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(54) Title: DIARYL ETHER β_2 ADRENERGIC RECEPTOR AGONISTS

(57) Abstract: The invention provides novel Diaryl Ether derivatives as beta2 adrenergic receptor agonists. The invention also provides pharmaceutical compositions comprising such compounds, methods of using such compounds to treat diseases associated with beta2 adrenergic receptor activity, and processes and intermediates useful for preparing such compounds.

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Diaryl Ether β_2 Adrenergic Receptor Agonists

Field of the Invention

The invention is directed to novel β_2 adrenergic receptor agonists. The invention is also directed to pharmaceutical compositions comprising such compounds, methods of using such compounds to treat diseases associated with β_2 adrenergic receptor activity, and processes and intermediates useful for preparing such compounds.

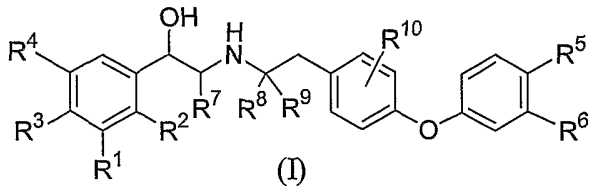
Background of the Invention

β_2 Adrenergic receptor agonists are recognized as effective drugs for the treatment of pulmonary diseases such as asthma and chronic obstructive pulmonary disease (including chronic bronchitis and emphysema). β_2 Adrenergic receptor agonists are also useful for treating pre-term labor, and are potentially useful for treating neurological disorders and cardiac disorders. In spite of the success that has been achieved with certain β_2 adrenergic receptor agonists, current agents possess less than desirable duration of action, potency, selectivity, and/or onset. Thus, there is a need for new β_2 adrenergic receptor agonists having improved properties, such as improved duration of action, potency, selectivity, and/or onset.

Summary of the Invention

The invention provides novel compounds that possess β_2 adrenergic receptor agonist activity. Among other properties, compounds of the invention are potent and selective β_2 adrenergic receptor agonists.

Accordingly, this invention provides a compound of formula (I):



(I)

wherein:

each of R^1, R^2, R^3, and R^4 is independently selected from hydrogen, hydroxy, amino, halo, -CH_2OH and -NHCHO, or R^1 and R^2 taken together are selected from -NHC(=O)CH=CH-, -CH=CHC(=O)NH-, -NHC(=O)S-, and –SC(=O)NH-;

R^5 and R^6 are independently selected from hydrogen, hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, -O-C_{1-6}alkylenyl-NR^aR^b; -O-C_{1-4}alkylenyl-O-C_{1-4}alkylenyl-NR^aR^b, -$SO_2NR^aR^b$, -NR^cR^d, phenyl, and heteroaryl; provided that R^5 and R^6 are not both hydrogen; wherein each phenyl is optionally substituted with 1 or 2 substituents selected from R^f; each heteroaryl is optionally substituted with 1 or 2 substituents selected from R^g; and each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

R^7 is hydrogen or C_{1-6}alkyl;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is hydrogen or C_{1-6}alkyl;

R^{10} is selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, aryl, heteroaryl, cycloalkyl, and heterocyclyl; or R^9 together with R^{10} is -CH_2- or -CH_2CH_2-;

R^a, R^b, R^c, R^d, and R^e are each independently hydrogen or C_{1-6} alkyl, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from hydroxy, C_{1-6}alkoxy, and amino; or R^a and R^b, or R^c and R^d together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclic ring having from 4 to 7 ring atoms, and containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R^f is selected from hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -C(=O)OH, -CN, -NO_2, -C(=O)R^e, -SO_2-C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, and -C(=O)NR^aR^b, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino; and

R^g is C_{1-6}alkyl or oxo, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

The invention also provides a pharmaceutical composition comprising a a pharmaceutically-acceptable carrier and a therapeutically effective amount of a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof. The pharmaceutical compositions of the invention optionally further comprises a therapeutically effective amount of one or more other therapeutic agents. Suitable additional agents include anti-inflammatory agents (e.g., corticosteroids and non-steroidal anti-inflammatory agents (NSAIDs)), anticholinergic agents (particularly muscarinic receptor antagonists), other β_2 adrenergic receptor agonists, antiinfective agents (e.g., antibiotics or antiviral), antihistamines, and a phosphodiesterase 4 (PDE4) inhibitor.

The invention further provides combinations comprising a compound of the invention and one or more other therapeutic agents and pharmaceutical compositions comprising such combinations and a pharmaceutically-acceptable carrier.

The invention also provides a method of treating a a mammal having a disease or condition associated with β_2 adrenergic receptor activity, (e.g. a pulmonary disease, such as asthma or chronic obstructive pulmonary disease, pre-term labor, a neurological disorder, a cardiac disorder, or inflammation), the method comprising administering to the mammal, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof. The invention further provides a method of treatment comprising administering a therapeutically effective amount of a compound of the invention with a therapeutically effective amount of one or more other therapeutic agents.

The invention also provides a method of treating a a mammal having a disease or condition associated with β_2 adrenergic receptor activity, the method comprising administering to the mammal, a therapeutically effective amount of a pharmaceutical composition of the invention.

The compounds of the invention can also be used as research tools, i.e. to study biological systems or samples, or for studying the activity of other chemical compounds. Accordingly, in another of its method aspects, the invention provides a method of using a compound of formula (I), or a pharmaceutically-acceptable salt or solvate or stereoisomer

thereof, as a research tool for studying a biological system or sample or for discovering new β_2 adrenergic receptor agonists.

In separate and distinct aspects, the invention also provides synthetic processes and novel intermediates, including compounds of formula (III) and (IV) described herein, which are useful for preparing compounds of the invention.

The invention also provides a compound of the invention as described herein for use in medical therapy, as well as the use of a compound of the invention in the manufacture of a formulation or medicament for treating a mammal having a disease or condition associated with β_2 adrenergic receptor activity, (e.g. a pulmonary disease, such as asthma or chronic obstructive pulmonary disease, pre-term labor, a neurological disorder, a cardiac disorder, or inflammation).

