2-({(1R,3S)-3-[(*R*)-2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethylamino]-cyclopentanecarbonyl}amino)ethyl]piperidin-4-yl ester	630.2
32	Biphenyl-2-ylcarbamic acid 1-[2-(3-{5-[(*R*)-2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethylamino]pentyl}ureido)ethyl]piperidin-4-yl ester	647.5
33	Biphenyl-2-ylcarbamic acid 1-[2-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)ethyl]piperidin-4-yl ester	662.5
34	Biphenyl-2-ylcarbamic acid 1-[3-(3-{5-[2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethylamino]pentyl}ureido)propyl]piperidin-4-yl ester	661.3
35	Biphenyl-2-ylcarbamic acid 1-{2-[(4-{2-[(*R*)-2-hydroxy-2-(8-	697.5

Ex.	Compound	MS
	hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}piperidine-1-carbonyl)amino]ethyl}piperidin-4-yl ester	
36	Biphenyl-2-ylcarbamic acid 1-[4-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}-phenylamino)benzyl]piperidin-4-yl ester	724.5
37	Biphenyl-2-ylcarbamic acid 1-[2-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzylcarbamoyl)ethyl]piperidin-4-yl ester	690.3
38	3-[4-(3-Biphenyl-2-yl-ureido)piperidin-1-yl]-N-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenyl)propionamide	675.5
39	Biphenyl-2-ylcarbamic acid 1-{2-[(6-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-l)ethylamino]methyl}pyridin-2-ylmethyl)carbamoyl]ethyl}piperidin-4-yl ester	691.5
40	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-cyclohexylcarbamoyl)ethyl]piperidin-4-yl ester	682.7
41	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-cyclohexylcarbamoyl)ethyl]piperidin-4-yl ester	682.7
42	Biphenyl-2-ylcarbamic acid 1-[2-({(1*R*,3*S*)-3-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]-cyclopentanecarbonyl}amino)ethyl]piperidin-4-yl ester	654.8
43	Biphenyl-2-ylcarbamic acid 1-{2-[(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzoyl)methylamino]ethyl}piperidin-4-yl ester	690.4
44	Biphenyl-2-ylcarbamic acid 1-{2-[(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-cyclohexanecarbonyl)methylamino]ethyl}piperidin-4-yl ester	696.5
45	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[2-hydroxy-2-(8-hydroxy-2-	NA

Ex.	Compound	MS
	oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	
46	Biphenyl-2-ylcarbamic acid 1-[2-(4-{(S)-1-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	690.7
47	Biphenyl-2-ylcarbamic acid 1-[2-(4-{(*R*)-1-[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	690.7
48	Biphenyl-2-ylcarbamic acid 1-((*S*)-1-{5-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentanoyl}pyrrolidin-2-ylmethyl)piperidin-4-yl ester	682.7
49	Biphenyl-2-ylcarbamic acid 1-[(*S*)-1-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzoyl)pyrrolidin-2-ylmethyl]piperidin-4-yl ester	716.8
50	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-(3-formylamino-4-hydroxy-phenyl)-2-hydroxy-ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	652.6
51	Biphenyl-2-ylcarbamic acid 1-[2-(4-{(*R*)-1-[(*R*)-2-(3-formylamino-4-hydroxy-phenyl)-2-hydroxy-ethylamino]ethyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	666.5
52	Biphenyl-2-ylcarbamic acid 1-[2-(4-chloro-3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	710.5
53	N-{2-[4-(3-Biphenyl-2-yl-ureido)-piperidin-1-yl]ethyl}-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}benzamide	675.5
54	1-Biphenyl-2-yl-3-{1-[3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}piperidin-1-yl)-3-oxo-propyl]piperidin-4-yl}urea	681.7
55	3-[4-(3-Biphenyl-2-yl-ureido)piperidin-1-yl]-*N*-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-	689.5

Ex.	Compound	MS
	benzyl)propionamide	
56	Biphenyl-2-ylcarbamic acid 1-(2-fluoro-3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzyl)piperidin-4-yl ester	637.5
57	Biphenyl-2-ylcarbamic acid 1-[2-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-4-methyl-phenylcarbamoyl)ethyl]piperidin-4-yl ester	690.4
58	Biphenyl-2-ylcarbamic acid 1-[2-(2-chloro-5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	710.6
59	Biphenyl-2-ylcarbamic acid 1-[2-(2,6-dichloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	745.2
60	Biphenyl-2-ylcarbamic acid 1-[1-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}benzoyl)-piperidin-4-ylmethyl]piperidin-4-yl ester	730.8
61	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-(3-formylamino-4-hydroxy-phenyl)-2-hydroxyethylamino]methyl}-benzoylamino)ethyl]piperidin-4-yl ester	652.5
62	Biphenyl-2-ylcarbamic acid 1-{2-[ethyl-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenyl)carbamoyl]ethyl}piperidin-4-yl ester	704.5
63	Biphenyl-2-ylcarbamic acid 1-(3-{4-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]piperidin-1-yl}-3-oxo-propyl)piperidin-4-yl ester	NA
64	Biphenyl-2-ylcarbamic acid 1-[2-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	690.3
65	Biphenyl-2-ylcarbamic acid 1-{2-[(5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-thiophene-2-carbonyl)amino]ethyl}piperidin-4-yl ester	682.5

Ex.	Compound	MS
66	Biphenyl-2-ylcarbamic acid 1-{2-[(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-3-nitro-benzoyl)methylamino]ethyl}piperidin-4-yl ester	735.7
67	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethylamino]methyl}-cyclohexylcarbamoyl)ethyl]piperidin-4-yl ester	658.8
68	Biphenyl-2-ylcarbamic acid 1-[2-({4-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]cyclohexanecarbonyl}-methylamino)ethyl]piperidin-4-yl ester	682.7
69	Biphenyl-2-ylcarbamic acid 1-(2-fluoro-3-{4-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]piperidin-1-ylmethyl}benzyl)piperidin-4-yl ester	720.5
70	Biphenyl-2-ylcarbamic acid 1-{2-[(6-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}pyridine-3-carbonyl)amino]ethyl}piperidin-4-yl ester	677.5
71	Biphenyl-2-ylcarbamic acid 1-[3-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}piperidin-1-yl)-propyl]piperidin-4-yl ester	654.5
72	Biphenyl-2-ylcarbamic acid 1-[2-(4-{2-[(*R*)-2-(3-formylamino-4-hydroxyphenyl)-2-hydroxy-ethylamino]ethyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	666.5
73	Biphenyl-2-ylcarbamic acid 1-[2-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)benzyl]piperidin-4-yl ester	690.3
74	Biphenyl-2-ylcarbamic acid 1-[2-fluoro-3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}piperidin-1-ylmethyl)benzyl]piperidin-4-yl ester	748.5
75	Biphenyl-2-ylcarbamic acid 1-[3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-	676.4

Ex.	Compound	MS
	yl)ethylamino]ethyl}phenylamino)propyl]piperidin-4-yl ester	
76	Biphenyl-2-ylcarbamic acid 1-[2-(3-chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	710.2
77	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-2-trifluoromethoxy-phenylcarbamoyl)ethyl]piperidin-4-yl ester	769.2
78	Biphenyl-2-ylcarbamic acid 1-{3-[3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)phenyl]propyl}piperidin-4-yl ester	752.6
79	Biphenyl-2-ylcarbamic acid 1-[3-(4-{2-[(*S*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)benzyl]piperidin-4-yl ester	NA
80	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-2-iodo-phenylcarbamoyl)ethyl]piperidin-4-yl ester	802.1
81	Biphenyl-2-ylcarbamic acid 1-[2-(2-chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-6-methylphenylcarbamoyl)ethyl]piperidin-4-yl ester	724.2
82	Biphenyl-2-ylcarbamic acid 1-(2-{5-[2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentylcarbamoyl}ethyl)-piperidin-4-yl ester	656.5
83	Biphenyl-2-ylcarbamic acid 1-[2-(2-bromo-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	756.2
84	Biphenyl-2-ylcarbamic acid 1-{3-[2-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)-phenyl]propyl}piperidin-4-yl ester	752.8
85	Biphenyl-2-ylcarbamic acid 1-[2-fluoro-3-(4-{3-[(*R*)-2-hydroxy-2-	762.8

Ex.	Compound	MS
	(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propyl}piperidin-1-ylmethyl)benzyl]piperidin-4-yl ester	
86	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-2-methoxy-phenylcarbamoyl)ethyl]piperidin-4-yl ester	706.3
87	Biphenyl-2-ylcarbamic acid 1-[5-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)pentyl]piperidin-4-yl ester	704.3
88	Biphenyl-2-ylcarbamic acid 1-{2-[1-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenyl)-piperidin-4-yl]ethyl}piperidin-4-yl ester	730.8
89	Biphenyl-2-ylcarbamic acid 1-[2-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]-1-methyl-ethyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	704.4
90	Biphenyl-2-ylcarbamic acid 1-{2-[4-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)cyclohexyl]ethyl}piperidin-4-yl ester	744.4
91	Biphenyl-2-ylcarbamic acid 1-[2-(2-fluoro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	694.3
92	Biphenyl-2-ylcarbamic acid 1-{2-[3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)phenyl]ethyl}piperidin-4-yl ester	738.8
93	Biphenyl-2-ylcarbamic acid 1-[2-(2,5-difluoro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	712.3
94	Biphenyl-2-ylcarbamic acid 1-[2-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}-benzoylamino)ethyl]piperidin-4-yl ester	690.3