Detailed Description of the Invention

The invention provides novel diaryl ether β_2 adrenergic receptor agonists of formula (I), or pharmaceutically-acceptable salts or solvates or stereoisomers thereof. The following substituents and values are intended to provide representative examples of various aspects of the invention. These representative values are intended to further define such aspects and are not intended to exclude other values or limit the scope of the invention.

In specific aspects of the invention, R^1 is halo, $-CH_2OH$, or –NHCHO; or R^1 is chloro, $-CH_2OH$, or –NHCHO.

In another specific aspect, R^1 is $-CH_2OH$ or –NHCHO.

In a specific aspect, R^2 is hydrogen.

In a specific aspect, R^1 and R^2 taken together are -NHC(=O)CH=CH-, -CH=CHC(=O)NH-, -NHC(=O)S-; or –SC(=O)NH-.

In another specific aspect, R^1 and R^2 taken together are -NHC(=O)CH=CH- or -CH=CHC(=O)NH-.

In a specific aspect, R^1 is $-CH_2OH$ or –NHCHO, and R^2 is hydrogen; or R^1 and R^2 taken together are -NHC(=O)CH=CH-, -CH=CHC(=O)NH-, -NHC(=O)S-, or -SC(=O)NH-.

In a specific aspect, R^3 is hydroxy or amino.

In another specific aspect, R^3 is hydroxy.

In specific aspects, R^4 is hydrogen or halo; or R^4 is hydrogen or chloro. In another specific aspect, R^4 is hydrogen.

In a specific aspect, R^1 is -NHCHO, R^3 is hydroxy, and R^2 and R^4 are each hydrogen.

In another specific aspect, R^1 is $-CH_2OH$, R^3 is hydroxy, and R^2 and R^4 are each hydrogen.

In another specific aspect, R^1 and R^2 taken together are -NHC(=O)CH=CH- or -CH=CHC(=O)NH-, R^3 is hydroxy, and R^4 is hydrogen.

In another specific aspect, R^1 and R^2 taken together are -NHC(=O)S- or -SC(=O)NH-; R^3 is hydroxy, and R^4 is hydrogen.

In yet another specific aspect, R^1 and R^4 are chloro, R^3 is amino, and R^2 is hydrogen.

In a specific aspect, R^5 is selected from hydrogen, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, -O-C_{1-6}alkylenyl-NR^aR^b, -$SO_2NR^aR^b$, and -NR^cR^d, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino.

In another specific aspect, R^5 is selected from hydrogen, hydroxy, C_{1-3}alkoxy, C_{1-4}alkyl, -C_{1-4}alkylenyl-NR^aR^b, -O-C_{1-4}alkylenyl-NR^aR^b, -$SO_2NR^aR^b$, and - NR^cR^d.

In yet another specific aspect, R^5 is selected from hydrogen, hydroxy, methoxy, ethoxy, methyl, ethyl, $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, $-CH_2C(CH_3)_2NH_2$, $-(CH_2)_2N(CH_3)_2$, $-O(CH_2)_2NH_2$, $-O(CH_2)_3NH_2$, $-OCH_2C(CH_3)_2NH_2$, $-O(CH_2)_4NH_2$, 4-morpholinylethoxy, and 4-piperazinylethoxy.

In a specific aspect, R^6 is heteroaryl, optionally substituted with 1 or 2 substituents selected from R^g. In another specific aspect, R^6 is furyl, thienyl, pyrrolyl, or pyridyl, optionally substituted with 1 or 2 methyl substituents.

In another specific aspect, R^6 is phenyl, optionally substituted with 1 or 2 substituents selected from R^f.

In another specific aspect, R^6 is hydrogen.

In yet another specific aspect, R^6 is $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, $-CH_2C(CH_3)_2NH_2$, or $-(CH_2)_2N(CH_3)_2$.

In a specific aspect of the invention, R^5 and R^6 are each independently selected from hydrogen, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, -O-C_{1-6}alkylenyl-NR^aR^b; -NR^cR^d, phenyl, and heteroaryl; provided that R^5 and R^6 are not

both hydrogen; wherein each phenyl is optionally substituted with 1 or 2 substituents selected from R^f; each heteroaryl is optionally substituted with 1 or 2 substituents selected from R^g; and each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino.

In another aspect, R^5 and R^6 are each independently selected from hydrogen, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, -O-C_{1-6}alkylenyl-NR^aR^b, and -NR^cR^d; provided that R^5 and R^6 are not both hydrogen; wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino.

In another specific aspect, one of R^5 and R^6 is selected from furyl, thienyl, pyrrolyl, and pyridyl; wherein furyl, thienyl, pyrrolyl, and pyridyl are optionally substituted with 1 or 2 methyl substituents; and the other of R^5 and R^6 is hydrogen or C_{1-6}alkoxy.

In yet another aspect, R^5 and R^6 are each independently selected from hydrogen, hydroxy, methoxy, ethoxy, methyl, ethyl, $-CF_3$, $-O(CH_2)_2NH_2$, $-O(CH_2)_3NH_2$, $-OCH_2C(CH_3)_2NH_2$, $-O(CH_2)_4NH_2$, $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, $-CH_2C(CH_3)_2NH_2$, $-(CH_2)_2N(CH_3)_2$, 4-morpholinylethoxy, 4-piperazinylethoxy, phenyl, furyl, thienyl, pyrrolyl, and pyridyl; provided that R^5 and R^6 are not both hydrogen; wherein each phenyl is optionally substituted with 1 or 2 substituents selected from R^f; and each furyl, thienyl, pyrrolyl, and pyridyl is optionally substituted with 1 or 2 substituents selected from R^g.

In another aspect, one of R^5 and R^6 is selected from $-O(CH_2)_2NH_2$, $-O(CH_2)_3NH_2$, $-OCH_2C(CH_3)_2NH_2$, $-O(CH_2)_4NH_2$, $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, $-CH_2C(CH_3)_2NH_2$, $-(CH_2)_2N(CH_3)_2$, 4-morpholinylethoxy, and 4-piperazinylethoxy; and the other of R^5 and R^6 is selected from hydrogen, methoxy, ethoxy, $-CF_3$, and methyl.

In another specific aspect, R^5 is selected from $-O(CH_2)_2NH_2$, $-O(CH_2)_3NH_2$, $-OCH_2C(CH_3)_2NH_2$, $-O(CH_2)_4NH_2$, $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, $-CH_2C(CH_3)_2NH_2$, $-(CH_2)_2N(CH_3)_2$, 4-morpholinylethoxy, and 4-piperazinylethoxy; and R^6 is hydrogen, methoxy, ethoxy, $-CF_3$, and methyl.

In another specific aspect, R^5 is hydrogen; and R^6 is selected from $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, $-CH_2C(CH_3)_2NH_2$, and $-(CH_2)_2N(CH_3)_2$.

In still another specific aspect, R^5 is selected from hydrogen, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, and -O-C_{1-6}alkylenyl-NR^aR^b; wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy,

and amino; and R^6 is selected from phenyl optionally substituted with 1 or 2 substituents selected from R^f, and heteroaryl, optionally substituted with 1 or 2 substituents selected from R^g. Within this group of compounds, a specific value for R^6 is phenyl optionally substituted with 1 or 2 substituents selected from R^f.

In another specific aspect, R^5 is selected from hydrogen, hydroxy, methoxy, ethoxy, methyl, and ethyl; and R^6 is selected from phenyl, furyl, thienyl, pyrrolyl, and pyridyl; wherein phenyl is optionally substituted with 1 or 2 substituents selected from R^f, and furyl, thienyl, pyrrolyl, and pyridyl are optionally substituted with 1 or 2 substituents selected from R^g. For example, R^5 is selected from hydrogen, methoxy, and ethoxy, and R^6 is phenyl optionally substituted with 1 or 2 substituents selected from R^f.

In a specific aspect, R^7 is hydrogen or C_{1-3}alkyl. In another specific aspect, R^7 is hydrogen.

In a specific aspect, R^8 is hydrogen or C_{1-3}alkyl. In another specific aspect, R^8 is hydrogen.

In a specific aspect, R^9 is hydrogen or C_{1-3}alkyl, such as methyl. In another specific aspect, R^9 is hydrogen.

In a specific aspect, when R^{10} is at the 3 position of the phenyl ring relative to the oxygen atom to which the phenyl ring is attached, R^9 together with R^{10} is $-CH_2-$ or $-CH_2CH_2-$.

In a specific aspect, R^{10} is hydrogen, chloro, bromo, C_{1-4}alkyl, C_{1-4}alkoxy, or R^9 together with R^{10} is $-CH_2-$ or $-CH_2CH_2-$.

In another specific aspect, R^{10} is hydrogen.

In a specific aspect, each of R^4, R^7, R^8, R^9, and R^{10} are hydrogen.

In a specific aspect, R^a, R^b, R^c, R^d, and R^e are each independently hydrogen or C_{1-4}alkyl, wherein each C_{1-4}alkyl is optionally substituted with 1 to 3 substituents selected from hydroxy, C_{1-6}alkoxy, and amino.

In another specific aspect, R^a and R^b, or R^c and R^d together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclic ring having from 4 to 7 ring atoms, and containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

In yet another specific aspect, R^a, R^b, R^c, R^d, and R^e are each independently hydrogen, methyl or ethyl; or R^a and R^b, or R^c and R^d together with the nitrogen atom to which they are attached form piperidine, piperazine, morpholine, pyrrolidine or pyridine.

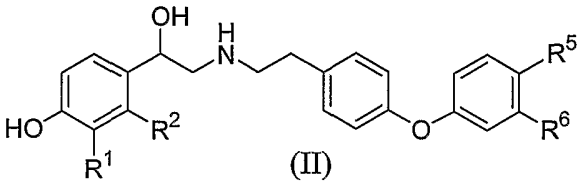
In a specific aspect, R^f is selected from hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, -C(=O)OH, -CN, $-NO_2$, $-C(=O)R^e$, $-C_{1-6}$alkylenyl-NR^aR^b, and $-C(=O)NR^aR^b$; wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino.

In another specific aspect, R^f is selected from hydroxy, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, isopropyl, hydroxymethyl, -C(=O)OH, -C(=O)H, $-C(=O)CH_3$, -CN, $-NO_2$, $-CH_2NH_2$, $-CH_2N(CH_3)_2$, $-CH_2NHCH(CH_3)_2$, $-C(CH_3)_2NH_2$, $-(CH_2)_2NH_2$, 4-morpholinylmethyl, 4-piperazinylmethyl, 1-piperidinylmethyl, and $-C(=O)NH_2$.

In a specific aspect, R^g is C_{1-4}alkyl or oxo, wherein each C_{1-4}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-4}alkoxy, and amino.

In another specific aspect, R^g is methyl or oxo. In yet another specific aspect, R^g is methyl.

In one aspect, the invention provides a compound of formula (II):



(II)

wherein:

R^1 is $-CH_2OH$ or –NHCHO, and R^2 is hydrogen; or R^1 and R^2 taken together are -NHC(=O)CH=CH-, -CH=CHC(=O)NH-, -NHC(=O)S-, or –SC(=O)NH-; and

R^5 and R^6 are as defined herein.