Ex.	Compound	MS
95	Biphenyl-2-ylcarbamic acid 1-[6-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}piperidin-1-ylmethyl)pyridin-2-ylmethyl]piperidin-4-yl ester	717.5
96	Biphenyl-2-ylcarbamic acid 1-[2-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}-naphthalen-1-ylcarbamoyl)ethyl]piperidin-4-yl ester	740.6
97	Biphenyl-2-ylcarbamic acid 1-{2-[1-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzoyl)piperidin-4-yl]ethyl}piperidin-4-yl ester	744.4
98	Biphenyl-2-ylcarbamic acid 1-[3-(4-{3-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propionylamino}phenyl)propyl]piperidin-4-yl ester	704.2
99	Biphenyl-2-ylcarbamic acid 1-[3-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)-propyl]piperidin-4-yl ester	663.7
100	Biphenyl-2-ylcarbamic acid 1-[2-(5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-1H-benzoimidazol-2-yl)ethyl]piperidin-4-yl ester	673.7
101	Biphenyl-2-ylcarbamic acid 1-[2-(4-{3-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propionylamino}cyclohexyl)ethyl]piperidin-4-yl ester	696.4
102	Biphenyl-2-ylcarbamic acid 1-[2-(4-{5-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentanoylamino}cyclohexyl)ethyl]piperidin-4-yl ester	724.4
103	Biphenyl-2-ylcarbamic acid 1-[2-(4-{6-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]-hexanoylamino}cyclohexyl)ethyl]piperidin-4-yl ester	738.4
104	Biphenyl-2-ylcarbamic acid 1-[2-(1-{3-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propionyl}piperidin-4-yl)ethyl]piperidin-4-yl ester	682.4

Ex.	Compound	MS
105	Biphenyl-2-ylcarbamic acid 1-{2-[3-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenyl)ureido]ethyl}piperidin-4-yl ester	691.7
106	Biphenyl-2-ylcarbamic acid 1-{2-[(2-{4-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]cyclohexyl}-ethyl)methylamino]ethyl}piperidin-4-yl ester	682.7
107	Biphenyl-2-ylcarbamic acid 1-[2-(2,3,5,6-tetrafluoro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]piperidin-4-yl ester	748.2
108	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-2,6-diiodo-phenylcarbamoyl)ethyl]piperidin-4-yl ester	928.0
109	Biphenyl-2-ylcarbamic acid 1-[2-(1-{4-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]-butyryl}piperidin-4-yl)ethyl]piperidin-4-yl ester	696.4
110	Biphenyl-2-ylcarbamic acid 1-[2-(1-{5-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentanoyl}piperidin-4-yl)ethyl]piperidin-4-yl ester	710.4
111	Biphenyl-2-ylcarbamic acid 1-[2-(1-{6-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]-hexanoyl}piperidin-4-yl)ethyl]piperidin-4-yl ester	724.4
112	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzylcarbamoyl)ethyl]piperidin-4-yl ester	690.5
113	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-(3-formylamino-4-hydroxy-phenyl)-2-hydroxyethylamino]methyl}-benzylcarbamoyl)ethyl]piperidin-4-yl ester	666.5
114	Biphenyl-2-ylcarbamic acid 1-{2-[3-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzyl)ureido]ethyl}piperidin-4-yl ester	705.6
115	Biphenyl-2-ylcarbamic acid 1-{2-[3-(4-{[(*R*)-2-(3-formylamino-4-	681.7

Ex.	Compound	MS
	hydroxyphenyl)-2-hydroxyethylamino]methyl}benzyl)-ureido]ethyl}piperidin-4-yl ester	
116	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-2-methyl-phenylcarbamoyl)ethyl]piperidin-4-yl ester	690.4
117	Biphenyl-2-ylcarbamic acid 1-(3-{4-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}piperidin-1-yl)ethyl]phenoxy}propyl)-piperidin-4-yl ester	774.4
118	Biphenyl-2-ylcarbamic acid 1-[2-(3-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}-benzylcarbamoyl)ethyl]piperidin-4-yl ester	690.4
119	Biphenyl-2-ylcarbamic acid 1-[2-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)ethyl]piperidin-4-yl ester	649.5
120	Biphenyl-2-ylcarbamic acid 1-(2-{[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetyl]methylamino}ethyl)-piperidin-4-yl ester	720.4
121	Biphenyl-2-ylcarbamic acid 1-(2-{[2-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetyl]methylamino}ethyl)-piperidin-4-yl ester	720.4
122	Biphenyl-2-ylcarbamic acid 1-{2-[(5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}furan-2-carbonyl) methylamino]ethyl}piperidin-4-yl ester	680.3
123	Biphenyl-2-ylcarbamic acid 1-{2-[(5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-thiophene-2-carbonyl)methylamino]ethyl}piperidin-4-yl ester	696.2
124	Biphenyl-2-ylcarbamic acid 1-[2-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-	679.3

Ex.	Compound	MS
	yl)ethylamino]ethoxy}phenoxy)ethyl]piperidin-4-yl ester	
125	Biphenyl-2-ylcarbamic acid 1-{2-[4-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzoylamino)cyclohexyl]ethyl}piperidin-4-yl ester	758.4
126	Biphenyl-2-ylcarbamic acid 1-(2-{4-[2-(2-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetylamino]cyclohexyl}ethyl)-piperidin-4-yl ester	788.4
127	Biphenyl-2-ylcarbamic acid 1-(2-{4-[2-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetylamino]cyclohexyl}ethyl)-piperidin-4-yl ester	788.4
128	Biphenyl-2-ylcarbamic acid 1-(2-{4-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetylamino]cyclohexyl}ethyl)-piperidin-4-yl ester	788.4
129	Biphenyl-2-ylcarbamic acid 1-(2-{4-[(5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}furan-2-carbonyl)amino]cyclohexyl}ethyl)piperidin-4-yl ester	748.4
130	Biphenyl-2-ylcarbamic acid 1-(2-{4-[(5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-thiophene-2-carbonyl)amino]cyclohexyl}ethyl)piperidin-4-yl ester	764.4
131	Biphenyl-2-ylcarbamic acid 1-(2-{1-[2-(2-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetyl]piperidin-4-yl}ethyl)-piperidin-4-yl ester	774.4
132	Biphenyl-2-ylcarbamic acid 1-(2-{1-[2-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetyl]piperidin-4-yl}ethyl)-piperidin-4-yl ester	774.4
133	Biphenyl-2-ylcarbamic acid 1-(2-{1-[2-(4-{[(*R*)-2-hydroxy-2-(8-	774.4

Ex.	Compound	MS
	hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetyl]piperidin-4-yl}ethyl)-piperidin-4-yl ester	
134	Biphenyl-2-ylcarbamic acid 1-{2-[1-(5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}furan-2-carbonyl) piperidin-4-yl]ethyl}piperidin-4-yl ester	734.4
135	Biphenyl-2-ylcarbamic acid 1-{2-[1-(5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-thiophene-2-carbonyl)piperidin-4-yl]ethyl}piperidin-4-yl ester	750.2
136	Biphenyl-2-ylcarbamic acid 1-{2-[4-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzoylamino)phenyl]ethyl}piperidin-4-yl ester	752.4
137	Biphenyl-2-ylcarbamic acid 1-{2-[4-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzoylamino)phenyl]ethyl}piperidin-4-yl ester	752.4
138	Biphenyl-2-ylcarbamic acid 1-(2-{4-[2-(2-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetylamino]phenyl}ethyl)-piperidin-4-yl ester	782.4
139	Biphenyl-2-ylcarbamic acid 1-(2-{4-[2-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetylamino]phenyl}ethyl)-piperidin-4-yl ester	782.4
140	Biphenyl-2-ylcarbamic acid 1-(2-{4-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)acetylamino]phenyl}ethyl)-piperidin-4-yl ester	782.4
141	Biphenyl-2-ylcarbamic acid 1-(2-{4-[(5-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}furan-2-carbonyl)amino]phenyl}ethyl)piperidin-4-yl ester	742.4
142	Biphenyl-2-ylcarbamic acid 1-(2-{4-[(5-{[(*R*)-2-hydroxy-2-(8-	758.2

Ex.	Compound	MS
	hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-thiophene-2-carbonyl)amino]phenyl}ethyl)piperidin-4-yl ester	
143	Biphenyl-2-ylcarbamic acid 1-{2-[4-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzoylamino)cyclohexyl]ethyl}piperidin-4-yl ester	758.4
144	Biphenyl-2-ylcarbamic acid 1-[3-(3-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)-propyl]piperidin-4-yl ester	663.4
145	Biphenyl-2-ylcarbamic acid 1-[2-hydroxy-3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)propyl]piperidin-4-yl ester	692.3
146	Biphenyl-2-ylcarbamic acid 1-[4-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)butyl]piperidin-4-yl ester	690.4
147	Biphenyl-2-ylcarbamic acid 1-{2-[4-({2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]acetylamino}-methyl)phenylcarbamoyl]ethyl}piperidin-4-yl ester	733.3
148	Biphenyl-2-ylcarbamic acid 1-{2-[4-(2-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]acetylamino}-ethyl)phenylcarbamoyl]ethyl}piperidin-4-yl ester	747.4
149	Biphenyl-2-ylcarbamic acid 1-{2-[(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-cyclohexylmethyl)carbamoyl]ethyl}piperidin-4-yl ester	696.6
150	Biphenyl-2-ylcarbamic acid 1-(2-{6-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]hexanoylamino}-ethyl)piperidin-4-yl ester	656.6
151	Biphenyl-2-ylcarbamic acid 1-[2-(3-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethoxy}phenoxy)ethyl]piperidin-4-yl ester	679.3
152	Biphenyl-2-ylcarbamic acid 1-[2-(2-{2-[(*S*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-	679.3

Ex.	Compound	MS
	yl)ethylamino]ethoxy}phenoxy)ethyl]piperidin-4-yl ester	
153	Biphenyl-2-ylcarbamic acid 1-[2-(2-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenoxy)benzyl]piperidin-4-yl ester	711.3
154	Biphenyl-2-ylcarbamic acid 1-(2-{6-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]hexylcarbamoyl}ethyl) piperidin-4-yl ester	670.4
155	Biphenyl-2-ylcarbamic acid 1-[2-({(1*R*,3*S*)-3-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]cyclopentanecarbonyl}amino)ethyl]piperidin-4-yl ester	654.8
156	Biphenyl-2-ylcarbamic acid 1-[3-(4-{3-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propyl}phenyl)propyl]piperidin-4-yl ester	675.5
157	Biphenyl-2-ylcarbamic acid 1-[3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenyl)propyl]piperidin-4-yl ester	661.3
158	Biphenyl-2-ylcarbamic acid 1-[4-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenyl)butyl]piperidin-4-yl ester	675.5
159	Biphenyl-2-ylcarbamic acid 1-[3-(5-{3-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propyl}furan-2-yl)propyl]piperidin-4-yl ester	665.6
160	Biphenyl-2-ylcarbamic acid 1-{2-[3-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenyl)-1-methylureido]ethyl}piperidin-4-yl ester	719.2
161	Biphenyl-2-ylcarbamic acid 1-{2-[1-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylcarbamoyl)piperidin-4-yl]ethyl}piperidin-4-yl ester	773.3