In another aspect, the invention provides a compound of formula (II) wherein:

R^5 and R^6 are each independently selected from hydrogen, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, $-C_{1-6}$alkylenyl-NR^aR^b, $-O-C_{1-6}$alkylenyl-NR^aR^b; $-NR^cR^d$, phenyl, and heteroaryl; provided that R^5 and R^6 are not both hydrogen; wherein each phenyl is optionally substituted with 1 or 2 substituents selected from R^f; each heteroaryl is optionally substituted with 1 or 2 substituents selected from R^g; and each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

R^a, R^b, R^c, R^d, and R^e are each independently hydrogen or C_{1-6} alkyl, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from hydroxy, C_{1-6}alkoxy, and amino; or R^a and R^b, or R^c and R^d together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclic ring having from 4 to 7 ring atoms, and containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R^f is selected from hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, -C(=O)OH, -CN, $-NO_2$, $-C(=O)R^e$, $-C_{1-6}$alkylenyl-NR^aR^b, and $-C(=O)NR^aR^b$; wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino; and

R^g is selected from C_{1-6}alkyl, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

A specific group of compounds within this aspect is the group of compounds of formula (II) wherein R^1 is $-CH_2OH$, and R^2 is hydrogen.

Another specific group of compounds within this aspect is the group of compounds of formula (II) wherein R^1 is –NHCHO, and R^2 is hydrogen.

Yet another specific group of compounds within this aspect is the group of compounds of formula (II) wherein R^1 and R^2 taken together are -NHC(=O)CH=CH- or -CH=CHC(=O)NH-.

Yet another specific group of compounds of formula (II) is the group wherein R^1 and R^2 taken together are -NHC(=O)CH=CH-, or -CH=CHC(=O)NH-; R^5 is hydrogen, methoxy or ethoxy; and R^6 is phenyl optionally substituted with 1 or 2 substituents selected from R^f.

Particular mention may be made of the following compounds:

8-hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(6-methoxybiphenyl-3-yloxy)phenyl]-ethylamino}ethyl)-1*H*-quinolin-2-one;

5-((*R*)-2-{2-[4-(biphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[4-(2-amino-2-methylpropoxy)phenoxy]phenyl}ethyl-amino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[3-(3-aminopropyl)-4-methoxyphenoxy]phenyl}ethyl-amino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[4-(2-aminoethoxy)-3-trifluoromethylphenoxy]phenyl}-ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[4-(3-aminopropoxy)phenoxy]phenyl}ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-{(*R*)-2-[2-(4-{4-[2-(2-aminoethoxy)ethoxy]phenoxy}phenyl)ethyl-amino]-1-hydroxyethyl}-8-hydroxy-1*H*-quinolin-2-one;

8-hydroxy-5-[(*R*)-1-hydroxy-2-(2-{4-[4-(2-morpholin-4-ylethoxy)-phenoxy]phenyl}ethylamino)ethyl]-1*H*-quinolin-2-one;

8-hydroxy-5-[(*R*)-1-hydroxy-2-(2-{4-[4-(2-piperazin-1-ylethoxy)phenoxy]-phenyl}ethylamino)ethyl]-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[3-(2-dimethylaminoethyl)-4-methoxyphenoxy]phenyl}-ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-((*R*)-2-{2-[4-(4'-chlorobiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

8-hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(4'-methoxybiphenyl-3-yloxy)phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one;

3'-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydro-quinolin-5-yl)ethylamino]ethyl}phenoxy)biphenyl-3-carbonitrile;

8-hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(4-morpholin-4-yl-phenoxy)-phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[3'-(2-aminoethyl)-6-methoxybiphenyl-3-yloxy]phenyl}-ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

8-hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(6-methoxy-3'-morpholin-4-ylmethylbiphenyl-3-yloxy)phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one;

N-[5-((*R*)-2-{2-[4-(biphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

N-{5-[(*R*)-2-(2-{4-[4-(2-aminoethoxy)phenoxy]phenyl}ethylamino)-1-hydroxyethyl]-2-hydroxyphenyl}formamide;

N-{5-[(*R*)-2-(2-{4-[3-(2-dimethylaminoethyl)-4-methoxyphenoxy]phenyl}-ethylamino)-1-hydroxyethyl]-2-hydroxyphenyl}formamide;

4-((*R*)-2-{2-[4-(biphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-2-hydroxymethylphenol;

4-((*R*)-2-{2-[4-(2'-amino-3'-ethyl-6-methoxybiphenyl-3-yloxy)phenyl]-ethylamino}-1-hydroxyethyl)-2-hydroxymethylphenol;

2-hydroxymethyl-4-((*R*)-1-hydroxy-2-{2-[4-(4-morpholin-4-ylphenoxy)phenyl]ethylamino}ethyl)phenol;

where the chemical nomenclature conforms to that of the automatic naming program AutoNom, as provided by MDL Information Systems, GmbH (Frankfurt, Germany).

Particular mention may also be made of the following compounds:

5-(2-{2-[4-(3'-chloro-6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

5'-(4-{2-[2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenoxy)-2'-methoxybiphenyl-3-carbonitrile;

5-(2-{2-[4-(3'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

5-(2-{2-[4-(4'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

N-[5-(2-{2-[4-(3'-chloro-6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

N-[5-(2-{2-[4-(3'-cyano-6-methoxybiphenyl-3-yloxy)phenyl]ethyl-amino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

N-[5-(2-{2-[4-(3'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]-ethylamino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

N-[5-(2-{2-[4-(4'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]-ethylamino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

4-(2-{2-[4-(3'-chloro-6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-2-hydroxymethylphenol;

5'-(4-{2-[2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethylamino]-ethyl}phenoxy)-2'-methoxybiphenyl-3-carbonitrile;

4-(2-{2-[4-(3'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-2-hydroxymethylphenol; and

4-(2-{2-[4-(4'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-2-hydroxymethylphenol.

As illustrated above, the compounds of the invention contain one or more chiral centers. Accordingly, the invention includes racemic mixtures, pure stereoisomers (i.e. individual enantiomers or diastereomers), and stereoisomer-enriched mixtures of such isomers, unless otherwise indicated. When a particular stereoisomer is shown, 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 the invention contain a chiral center at the alkylene carbon in formulas (I) and (II) to which the hydroxy group is attached. When a mixture of stereoisomers is employed, it is advantageous for the amount of the stereoisomer with the (*R*) orientation at the chiral center bearing the hydroxy group to be greater than the amount of the corresponding (*S*) stereoisomer. When comparing stereoisomers of the same compound, the (*R*) stereoisomer is preferred over the (*S*) stereoisomer.

Definitions

When describing the compounds, compositions and methods of the 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 or combinations thereof. Representative alkyl groups include, by way of example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, *n*-hexyl, and the like.

When a specific number of carbon atoms is intended for a particular term used herein, the number of carbon atoms is shown preceding the term. For example, the term "C_{1-6}alkyl" means an alkyl group having from 1 to 6 carbon atoms.

The term "alkoxy" means the monovalent group –O-alkyl, where alkyl is defined as above. Representative alkoxy groups include, by way of example, methoxy, ethoxy, propoxy, butoxy, and the like.

The term "alkenyl" means a monovalent unsaturated hydrocarbon group containing at least one carbon-carbon double bond, typically 1 or 2 carbon-carbon double bonds, and which may be linear or branched or combinations thereof. Representative alkenyl groups include, by way of example, vinyl, allyl, isopropenyl, but-2-enyl, *n*-pent-2-enyl, and *n*-hex-2-enyl, and the like.

The term "alkynyl" means a monovalent unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, typically 1 carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Representative alkynyl groups include, by way of example, ethynyl, propargyl, but-2-ynyl and the like.

The term "alkylenyl" means a divalent saturated hydrocarbon group which may be linear or branched or combinations thereof. Representative alkylenyl groups include, by way of example, methylene, ethylene, *n*-propylene, *n*-butylene, propane–1,2-diyl (1-methylethylene), 2-methylpropane-1,2-diyl (1,1-dimethylethylene) and the like.

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 "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 "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, and sulfur. Unless otherwise defined, such heteroaryl groups typically contain from 5 to 10 atoms total ring atoms. Representative heteroaryl groups include, by way of example, pyrroyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl (or, equivalently, pyridinyl), oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, quinolyl, indolyl, isoquinolyl and the like, where the point of attachment is at any available carbon or nitrogen ring atom.

The term "heterocyclyl" or "heterocyclic ring" means a monovalent saturated or partially unsaturated cyclic non-aromatic group, which may be monocyclic or multicyclic (i.e., fused or bridged), and which contains at least one heteroatom (typically 1 to 3 heteroatoms) selected from nitrogen, oxygen, and sulfur. Unless otherwise defined, such heterocyclyl groups typically contain from 5 to 10 total ring atoms. Representative heterocyclyl groups include, by way of example, pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, morpholinyl, indolin-3-yl, 2-imidazolinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, quinuclidinyl, and the like.

The term "amino" means $-NH_2$.

The term "oxo" means (=O).

The term "halo" means a fluoro, chloro, bromo or iodo.

The term "compound" means a compound that was synthetically prepared or prepared in any other way, such as by metabolism.

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

The term "treatment" as used herein means the treatment of a disease or medical condition in a patient, such as a mammal (particularly a human) which 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 phrase "disease or condition associated with β_2 adrenergic receptor activity" includes all disease states and/or conditions that are acknowledged now, or that are found in the future, to be associated with β_2 adrenergic receptor activity. Such disease states include, but are not limited to, pulmonary diseases, such as asthma and chronic obstructive pulmonary disease (including chronic bronchitis and emphysema), as well as neurological disorders and cardiac disorders. β_2 Adrenergic receptor activity is also known to be associated with pre-term labor (see United States Patent Number 5,872,126) and some types of inflammation (see International Patent Application Publication Number WO 99/30703 and United States Patent Number 5,290,815).

The term "pharmaceutically-acceptable salt" means a salt prepared from a base or acid which is acceptable for administration to a patient, such as a mammal. 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 acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphosulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, xinafoic (1-hydroxy-2-naphthoic acid) and the like. Salts derived from fumaric, hydrobromic, hydrochloric, acetic, sulfuric, methanesulfonic, xinafoic, and tartaric acids are of particular interest.

Salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic,

manganous, potassium, sodium, zinc and the like. Ammonium, calcium, magnesium, potassium and sodium salts are of particular interest. 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.

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 the invention or a pharmaceutically-acceptable salt thereof, and one or more molecules of a solvent. Such solvates are typically crystalline solids having a substantially fixed molar ratio of solute and solvent. Representative solvents include by way of example, water, methanol, ethanol, isopropanol, acetic acid, and the like. When the solvent is water, the solvate formed is a hydrate.

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

The term "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 "amino-protecting group" means a protecting group suitable for preventing undesired reactions at an amino nitrogen. Representative amino-protecting

groups include, but are not limited to, formyl; acyl groups, for example alkanoyl groups, such as acetyl, trichloroacetyl or trifluoroacetyl; alkoxycarbonyl groups, such as *tert*-butoxycarbonyl (Boc); arylmethoxycarbonyl groups, such as benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc); arylmethyl groups, such as benzyl (Bn), trityl (Tr), and 1,1-di-(4'-methoxyphenyl)methyl; silyl groups, such as trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBS); and the like.