Ex.	Compound	MS
162	Biphenyl-2-ylcarbamic acid 1-[3-(3-{3-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propyl}phenyl)propyl]piperidin-4-yl ester	675.5
163	Biphenyl-2-ylcarbamic acid 1-[3-(5-{3-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propyl}tetrahydrofuran-2-yl)propyl]piperidin-4-yl ester	669.6
164	Biphenyl-2-ylcarbamic acid 1-[2-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethylcarbamoyl}phenoxy)ethyl]piperidin-4-yl ester	706.5
165	(5-Bromobiphenyl-2-yl)carbamic acid 1-{9-[2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}-piperidin-4-yl ester	NA
166	(2'-Fluorobiphenyl-2-yl)carbamic acid 1-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}-piperidin-4-yl ester	659.5
167	(3'-Chloro-3,5-difluorobiphenyl-2-yl)carbamic acid 1-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethylamino]nonyl}piperidin-4-yl ester	711.8
168	(3',5'-Dichloro-3,5-difluorobiphenyl-2-yl)carbamic acid 1-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethylamino]nonyl}piperidin-4-yl ester	745.5
169	(3,5-Difluorobiphenyl-2-yl)carbamic acid 1-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}-piperidin-4-yl ester	677.5

5

Preparation 99

Biphenyl-2-ylcarbamic Acid 1-[2-(4-[1,3]dioxolan-2-ylphenylcarbamoyl)-ethyl]-4-methylpiperidin-4-yl Ester

A mixture of biphenyl-2-ylcarbamic acid 4-methylpiperidin-4-yl ester (2.73 g, 8.79 mmol) and *N*-(4-[1,3]dioxolan-2-yl-phenyl)acrylamide (2.05 g, 8.80 mmol) were heated in 100 mL of 1:1 methanol/dichloromethane at 50 °C under nitrogen for 1 h. The solution was then diluted with ethyl acetate and the organic layer was washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound. MS *m/z* calcd for $C_{31}H_{35}N_3O_5$ $(M+H)^+$ 530.6; found 530.4.

Preparation 100

Biphenyl-2-ylcarbamic Acid 1-[2-(4-Formylphenylcarbamoyl)ethyl]-4-methylpiperidin-4-yl Ester

The product of Preparation 99 was redissolved in 40 mL of methanol and 25 mL of aqueous 1 N hydrochloric acid was added. The resulting mixture was stirred at room temperature overnight and the organic solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was triturated with dichloromethane to give the title compound as a white powder (2.47 g). LCMS (2-90) R_t = 4.27 min; MS *m/z* calcd for $C_{29}H_{31}N_3O_4$ $(M+H)^+$ 486.6, found 486.5.

Preparation 101

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-(*tert*-butyldimethylsilanyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]-4-methyl-piperidin-4-yl Ester

A mixture of the product of Preparation 100 (1.70 g, 3.51 mmol) and 5-[(*R*)-2-amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one acetate (1.65 g, 4.19mmol) in 40 mL of 1:1 methanol and dichloromethane was stirred at room temperature overnight. Sodium triacetoxyborohydride (2.23 g, 10.5 mmol) was then added in one portion and the reaction mixture was stirred at room temperature for 6 hr. The reaction was then quenched with water and diluted with ethyl acetate. The layers were separated and the organic layer was washed with saturated sodium bicarbonate, brine, dried

($MgSO_4$) and the solvent removed under reduced pressure to give the title compound (2.9 g). MS *m/z* calcd for $C_{46}H_{57}N_5O_6Si$ (M+H)+ 805.0, found 804.6.

Example 170

Biphenyl-2-ylcarbamic Acid 1-[2-(4-{[(*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-phenylcarbamoyl)ethyl]-4-methylpiperidin-4-yl Ester

The product of Preparation 101 (2.9 g, 3.6mmol) was dissolved in 75 mL of dichloromethane and triethylamine trihydrofluoride (0.85 mL , 5.2mmol) was added. The resulting mixture was stirred at room temperature overnight and then the solvent was removed under reduced pressure to give the crude product as an oil. The product was then dissolved in acetic acid/water (1:1) and purified by prep HPLC to give the title compound as an off-white solid. LCMS (2-90) R_t = 3.67 min.; MS *m/z* calcd $C_{40}H_{43}N_5O_6$ $(M+H)^+$ 690.8, found 690.3.

Using the methods described herein and the appropriate starting materials, the following compounds can be prepared.

Ex.	Compound	MS
171	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethylamino]methyl}phenylcarbamoyl)-ethyl]-4-methylpiperidin-4-yl ester	NA
172	Biphenyl-2-ylcarbamic acid 1-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}-4-methylpiperidin-4-yl ester	NA
173	Biphenyl-2-ylcarbamic acid 1-{9-[(*R*)-2-(3-formylamino-4-hydroxy-phenyl)-2-hydroxyethylamino]nonyl}-4-methylpiperidin-4-yl ester	NA
174	Biphenyl-2-ylcarbamic acid 1-(2-{5-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]pentylcarbamoyl}-ethyl)-4-methylpiperidin-4-yl ester	NA
175	Biphenyl-2-ylcarbamic acid 1-(2-{5-[(*R*)-2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethylamino]pentylcarbamoyl}ethyl)-4-methylpiperidin-4-yl ester	NA

Ex.	Compound	MS
176	Biphenyl-2-ylcarbamic acid 1-(2-{6-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]hexanoylamino}ethyl)-4-methylpiperidin-4-yl ester	NA
177	Biphenyl-2-ylcarbamic acid 1-(2-{6-[(*R*)-2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethylamino]hexanoylamino}ethyl)-4-methylpiperidin-4-yl ester	NA
178	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-benzoylamino)ethyl]-4-methylpiperidin-4-yl ester	NA
179	Biphenyl-2-ylcarbamic acid 1-[2-(4-{[(*R*)-2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethylamino]methyl}benzoylamino)-ethyl]-4-methylpiperidin-4-yl ester	NA
180	Biphenyl-2-ylcarbamic acid 1-{3-[4-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenylamino)phenyl]propyl}-4-methylpiperidin-4-yl ester	776.5
181	Biphenyl-2-ylcarbamic acid 1-[2-(2-chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)ethyl]-4-methylpiperidin-4-yl ester	724.5
182	Biphenyl-2-ylcarbamic acid 1-[2-(2-chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]-4-methylpiperidin-4-yl ester	754.5

Preparation 102

Biphenyl-2-ylcarbamic acid (*R*)-(1-azabicyclo[3.2.1]oct-4-yl) Ester

2-Biphenyl isocyanate (1.00 g, 5.12 mmol) and (*R*)-(-)-3-quinuclidinol hydrochloride (921 mg, 5.63 mmol) were heated together in *N*,*N*-dimethylformamide (2.06 mL) at 110 °C for 12 h. The reaction mixture was cooled and diluted with ethyl acetate (15 mL) and then washed with saturated aqueous sodium bicarbonate (2 x 10 mL). The organic layer was extracted with 1 M hydrochloric acid (3 x 20 mL) and the combined

aqueous extracts were made basic to pH 8-9 with potassium carbonate. The aqueous layer was then extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried (magnesium sulfate) and solvent was removed under reduced pressure to give the title compound as a yellow oil (1.64 g, 99% yield).

Preparation 103

(*R*)-4-(Biphenyl-2-ylcarbamoyloxy)-1-(9-bromononyl)-1-azoniabicyclo[3.2.1]octane Bromide

To a stirred solution of the product of Preparation 102 (1.21 g, 3.76 mmol) and triethylamine (1.05 mL, 7.52 mmol) in acetonitrile (18.8 mL) was added 1,9-dibromononane (994 μL, 4.89 mmol) and the reaction mixture was heated at 50 °C for 4 h. The reaction mixture was then cooled and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (20 mL) and the organic layer was washed with saturated aqueous sodium bicarbonate (10 mL), dried (magnesium sulfate) and solvent removed under reduced pressure. The crude product was purified by flash chromatography (10% methanol/dichloromethane, 0.5 % ammonium hydroxide) to give the title compound (1.04 g, 1.97 mmol, 52% yield).

Preparation 104

(*R*)-1-(9-*N*,*N*-Di(*tert*-butoxycarbonyl)aminononyl)-4-(biphenyl-2-ylcarbamoyloxy)-1-azoniabicyclo[3.2.1]octane Bromide

To a stirred solution of sodium hydride (60% dispersion in mineral oil) (126 mg, 3.15 mmol) in *N*,*N*-dimethylformamide (10 mL) under an atmosphere of nitrogen at 0°C, was added di-*tert*-butyl iminodicarboxylate (513 mg, 2.36 mmol) in *N*,*N*-dimethylformamide (5 mL). The reaction mixture was stirred at room temperature for 15 min and then it was cooled to 0 °C and the product of Preparation 103 (1.04 g, 1.97 mmol) in *N*,*N*-dimethylformamide (5 mL) was added. The reaction mixture was allowed to warm to room temperature over a 12 h period and then the solvent was removed under reduced pressure to give the title compound, which was used without further purification.

Preparation 105

(*R*)-1-(9-Aminononyl)-4-(biphenyl-2-ylcarbamoyloxy)-1-azoniabicyclo[3.2.1]octane Bromide

The product of Preparation 104 (1.31 g, 1.97 mmol) was dissolved in dichloromethane (15 mL) and trifluoroacetic acid (5 mL) was added slowly. The reaction mixture was stirred at room temperature for 1 h and then the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (20 mL) and washed with aqueous 1 M sodium hydroxide (20 mL). The organic layer was extracted with 1 M hydrochloric acid (3 x 20 mL) and the combined aqueous extracts were made basic with potassium carbonate and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (magnesium sulfate) and solvent was removed under reduced pressure to give the title compound (210 mg, 23% yield over 2 steps).

Preparation 106

(*R*)-1-{9-[(*R*)-2-(8-Benzyloxy-2-oxo-1,2-dihydroquinolin-5-yl)-2-hydroxyethylamino]-nonyl}-4-(biphenyl-2-ylcarbamoyloxy)-1-azoniabicyclo[3.2.1]octane Bromide

The product of Preparation 105 (210 mg, 0.45 mmol) and sodium triacetoxyborohydride (286 mg, 1.35 mmol) were stirred in dichloroethane (4.5 mL) at room temperature for 2 h and then the product of Preparation 6 (163 mg, 0.50 mmol) was added. The reaction mixture was stirred for 12 h and then diluted with dichloromethane (10 mL) and washed with saturated aqueous sodium bicarbonate (10 mL), dried (magnesium sulfate) and solvent removed under reduced pressure. The crude reaction product was purified by flash chromatography (10-50% methanol/dichloromethane, 0.5% ammonium hydroxide) to give the title compound (131 mg, 38% yield).

Example 183

4-(Biphenyl-2-ylcarbamoyloxy)-1-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethylamino]nonyl}-1-azoniabicyclo[2.2.2]octane Bromide Ditrifluoroacetate

To a stirred solution of the product of Preparation 105 (131 mg, 0.17 mmol) in methanol (1.8 mL) was added palladium (10 wt. % dry basis on activated carbon; 39 mg) and the reaction mixture was placed under an atmosphere of hydrogen. After stirring for 12 h, the reaction mixture was filtered through a pad of Celite, washing with methanol (2

mL) and solvent removed under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as its ditrifluoroacetate salt (8 mg). MS *m/z* 667.5.

Using the methods described herein and the appropriate starting materials, the following compounds can be prepared.

Ex.	Compound	MS
184	Biphenyl-2-ylcarbamic acid 8-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}-8-aza-bicyclo[3.2.1]oct-3-yl ester	667.3
185	7-(Biphenyl-2-ylcarbamoyloxy)-9-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethylamino]nonyl}-9-methyl-3-oxa-9-azoniatricyclo[3.3.1.0*2,4*]nonane bromide	695.5
186	Biphenyl-2-ylcarbamic acid 9-{9-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]nonyl}-3-oxa-9-aza-tricyclo[3.3.1.0*2,4*]non-7-yl ester	681.5

Members of the library of compounds prepared by the above procedures were evaluated using the following *in vitro* and *in vivo* assays:

Preparation A

Cell Culture and Membrane Preparation From Cells Expressing Human β_1, β_2 or β_3 Adrenergic Receptors

Chinese hamster ovarian (CHO) cell lines stably expressing cloned human β_1, β_2 or β_3 adrenergic receptors, respectively, were grown to near confluency in Hams F-12 media with 10% FBS in the presence of 500 μg/mL Geneticin. The cell monolayer was lifted 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 β_1 and β_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 more protease-sensitive β_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 $MgCl_2$, 1 mM EDTA). The protein concentration of the membrane suspension was determined by the methods 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

Cell Culture and Membrane Preparation From Cells Expressing Human M_1, M_2, M_3 and M_4 Muscarinic Receptors

CHO cell lines stably expressing cloned human hM_1, hM_2, hM_3 and hM_4 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% CO_2, 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 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_5 receptor membranes were purchased directly from Perkin Elmer and stored at –80 °C until use.

Assay Test Procedure A

Radioligand Binding Assay for Human β_1, β_2 and β_3 Adrenergic Receptors

Binding assays were performed in 96-well microtiter plates in a total assay volume of 100 μL with 10-15 μg of membrane protein containing the human β_1, β_2 or β_3

adrenergic receptors in assay buffer (75 mM Tris/HCl pH 7.4 at 25°C, 12.5 mM $MgCl_2$, 1 mM EDTA, 0.2% BSA). Saturation binding studies for determination of K_d values of the radioligand were done using [^{3}H]-dihydroalprenolol (NET-720, 100 Ci/mmol, PerkinElmer Life Sciences Inc., Boston, MA) for the β_1 and β_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 μM. Non-specific binding was determined in the presence of 10 μM propranolol. Assays were incubated for 1 hour at 37°C, and then binding reactions were terminated by rapid filtration over GF/B for the β_1 and β_2 receptors or GF/C glass fiber filter plates for the β_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 $MgCl_2$, 1 mM EDTA) to remove unbound radioactivity. The plates were then dried and 50 μL 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 μM propranolol. K_i values for test compounds were calculated from observed IC_{50} 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 that were tested in this assay typically were found to have a K_i value of less than about 300 nM for the β_2 adrenergic receptor. For example, the compounds of Examples 3 and 6 were identified as having K_i values of less than 10 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 β_2 adrenergic receptor compared to the β_1 or β_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 β_2 adrenergic receptor over the β_1 or β_3 adrenergic receptors are preferred; especially compounds having a selectivity greater than about 5; and in particular, greater than about 8. By way of example, the compounds of Examples 3 and 6 had a ratio of $K_i(\beta_1)/K_i(\beta_2)$ greater than 8.

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 µL. CHO cell membranes stably expressing either the hM_1, hM_2, hM_3, hM_4 or hM_5 muscarinic subtype were diluted in assay buffer to the following specific target protein concentrations (µg/well): 10 µg for hM_1, 10-15 µg for hM_2, 10-20 µg for hM_3, 10-20 µg for hM_4, and 10-12 µg for hM_5 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-^{3}*H*]scopolamine methyl chloride ([^{3}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 [^{3}H]-NMS at 1 nM and eleven different test compound concentrations. The test compounds were initially dissolved to a concentration of 400 µM in dilution buffer and then serially diluted 5x with dilution buffer to final concentrations ranging from 10 pM to 100 µM. The addition order and volumes to the assay plates were as follows: 25 µL radioligand, 25 µL diluted test compound, and 50 µL 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 µL 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_{50} 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_i 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 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 compounds of Examples 3 and 6 were identified as having K_i values of less than 10 nM.

Assay Test Procedure C

Whole-cell cAMP Flashplate Assay in CHO Cell Lines Heterologously Expressing Human β_1, β_2 or β_3 Adrenergic Receptors

cAMP assays were 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 β receptor agonist potency (EC_{50}), CHO-K1 cell lines stably expressing cloned human β_1, β_2 or β_3 adrenergic receptors were grown to near confluency in HAM's F-12 media supplemented with 10% FBS and Geneticin (250 μg/mL). Cells were 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 were 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 x 10^6 to 2.8 x 10^6 cells/mL. About 60,000 to 80,000 cells per well were used in this assay. Test compounds (10 mM in DMSO) were diluted into PBS containing 0.1% BSA in Beckman Biomek-2000 and tested at 11 different concentrations ranging from 100 μM to 1 pM. Reactions were incubated for 10 min at 37 °C and stopped by adding 100 μL of cold detection buffer containing [^{125}I]-cAMP (NEN SMP004, PerkinElmer Life Sciences, Boston, MA). The amount of cAMP produced (pmol/well) was calculated based on the counts observed for the samples and cAMP standards as described in the manufacturer's

user manual. Data were 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) was used to calculate the EC50 values.

In this assay, a lower EC_{50} value indicates that the test compound has a higher functional activity at the receptor tested. Exemplified compound that were tested in this assay typically were found to have a EC_{50} value of less than about 300 nM for the β_2 adrenergic receptor. For example, the compounds of Examples 3 and 6 were identified as having EC_{50} values of less than 10 nM.

If desired, the receptor subtype selectivity for a test compound can be calculated as the ratio of $EC_{50}(\beta_1)/EC_{50}(\beta_2)$ or $EC_{50}(\beta_3)/EC_{50}(\beta_2)$. Typically, compounds of this invention demonstrated greater functional activity at the β_2 adrenergic receptor compared to the β_1 or β_3 adrenergic receptor, i.e. $EC_{50}(\beta_1)$ or $EC_{50}(\beta_3)$ is typically greater than $EC_{50}(\beta_2)$. Generally, compounds having selectivity for the β_2 adrenergic receptor over the β_1 or β_3 adrenergic receptors are preferred; especially compounds having a selectivity greater than about 5; and in particular, greater than about 10. By way of example, the compounds of Examples 3 and 6 had ratios of $EC_{50}(\beta_1)/EC_{50}(\beta_2)$ greater than 10.

Assay Test Procedure D

Functional Assays of Antagonism for Muscarinic Receptor Subtypes

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_2 receptor. cAMP assays are performed in a radioimmunoassay format using the Flashplate Adenylyl Cyclase Activation Assay System with ^{125}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 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 $1.6 \times 10^6 - 2.8 \times 10^6$ cells/mL.

The test compound is initially dissolved to a concentration of 400 μM in dilution 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 μL forskolin (25 μM final concentration diluted in dPBS), 25 μL diluted oxotremorine, and 50 μL cells are added to agonist assay wells. To measure the ability of a test compound to block oxotremorine-inhibited AC activity, 25 μL forskolin and oxotremorine (25 μM and 5 μM final concentrations, respectively, diluted in dPBS), 25 μL diluted test compound, and 50 μL cells are added to remaining assay wells.

Reactions are incubated for 10 minutes at 37 °C and stopped by addition of 100 μL 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. Exemplified compound that were tested in this assay typically were found 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_2 receptor. For example, the compound of Example 3 was identified as having a K_i value of less than 10 nM.

B. Blockade of Agonist-Mediated [^{35}S]GTPγS 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 [^{35}S]GTPγS binding in CHO-K1 cells expressing the hM_2 receptor.