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

General Synthetic Procedures

Compounds of the invention can be prepared from readily available starting materials using the following general methods and procedures. Although a particular aspect of the present invention is illustrated in the schemes below, those skilled in the art will recognize that all 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. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be 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 to prevent certain functional groups from undergoing undesired reactions. For example, when R^5 or R^6 includes an amino or hydroxy group, additional protecting groups may be necessary to prevent these 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, is well known in the art. For example, numerous protecting groups, and their introduction and removal, are

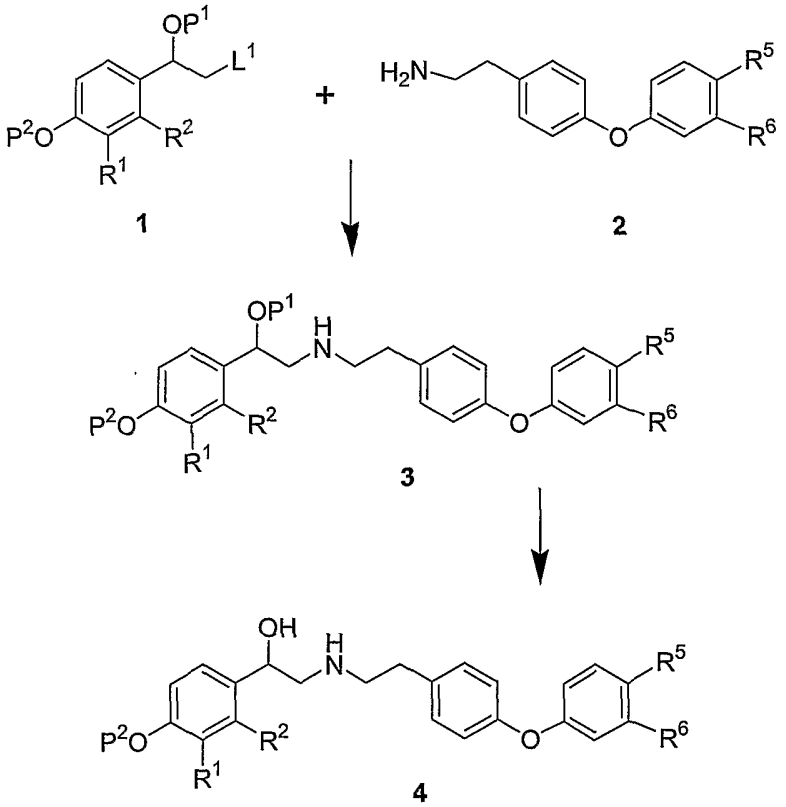
described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

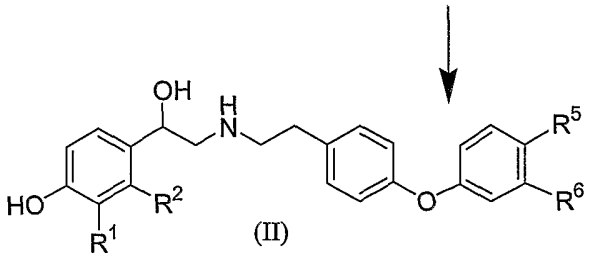
Removal of the protecting groups may be effected using conventional techniques. Typical procedures for the removal of amino-protecting groups and hydroxy-protecting groups include the following. Arylmethyl groups, such as a benzyl protecting group, are conveniently removed by catalytic hydrogenation 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.

The substituents and variables shown in the following synthetic processes or schemes have the definitions provided above unless otherwise indicated.

In one method of synthesis, compounds of formulas (I) and (II) are prepared as illustrated in Scheme A. (The substituents and variables shown in the following schemes have the definitions provided herein unless otherwise indicated.)

Scheme A





(II)

As shown in Scheme A, a compound of formula **1**, (wherein P^1 and P^2 are hydroxy-protecting groups; and L^1 is a leaving group, such as bromide), is reacted with an amine compound of formula **2** to provide an intermediate compound of formula **3**. Typically, this reaction is conducted in a polar aprotic solvent in the presence of a base. Suitable solvents include dimethylsulfoxide, dimethyl formamide, dimethylacetamide and the like. The reaction is typically heated at a temperature of between about 60 °C and about 140 °C for between about 0.25 and about 7 hours.

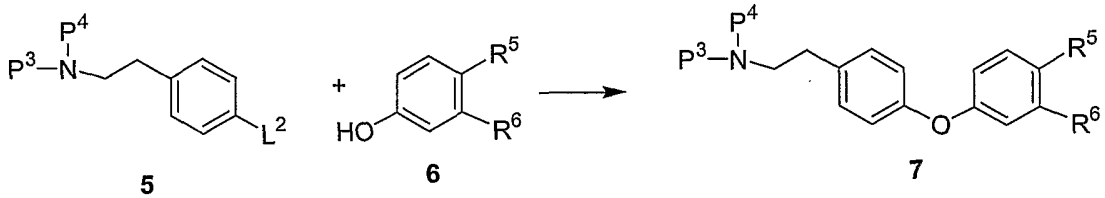
The protecting group P^1 is typically a silyl protecting group, which is typically removed from the intermediate of formula **3** using a fluoride reagent, for example triethylamine trihydrofluoride, or an acid, to provide an intermediate of formula **4**.

The protecting group P^2 is typically a benzyl protecting group, which is typically removed from the intermediate of formula **4** using a Lewis acid, for example, boron trichloride, or by hydrogenation using a palladium on carbon catalyst.

Compounds of formula **1** are readily prepared by procedures known in the art, and are described, for example, in U.S. Patent Nos. 6,653,323 B2 and 6,670,376 B1, which are incorporated herein by reference, and references therein.

Intermediates of formula **2** can be prepared from readily available starting materials, for example, by the procedure illustrated in Scheme B:

Scheme B



5 **6** **7**

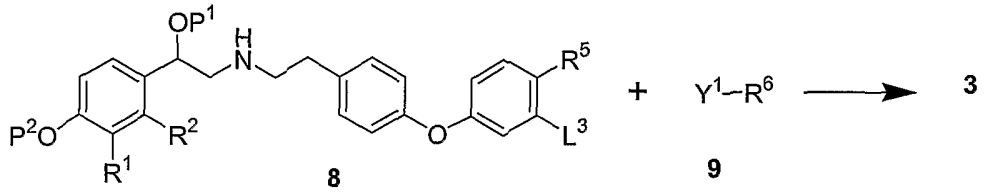
wherein one of P^3 and P^4 is an amino protecting group and the other of P^3 and P^4 is hydrogen, or P^3 and P^4 together with the N atom to which they are attached form an amino

protecting group; and L^2 is a leaving group, such as halo. The protecting groups are removed from intermediate **7** to provide a compound of formula **2**.

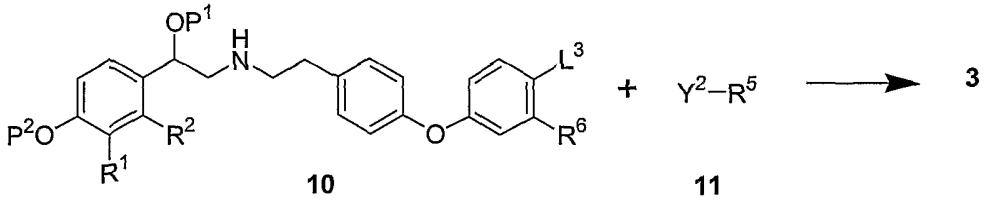
A protected amine **5** is coupled with a substituted phenol **6**, typically in the presence of a base and a catalyst, such as cesium carbonate and copper (I) chloride, to provide an intermediate of formula **7**. Then, the amino-protecting group is removed from the intermediate of formula **7** to provide a compound of formula **2**. For example, when P^3 and P^4 together with the nitrogen atom to which they are attached form a phthalimido group, compound **7** can be reacted with hydrazine in dichloromethane at room temperature to remove the amino-protecting group to provide a compound of formula **2**.

In another method, for example, when one of R^5 and R^6 is phenyl or heteroaryl, a compound of formula **3** can be synthesized as illustrated in Schemes C and D below:

Scheme C

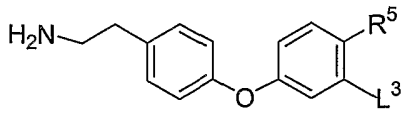


Scheme D



where L^3 is a leaving group, such as halo, and Y^1 and Y^2 are metal coupling agents. The compounds Y^1-R^6 or Y^2-R^5 are, for example, phenyl- or heteroaryl-boronic acid; phenyl- or heteroaryl-trialkyl-tin; phenyl or heteroaryl zinc halide; and phenyl or heteroaryl magnesium halide and the like. These reactions typically make use of a catalyst, such as a transition metal catalyst, such as soluble or insoluble complexes of platinum, palladium or nickel. For example, in Scheme C, when Y^1-R^6 is phenylboronic acid, L^3 can be halo, such as iodo, bromo, or chloro, and a palladium catalyst can be used. Reactions similar to Schemes C and D are described, for example, in US 6,395,916, which is incorporated herein by reference.

A compound of formula **8** can be prepared by reacting a compound of formula **12**:



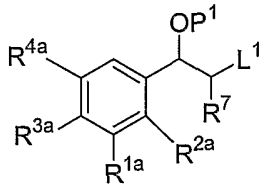
12

wherein L^3 is a leaving group, such as bromo, with a compound of formula **1**. A compound of formula **10** can be made in a similar fashion.

A compound of formula **12** can be prepared by conventional procedures from, a compound of formula **5**. For example, a compound of formula **12** in which R^5 is hydrogen and L^3 is chloro, can be prepared by reacting a compound of formula **5** with 3-chlorophenol, and then removing the amino-protecting group from the resulting product to provide a compound of formula **12**.

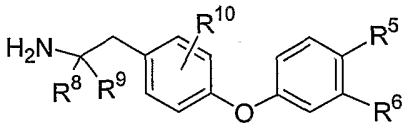
Accordingly, the invention provides a process for preparing a compound of formula (I), the process comprising:

(a) reacting a compound of formula (i):



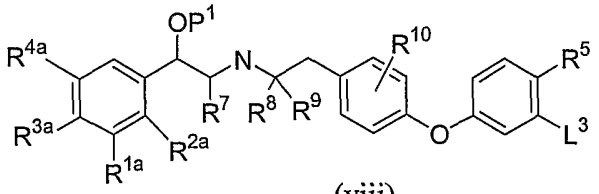
(i)

with a compound of formula (ii):



(ii) ; or

(b) for a compound of formula (I) wherein R^6 is phenyl or heteroaryl, reacting a compound of formula (viii):



(viii)

with a compound of formula (ix):

Y^1–R^6

(ix)

in the presence of a transition metal catalyst;

wherein:

P^1 is a hydroxy-protecting group;

each of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is defined to be the same as R^1, R^2, R^3, and R^4 in formula (I), or one or more of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is independently $-OP^2$, wherein P^2 is a hydroxy-protecting group;

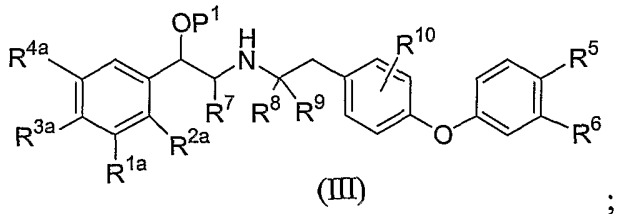
L^1 is a leaving group;

L^3 is a leaving group;

Y^1-R^6 is selected from phenyl- or heteroaryl-boronic acid, phenyl- or heteroaryl-trialkyl-tin, phenyl or heteroaryl zinc halide, and phenyl or heteroaryl magnesium halide; and

R^5, R^6, R^7, R^8, R^9, and R^{10}, are as defined for compounds of formula (I);

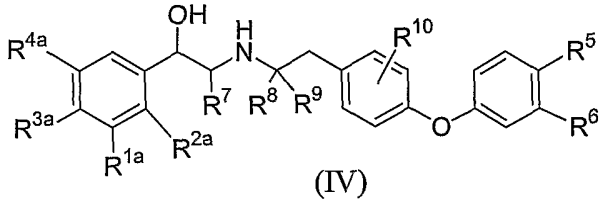
to provide a compound of formula (III):



(III)

;

removing the protecting group P^1 to provide a compound of formula (IV):



(IV)

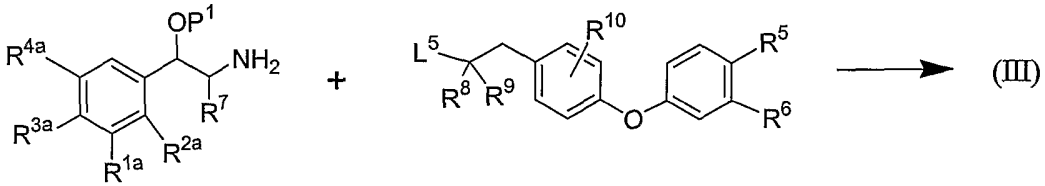
; and

when one or more of R^{1a}, R^{2a}, R^{3a}, and R^{4a} are $-OP^2$, removing the protecting groups P^2;

to provide a compound of formula (I), or a salt thereof.