At the time of use, frozen membranes were thawed and then diluted in assay buffer with a final target tissue concentration of 5-10 μg protein per well. The membranes were 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 [^{35}S]GTPγS binding by the agonist oxotremorine was determined in each experiment.

To determine the ability of a test compound to inhibit oxotremorine-stimulated [^{35}S]GTPγS binding, the following was added to each well of 96 well plates: 25 μL of assay buffer with [^{35}S]GTPγS (0.4nM), 25 μL of oxotremorine(EC_{90}) and GDP (3uM), 25 μL of diluted test compound and 25 μL CHO cell membranes expressing the hM_2 receptor. The assay plates were then incubated at 37 °C for 60 minutes. The assay plates were filtered over 1% BSA-pretreated GF/B filters using a PerkinElmer 96-well harvester. The plates were rinsed with ice-cold wash buffer for 3 x 3 seconds and then air or vacuum dried. Microscint-20 scintillation liquid (50 μL) was added to each well, and each plate was sealed and radioactivity counted on a Topcounter (PerkinElmer). Data were 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 was used to calculate the K_i, using the IC_{50} values of the concentration-response curve for the test compound and the oxotremorine concentration in the assay as the K_D and [L], ligand concentration, respectively.

In this assay, a lower K_i value indicates that the test compound has a higher functional activity at the receptor tested. Exemplified compound that were tested in this assay typically were found to have a K_i value of less than about 300 nM for blockade of oxotremorine-stimulated [^{35}S]GTPγS binding in CHO-K1 cells expressing the hM_2 receptor. For example, the compound of Example 3 was identified as having a K_i value of less than 10 nM.

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

Muscarinic receptor subtypes (M_1, M_3 and M_5 receptors), which couple to G_q proteins, activate the phospholipase C (PLC) pathway upon agonist binding to the receptor. As a result, activated PLC hydrolyzes phosphatyl inositol diphosphate (PIP_2) to diacylglycerol (DAG) and phosphatidyl-1,4,5-triphosphate (IP_3), 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_1 and M_3, and chimpanzee M_5 receptors. Antagonist potency can be determined by the ability of antagonists to inhibit agonist-mediated increases in intracellular calcium.

For FLIPR calcium stimulation assays, CHO cells stably expressing the hM_1, hM_3 and cM_5 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 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.

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

The change of fluorescence is expressed as maximum fluorescence minus baseline fluorescence for each well. The raw data is analyzed 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_i values are determined by Prism using the oxotremorine EC_{50} value as the K_D and the oxotremorine EC_{90} for the ligand concentration according to the Cheng-Prusoff equation (Cheng & Prusoff, 1973).

In this assay, a lower K_i value indicates that the test compound has a higher functional activity at the receptor tested. Exemplified compound that were tested in this assay typically were found 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. For example, the compound of Example 3 was identified as having a K_i value of less than 10 nM for the hM_1, hM_3 and cM_5 receptors.

Assay Test Procedure E

Whole-cell cAMP Flashplate Assay With a Lung Epithelial Cell Line Endogenously Expressing Human β_2 Adrenergic Receptor

For the determination of agonist potencies and efficacies (intrinsic activities) in a cell line expressing endogenous levels of the β_2 adrenergic receptor, a human lung epithelial cell line (BEAS-2B) was used (ATCC CRL-9609, American Type Culture Collection, Manassas, VA) (January B, et al., *British Journal of Pharmacology*, 1998, *123*, 4, 701-11). Cells were 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 was switched to LHC-8 (no epinephrine or retinoic acid, cat # 141-500, Biosource International, Camarillo, CA). cAMP assays were 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 were rinsed with PBS, lifted by scraping with 5mM EDTA in PBS, and counted. Cells were 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 were used at a final concentration of 100,000 to 120,000 cells/well in this assay. Test compounds were 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 were tested in the assay at 11 different concentrations, ranging from 10 μM to 10 pM. Reactions were incubated for 10 min at 37 °C and stopped by addition of 100 μL of ice-cold detection buffer. Plates were 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 was calculated based on the counts observed for samples and cAMP standards, as described in the manufacturer's user manual. Data were 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_{50} value indicates that the test compound has a higher functional activity at the receptor tested. Exemplified compound that were tested in this assay typically were found to have a EC_{50} value of less than about 300 nM for the β_2 adrenergic receptor. For example, the compounds of Examples 3 and 6 were identified as having EC_{50} values of less than 10 nM.

If desired, test compound efficacy (%Eff) was calculated from the ratio of the observed Emax (TOP of the fitted curve) and the maximal response obtained for isoproterenol dose response curve and was expressed as %Eff relative to isoproterenol. Exemplified compounds tested in this assay typically demonstrated 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 were used to assess the bronchoprotective effects of test compounds exhibiting both muscarinic receptor antagonist and β_2 adrenergic receptor agonist activity. To isolate muscarinic antagonist activity in the acetylcholine-induced bronchoconstriction model, the animals were administered propanolol, a compound that blocks β receptor activity, prior to the administration of acetylcholine. Duration of bronchoprotection in the histamine-induced bronchoconstriction model reflects β_2 adrenergic receptor agonist activity.

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

Test compounds were administered *via* inhalation over 10 minutes in a whole-body exposure dosing chamber (R&S Molds, San Carlos, CA). The dosing chambers were arranged so that an aerosol was simultaneously delivered to 6 individual chambers from a central manifold. Guinea pigs were exposed to an aerosol of a test compound or vehicle (WFI). These aerosols were 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_2 = 5%, O_2 = 21% and N_2 = 74%) at a pressure of 22 psi. The gas flow through the nebulizer at this operating pressure was approximately 3 L/ minute. The generated aerosols were driven into the chambers by positive pressure. No dilution air was used during the delivery of aerosolized solutions. During the 10 minute nebulization, approximately 1.8 mL of solution was nebulized. This value was measured gravimetrically by comparing pre-and post-nebulization weights of the filled nebulizer.

The bronchoprotective effects of test compounds administered *via* inhalation were 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 was 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 was shaved and cleaned with 70% alcohol, a 2-3 cm midline incision of the ventral aspect of the neck was made. Then, the jugular vein was 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 was then dissected free and cannulated with a 14G teflon tube (#NE- 014, Small Parts, Miami Lakes, FL). If required, anesthesia was maintained by additional intramuscular injections of the aforementioned anesthetic mixture. The depth of anesthesia was monitored and adjusted if the animal responds to pinching of its paw or if the respiration rate was greater than 100 breaths/minute.

Once the cannulations were completed, the animal was placed into a plethysmograph (#PLY3114, Buxco Electronics, Inc., Sharon, CT) and an esophageal pressure cannula (PE-160, Becton Dickinson, Sparks, MD) was inserted to measure pulmonary driving pressure (*pressure)*. The teflon tracheal tube was attached to the

opening of the plethysmograph to allow the guinea pig to breathe room air from outside the chamber. The chamber was then sealed. A heating lamp was used to maintain body temperature and the guinea pig's lungs were 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 collapse and that the animal did not suffer from hyperventilation.

Once it was determined that baseline values were within the range of 0.3 - 0.9 mL/cm H_2O for compliance and within the range of 0.1 - 0.199 cm H_2O/mL per second for resistance, the pulmonary evaluation was initiated. A Buxco pulmonary measurement computer progam enabled the collection and derivation of pulmonary values.

Starting this program initiated the experimental protocol and data collection. The changes in volume over time that occur within the plethysmograph with each breath were measured *via* a Buxco pressure transducer. By integrating this signal over time, a measurement of *flow* was calculated for each breath. This signal, together with the pulmonary driving *pressure* changes, which were collected using a Sensym pressure transducer (#TRD4100), was connected *via* a Buxco (MAX 2270) preamplifier to a data collection interface (#'s SFT3400 and SFT3813). All other pulmonary parameters were derived from these two inputs.

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

When evaluating the β_2 adrenergic receptor agonist effects of test compounds, histamine (25 μg/mL) (Sigma-Aldrich, St. Louis, MO) was infused intravenously for 1 minute from a syringe pump at the following doses and prescribed times from the start of the experiment: 0.5 μg/minute at 5 minutes, 0.9 μg/minute at 10 minutes, 1.9 μg/minute at 15 minutes, 3.8 μg/minute at 20 minutes, 7.5 μg/minute at 25 minutes and 15 μg/minute at 30 minutes. If resistance or compliance had not returned to baseline values at 3 minutes

following each Ach or histamine dose, the guinea pig's lungs were 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_2O) and pulmonary resistance (cm H_2O/ mL per second). Once the pulmonary function measurements were completed at minute 35 of this protocol, the guinea pig was removed from the plethysmograph and euthanized by carbon dioxide asphyxiation.

The data were evaluated in one of two ways:

(a) Pulmonary resistance (R_L, cm H_2O/mL per second) was calculated from the ratio of "change in pressure" to "the change in flow." The R_L response to ACh (60 μg/min, IH) was computed for the vehicle and the test compound groups. The mean ACh response in vehicle-treated animals, at each pre-treatment time, was 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_{50} (dose required to inhibit the ACh (60 μg/min) bronchocontrictor response by 50%). The equation used was as follows:

$$Y = Min + (Max–Min)/(1 + 10^{((\log ID50–X)* Hillslope)})$$

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

(b) The quantity PD_2, which is defined as the amount of Ach or histamine needed to cause a doubling of the baseline pulmonary resistance, was 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 (derived from the equation used to calculate PC_{20} values in the clinic (see *Am. Thoracic Soc*, 2000):

$$PD_2 = \text{antilog}\left[\log C_1 + \frac{(\log C_2 - \log C_1)(2R_0 - R_1)}{R_2 - R_1}\right]$$

where:

C_1 = concentration of Ach or histamine preceding C_2

C_2 = concentration of Ach or histamine resulting in at least a 2-fold increase in pulmonary resistance (R_L)

R_0 = Baseline R_L value

R_1 = R_L value after C_1

R_2 = R_L value after C_2

Statistical analysis of the data was performed using a two tailed – Students t-test. A *P*-value <0.05 was considered significant.

Exemplified compounds that were tested in this assay typically produced a dose-dependent bronchoprotective effect against MCh-induced bronchoconstriction and His-induced bronchoconstriction. Generally, test compounds having a potency (ID_{50} 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 preferred. For example, the compounds of Examples 3 and 6 were found to have an ID_{50} less than about 100 μg/mL for ACh-induced bronchoconstriction and an ID_{50} less than about 100 μg/mL for His-induced bronchoconstriction at 1.5 hours post-dose.

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. By way of example, the compounds of Examples 3 and 6 were identified as having a PD $T_{1/2}$ of at least about 24 hours post-dose.

Assay Test Procedure G

Einthoven Model for Measuring Changes in Ventilation in Guinea Pigs

The bronchodilator activity of test compounds was 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) *Pfugers Arch. 51*: 367 – 445; and Mohammed et al. (2000) *Pulm Pharmacol Ther.13(6):*287-92. In this model, muscarinic antagonist and β_2 agonist activity was assessed by determining the protective effects against methacholine (MCh) and histamine (His)-induced bronchoconstriction.

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

The test compound or vehicle (i.e., sterile water) was dosed by inhalation (IH) over a 10 minute time period in a whole body exposure dosing chamber (R+S Molds, San Carlos, CA) using 5 mL of dosing solution. Animals were exposed to an aerosol, which was generated from an LC Star Nebulizer Set (Model 22F51, PARI Respiratory Equipment, Inc. Midlothian, VA) driven by Bioblend a mixture of gasses (5% CO_2; 21% O_2; and 74% N_2) at a pressure of 22 psi. Pulmonary function was evaluated at various time-points after inhalation dosing.

Forty five minutes prior to the start of pulmonary function evaluation, the guinea pigs were 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) was administered as needed. The jugular vein and carotid artery were isolated and cannulated with saline-filled polyethylene catheters (micro-renathane and PE-50, respectively, Beckton Dickinson, Sparks, MD). The carotid artery was connected to a pressure transducer to allow the measurement of blood pressure and the jugular vein cannula was used for IV injection of either MCh or His. The trachea was then dissected free and cannulated with a 14G needle (#NE-014, Small Parts, Miami Lakes, FL). Once the cannulations were complete, the guinea pigs were ventilated using a respirator (Model 683, Harvard Apparatus, Inc., MA) set at a stroke volume of 1mL/100 g body weight but not exceeding 2.5 mL volume, and at a rate of 100 strokes per minute. Ventilation pressure (VP) was measured in the tracheal cannula using a Biopac transducer that was connected to a Biopac (TSD 137C) pre-amplifier. Body temperature was maintained at 37 °C using a heating pad. Prior to initiating data collection, pentobarbital (25mg/kg) was administered intraperitoneally (IP) to suppress spontaneous breathing and obtain a stable baseline. The changes in VP were recorded on a Biopac Windows data collection interface. Baseline values were collected for at least 5 minutes, after which time guinea pigs were challenged IV non-cumulatively with 2-fold incremental doses of the bronchoconstrictor (MCh or His). When MCh was used as the bronchoconstrictor agent, animals were pre-treated with propranolol (5 mg/kg, IV) to isolate the antimuscarinic effects of the test compound. Changes in VP were recorded using the Acknowledge Data Collection Software (Santa Barbara, CA). After the completion of study, the animals were euthanized.

Change in VP was measured in cm of water. Change in VP (cm H_2O) = peak pressure (after bronchoconstrictor challenge) - peak baseline pressure. The dose-response

curve to MCh or His was fitted to a four parameter logistic equation using GraphPad Prism, version 3.00 for Windows (GraphPad Software, San Diego, California) The equation used was as follows:

$$Y = Min + (Max–Min)/(1 + 10^{((\log ID50–X)* Hillslope)})$$

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

The percent inhibition of the bronchoconstrictor response to a submaximal dose of MCh or His was 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 challenge, water) - peak baseline pressure (water)). Inhibition curves were fitted using the four parameter logistic equation from GraphPad software. ID_{50} (dose required to produce 50% inhibition of the bronchoconstrictor response) and Emax (maximal inhibition) were also estimated wherever appropriate.

The magnitude of bronchoprotection at different time-points after inhalation of the test compound was used to estimate the pharmacodynamic half-life (PD $T_{1/2}$). PD $T_{1/2}$ was 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 was constrained to 0.

Exemplified compounds that were tested in this assay typically produced a dose-dependent bronchoprotective effect against MCh-induced bronchoconstriction and His-induced bronchoconstriction. Generally, test compounds having an ID_{50} less than about 300 μg/mL for MCh-induced bronchoconstriction and an ID_{50} less than about 300 μg/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 brochoprotective activity of at least about 24 hours in this assay are generally preferred.

Assay Test Procedure H

Inhalation Guinea Pig Salivation Assay

Guinea pigs (Charles River, Wilmington, MA) weighing 200-350 g were acclimated to the in-house guinea pig colony for at least 3 days following arrival. Test compound or vehicle were dosed via inhalation (IH) over a 10 minute time period in a pie shaped dosing chamber (R+S Molds, San Carlos, CA). Test solutions were dissolved in sterile water and delivered using a nebulizer filled with 5.0 mL of dosing solution. Guinea pigs were restrained in the inhalation chamber for 30 minutes. During this time, guinea pigs were restricted to an area of approximately 110 sq. cm. This space was adequate for the animals to turn freely, reposition themselves, and allow for grooming. Following 20 minutes of acclimation, guinea pigs were 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 were evaluated at 1.5, 6, 12, 24, 48, or 72 hrs after treatment.

Guinea pigs were 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 were 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) was inserted in the guinea pig's mouth. Five minutes later, the muscarinic agonist pilocarpine (3.0 mg/kg, s.c.) was administered and the gauze pad was immediately discarded and replaced by a new pre-weighed gauze pad. Saliva was collected for 10 minutes, at which point the gauze pad was weighed and the difference in weight recorded to determine the amount of accumulated saliva (in mg). The mean amount of saliva collected for animals receiving the vehicle and each dose of test compound was calculated. The vehicle group mean was considered to be 100% salivation. Results were calculated using result means (n = 3 or greater). Confidence intervals (95%) were calculated for each dose at each time point using 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, was calculated and used to compute % inhibition of salivation, at the corresponding pre-

treatment time, at each dose. The inhibition dose-response data were 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_{50} (dose required to inhibit 50% of pilocarpine-evoked salivation). The equation used was as follows:

$$Y = Min + (Max–Min)/(1 + 10^{((\log ID50–X)* Hillslope)})$$

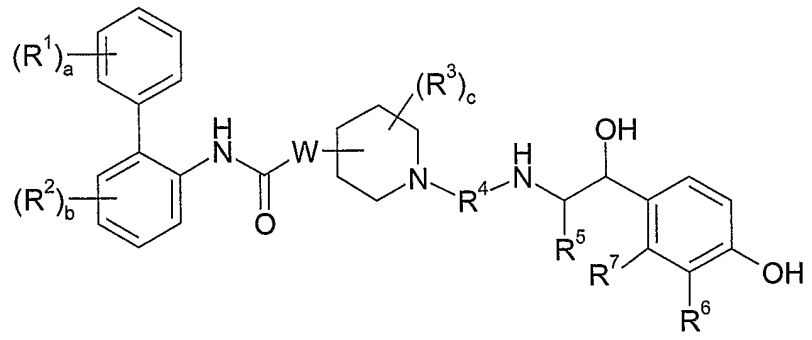
where X is the logarithm of dose, Y is the response (% inhibition of salivation). Y starts at Min and approaches asymptotically to Max with a sigmoidal shape.

The ratio of the anti-sialagogue ID_{50} to bronchoprotective ID_{50} was used to compute the apparent lung-selectivity index of the test compound. Generally, compounds having an apparent lung-selectivity index greater than about 5 are preferred. In this assay, the compound of Example 3 was identified as having an apparent lung-selectivity index greater than 5.

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 true spirit and scope of the invention. Additionally, to the extent permitted by applicable patent statues 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.

WHAT IS CLAIMED IS:

1. A library comprising compounds of formula I:



I

wherein:

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

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

each of R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f} and R^{1g} is independently hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl;

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

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

each of R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f} and R^{2g} is independently hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl;

W is attached to the 3- or 4-position with respect to the nitrogen atom in the piperidine ring and represents O or NW^a;

W^a is hydrogen or (1-4C)alkyl;

c is 0 or an integer of from 1 to 4;

each R^3 is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, $-OR^{3a}$, $-C(O)OR^{3b}$, $-SR^{3c}$, $-S(O)R^{3d}$, $-S(O)_2R^{3e}$ and $-NR^{3f}R^{3g}$; or two R^3 groups are joined to form (1-3C)alkylene, (2-3C)alkenylene or oxiran-2,3-diyl;

each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^{3e}, R^{3f} and R^{3g} is independently hydrogen or (1-4C)alkyl;

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;

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

R^6 is $-NR^{6a}CR^{6b}(O)$ or $-CR^{6c}R^{6d}OR^{6e}$ and R^7 is hydrogen; or R^6 and R^7 together form $-NR^{7a}C(O)-CR^{7b}=CR^{7c}-$, $-CR^{7d}=CR^{7e}-C(O)-NR^{7f}-$, $-NR^{7g}C(O)-CR^{7h}R^{7i}-CR^{7j}R^{7k}-$ or $-CR^{7l}R^{7m}-CR^{7n}R^{7o}-C(O)-NR^{7p}-$;

each of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} is independently hydrogen or (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 hydrogen or (1-4C)alkyl;

or a salt or stereoisomer thereof.

2. The library of Claim 1, wherein the library contains a compound of formula I in which W is attached to the piperidine ring at the 4-position with respect to the nitrogen atom.

3. The library of Claim 1, wherein the library contains a compound of formula I in which a, b, and c are each 0, and W^a and R^5 are both hydrogen.

4. The library of Claim 1, wherein the library contains a compound of formula I in which W represents O.

5. The library of Claim 1, wherein the library contains a compound of formula I in which 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=CH-C(O)-NH-, $-CH_2-CH_2-C(O)NH-$ or –NHC(O)-CH_2-CH_2-.

6. The library of Claim 1, wherein the library contains a compound of formula I in which R^4 is a divalent group of the formula:

$$-(R^{4a})_d-(A^1)_e-(R^{4b})_f-Q-(R^{4c})_g-(A^2)_h-(R^{4d})_i-$$

wherein

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

R^{4a}, R^{4b}, R^{4c} and R^{4d} 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;

A^1 and A^2 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 substitutents 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, $-S(O)_2$-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy;

Q is selected from a bond, -O-, -C(O)O-, -OC(O)-, -S-, -S(O)-, $-S(O)_2$-, $-N(Q^a)C(O)$-, $-C(O)N(Q^b)$-, $-N(Q^c)S(O)_2$-, $-S(O)_2N(Q^d)$-, $-N(Q^e)C(O)N(Q^f)$-, $-N(Q^g)S(O)_2N(Q^h)$-, $-OC(O)N(Q^i)$-, $-N(Q^j)C(O)O$- and $-N(Q^k)$;

Q^a, Q^b, Q^c, Q^d, Q^e, Q^f, Q^g, Q^h, Q^i, Q^j and Q^k are each independently selected from hydrogen, (1-6C)alkyl, A^3 and (1-4C)alkylene-A^4, 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^{4b} or R^{4c} to which they are attached, form a 4-6 membered azacycloalkylene group;

A^3 and A^4 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 substitutents 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.

7. The library of Claim 6, wherein the library contains a compound of formula I in which R^4 is a divalent group of the formula: $-(R^{4a})_d-$ where R^{4a} is (4-10C)alkylene.

8. The library of Claim 6, wherein the library contains a compound of formula I in which R^4 is $-(CH_2)_8-$, $-(CH_2)_9$, and $-(CH_2)_{10}-$.

9. The library of Claim 6, wherein the library contains a compound of formula I in which R^4 is a divalent group of the formula:

$$-(R^{4a})_d-(A^2)_h-(R^{4d})_i-$$

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

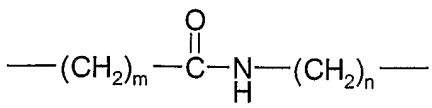
10. The library of Claim 6, wherein the library contains a compound of formula I in which R^4 is a divalent group of the formula:

$$-(R^{4a})_d-Q-(A^2)_h-(R^{4d})_i-$$

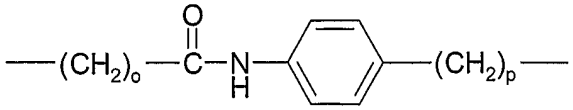
wherein Q is -O- or $-N(Q^k)-$; Q^k is hydrogen or (1-3C)alkyl; R^{4a} is (1-10C)alkylene; A^2 is (6-10C)arylene or (2-9C)heteroarylene; and R^{4d} is (1-10C)alkylene.

11. The library of Claim 6, wherein the library contains a compound of formula I in which Q is $-N(Q^a)C(O)-$ or $-C(O)N(Q^b)-$.

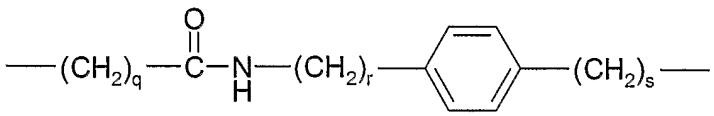
12. The library of Claim 11, wherein the library contains a compound of formula I in which R^4 is selected from:



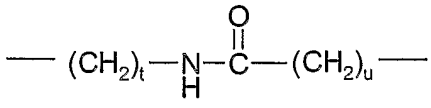
wherein m is an integer from 2 to 10; and n is an integer from 2 to 10; provided that m + n is an integer from 4 to 12;



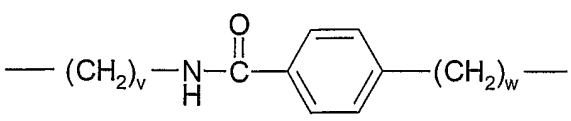
wherein o is an integer from 2 to 7; and p is an integer from 1 to 6; provided that o + p is an integer from 3 to 8; and wherein the phen-1,4-ylene group is optionally substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, –S-(1-4C)alkyl, -S(O)-(1-4C)alkyl, -S(O)$_2$-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy;



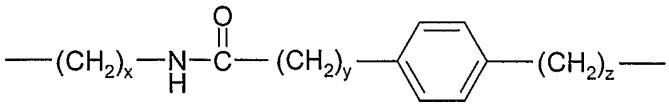
wherein q is an integer from 2 to 6; r is an integer from 1 to 5; and s is an integer from 1 to 5; provided that q + r + s is an integer from 4 to 8; and wherein the phen-1,4-ylene group is optionally substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, –S-(1-4C)alkyl, -S(O)-(1-4C)alkyl, -S(O)$_2$-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy;



wherein t is an integer from 2 to 10; and u is an integer from 2 to 10; provided that t + u is an integer from 4 to 12;

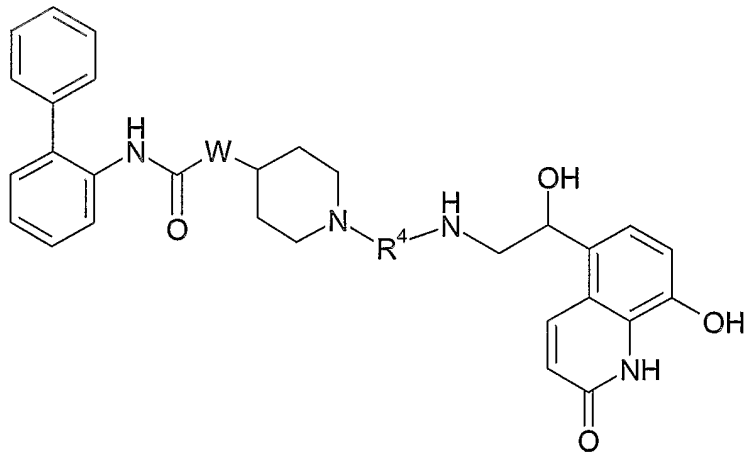


wherein v is an integer from 2 to 7; and w is an integer from 1 to 6; provided that v + w is an integer from 3 to 8; and wherein the phen-1,4-ylene group is optionally substituted with from 1 to 4 substituents independently selected from halo, (1-4C)alkyl, (1-4C)alkoxy, –S-(1-4C)alkyl, -S(O)-(1-4C)alkyl, -$S(O)_2$-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy; and



wherein x is an integer from 2 to 6; y is an integer from 1 to 5; and z is an integer from 1 to 5; provided that x + y + z is an integer from 4 to 8; and wherein the phen-1,4-ylene group is optionally 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, -$S(O)_2$-(1-4C)alkyl, -C(O)O(1-4C)alkyl, carboxy, cyano, hydroxy, nitro, trifluoromethyl and trifluoromethoxy.

13. The library of Claim 1, wherein the library contains a compound of formula II:



II

wherein

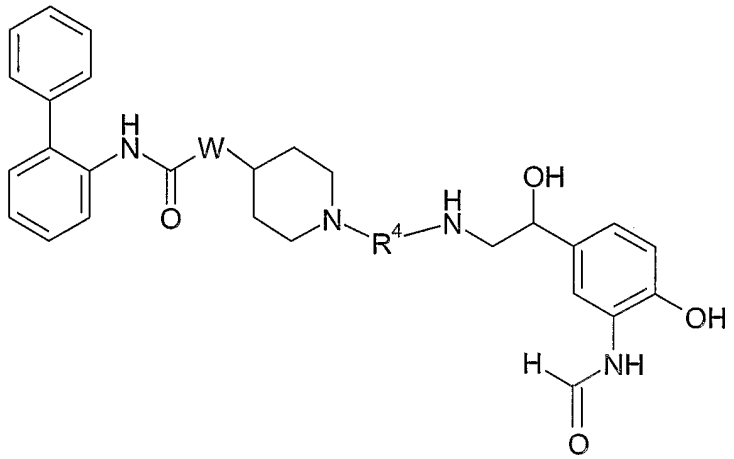
W represents O or NW^a;

W^a is hydrogen or (1-4C)alkyl;

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,

or a salt or stereoisomer thereof.

14. The library of Claim 1, wherein the library contains a compound of formula III:



III

wherein

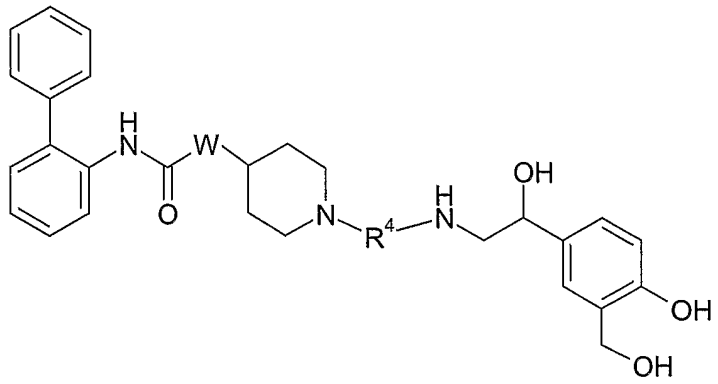
W represents O or NW^a;

W^a is hydrogen or (1-4C)alkyl;

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,

or a salt or stereoisomer thereof.

15. The library of Claim 1, wherein the library contains a compound of formula IV:



IV

wherein

W represents O or NW^a;

W^a is hydrogen or (1-4C)alkyl;

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,

or a salt or stereoisomer thereof.

16. A method of identifying a compound of formula I having both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity; the method comprising:

evaluating the library of any one of Claims 1 to 15 to determine whether a compound of formula I in the library has both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity.

17. A method of identifying a compound of formula I having both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity; the method comprising:

(a) preparing the library of any one of Claims 1 to 15;

(b) evaluating the compounds of formula I in the library to determine whether a compound has both β_2 adrenergic receptor agonist activity and muscarinic receptor antagonist activity.

18. A method of identifying a compound of formula I that binds to a β_2 adrenergic receptor and a muscarinic receptor; the method comprising:

evaluating the library of any one of Claims 1 to 15 to determine whether a compound of formula I in the library has a K_i value of less than about 300 nM for a β_2 adrenergic receptor and a K_i value less than 300 nM for a muscarinic receptor.

19. A method of identifying a compound of formula I that binds to a β_2 adrenergic receptor and a muscarinic receptor; the method comprising:

(a) preparing the library of any one of Claims 1 to 15; and

(b) evaluating the compounds of formula I in the library to determine whether a compound has a K_i value of less than about 300 nM for a β_2 adrenergic receptor and a K_i value less than 300 nM for a muscarinic receptor.

20. A method of identifying a compound of formula I that binds to a β_2 adrenergic receptor and a muscarinic receptor; the method comprising:

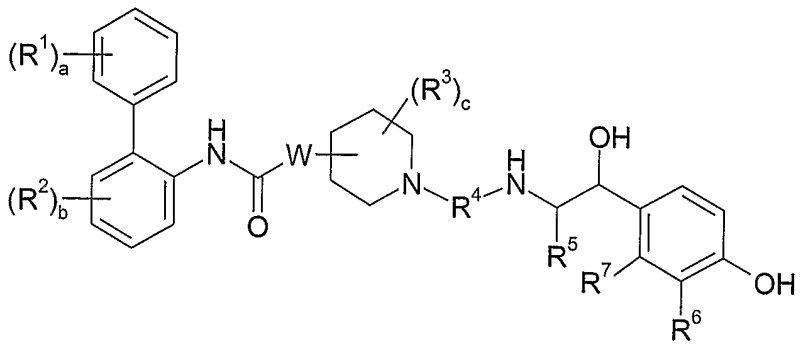
evaluating the library of any one of Claims 1 to 15 to determine whether a compound of formula I in the library has an EC_{50} value of less than about 100 nM for a β_2 adrenergic receptor and a K_i value less than 100 nM for a muscarinic receptor.

21. A method of identifying a compound of formula I that binds to a β_2 adrenergic receptor and a muscarinic receptor; the method comprising:

(a) preparing the library of any one of Claims 1 to 15;

(b) evaluating the compounds of formula I in the library to determine whether a compound has a EC_{50} value of less than about 100 nM for a β_2 adrenergic receptor and a K_i value less than 100 nM for a muscarinic receptor.

22. A process for preparing a library comprising compounds of formula I:



I

wherein:

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

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

each of R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{1f} and R^{1g} is independently hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl;

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

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

each of R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f} and R^{2g} is independently hydrogen, (1-4C)alkyl or phenyl-(1-4C)alkyl;

W is attached to the 3- or 4-position with respect to the nitrogen atom in the piperidine ring and represents O or NW^a;

W^a is hydrogen or (1-4C)alkyl;

c is 0 or an integer of from 1 to 4;

each R^3 is independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, $-OR^{3a}$, $-C(O)OR^{3b}$, $-SR^{3c}$, $-S(O)R^{3d}$, $-S(O)_2R^{3e}$ and $-NR^{3f}R^{3g}$; or two R^3 groups are joined to form (1-3C)alkylene, (2-3C)alkenylene or oxiran-2,3-diyl;

each of R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^{3e}, R^{3f} and R^{3g} is independently hydrogen or (1-4C)alkyl;

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;

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

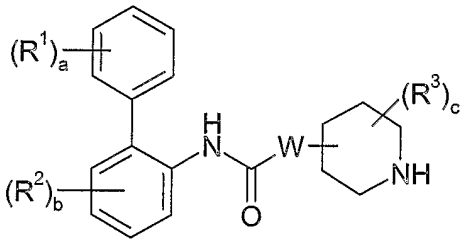
R^6 is $-NR^{6a}CR^{6b}(O)$ or $-CR^{6c}R^{6d}OR^{6e}$ and R^7 is hydrogen; or R^6 and R^7 together form $-NR^{7a}C(O)-CR^{7b}=CR^{7c}-$, $-CR^{7d}=CR^{7e}-C(O)-NR^{7f}-$, $-NR^{7g}C(O)-CR^{7h}R^{7i}-CR^{7j}R^{7k}-$ or $-CR^{7l}R^{7m}-CR^{7n}R^{7o}-C(O)-NR^{7p}-$;

each of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} is independently hydrogen or (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 hydrogen or (1-4C)alkyl;

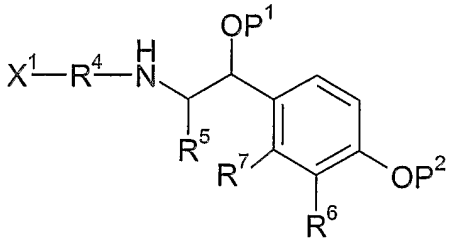
or a stereoisomer thereof; the process comprising:

(a) reacting a compound of formula **1**:



1

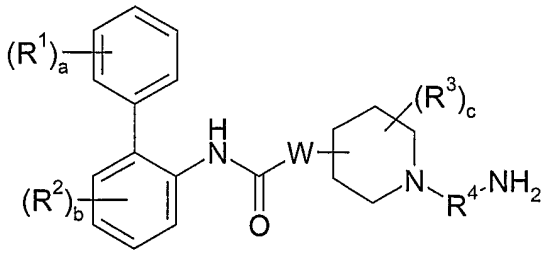
or a salt thereof; with a compound of formula **2**:



2

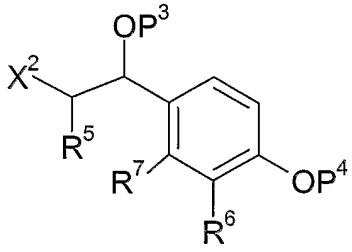
wherein X^1 represents a leaving group, and P^1 and P^2 each independently represent a hydrogen atom or a hydroxyl-protecting group;

(b) reacting a compound of formula **3**:



3

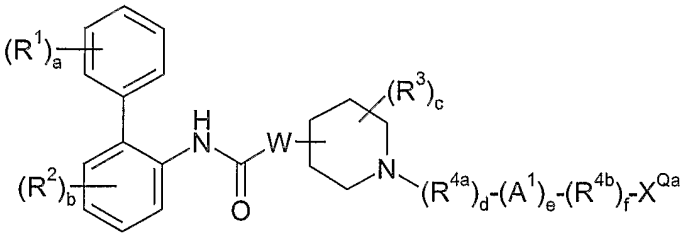
or salt thereof; with a compound of formula 4:



4

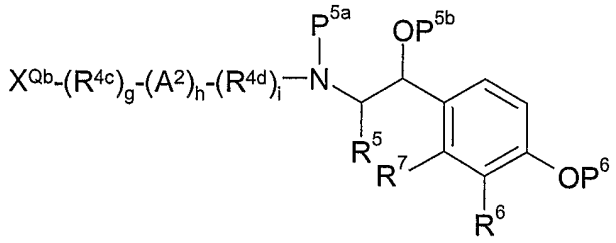
wherein X^2 represents a leaving group, and P^3 and P^4 each independently represent a hydrogen atom or a hydroxyl-protecting group;

(c) coupling a compound of formula 5:



5

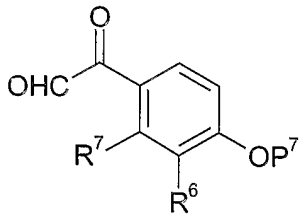
with a compound of formula **6**:



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;

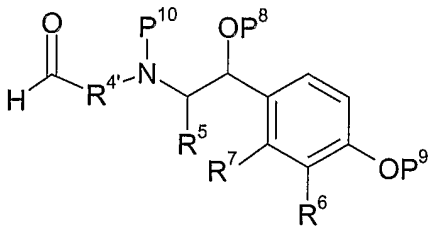
(d) for a compound of formula I wherein R^5 represents a hydrogen atom, reacting a compound of formula **3** with a compound of formula **7**:



7

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;

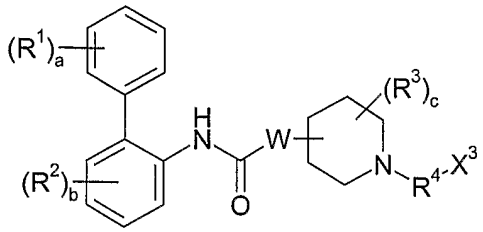
(e) reacting a compound of formula **1** with a compound of formula **8**:



8

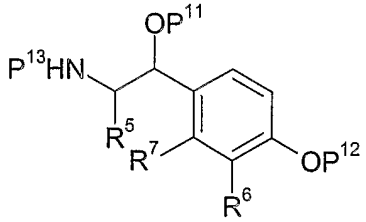
or a hydrate thereof, in the presence of a reducing agent, wherein P^8 and P^9 each independently represent a hydrogen atom or a hydroxyl-protecting group, P^{10} represents a hydrogen atom or an amino-protecting group, and $R^{4'}$ represents a residue that, together with the carbon to which it is attached,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

(f) reacting a compound of formula **9**:



9

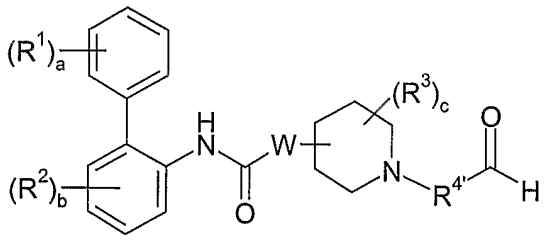
wherein X^3 represents a leaving group, with a compound of formula **10**:



10

wherein P^{11} and P^{12} each independently represent a hydrogen atom or a hydroxyl-protecting group, and P^{13} represents a hydrogen atom or an amino-protecting group; or

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



11

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

(h) removing any protecting groups to form a compound of formula I;

(i) repeating step (a), (b), (c), (d), (e), (f) or (g) and step (h) to prepare a library comprising compounds of formula I.