Another method of preparing a compound of formula (III) is illustrated in Scheme E.

Scheme E

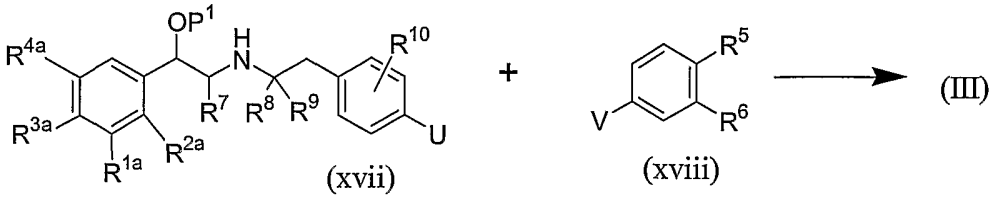


(xv) (xvi)

wherein L^5 is a leaving group.

Alternatively, a compound of formula (III) can be prepared, as illustrated in Scheme F, by reacting a compound of formula (xvii) with a compound of formula (xviii):

Scheme F



(xvii) (xviii) (III)

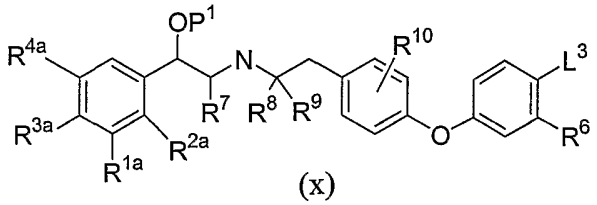
where one of U and V is a leaving group, such as chloro or fluoro, and the other of U and V is a hydroxy group. For Scheme F, the hydroxy group of the phenol becomes a phenoxy anion in the presence of a base.

Accordingly, the invention also provides a process for preparing a compound of formula (I), the process comprising:

(a) reacting a compound of formula (i) with a compound of formula (ii);

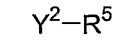
(b) for a compound of formula (I) wherein R^6 is phenyl or heteroaryl, reacting a compound of formula (viii) with a compound of formula (ix) in the presence of a transition metal catalyst,;

(c) for a compound of formula (I) wherein R^5 is phenyl or heteroaryl, reacting a compound of formula (x):



(x)

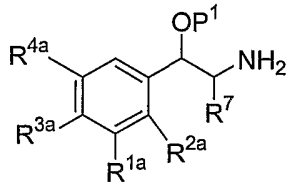
with a compound of formula (xi):



(xi)

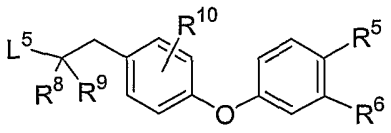
in the presence of a transition metal catalyst,

(d) reacting a compound of formula (xv):



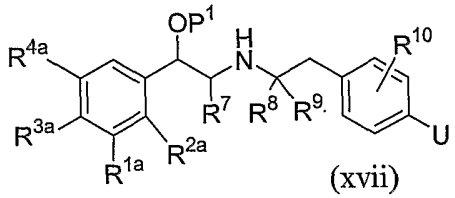
(xv) ;

with a compound of formula (xvi):



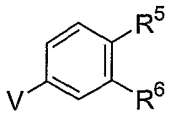
(xvi) ; or

(e) reacting a compound of formula (xvii):



(xvii)

with a compound of formula (xviii):



(xviii)

wherein:

P^1 is a hydroxy-protecting group;

each of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is defined to be the same as R^1, R^2, R^3, and R^4 in formula (I), or one or more of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is independently -OP^2, wherein P^2 is a hydroxy-protecting group;

L^1 is a leaving group;

L^3 is a leaving group;

L^5 is a leaving group;

one of U and V is a leaving group, and the other of U and V is a hydroxy group;

Y^1-R^6 and Y^2-R^5 are independently selected from phenyl- or heteroaryl-boronic acid, phenyl- or heteroaryl-trialkyl-tin, phenyl or heteroaryl zinc halide, and phenyl or heteroaryl magnesium halide; and

R^5, R^6, R^7, R^8, R^9, and R^{10}, are as defined for compounds of formula (I);

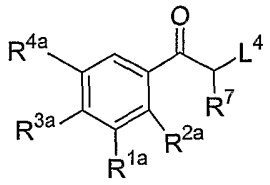
to provide a compound of formula (III); and

removing the protecting group P^1 and any P^2 protecting groups that are present, to provide a compound of formula (I), or a salt thereof.

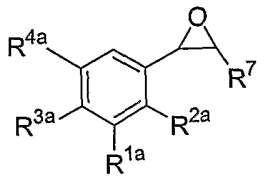
The invention also provides a process for preparing a compound of formula (I), the process comprising deprotecting a compound of formula (III), by removing the

protecting group P^1 and any P^2 protecting groups that are present, to provide a compound of formula (I), or a salt thereof.

A compound of formula (IV) can also be prepared by reacting an amine of formula (ii) with a compound of formula (xiii) or (xiv):



(xiii)



(xiv)

wherein L^4 is a leaving group, such as bromo.

The invention also provides a process for preparing a compound of formula (I), the process comprising deprotecting a compound of formula (IV), wherein at least one or more of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is $-OP^2$, by removing the protecting groups P^2, to provide a compound of formula (I), or a salt thereof.

Unless otherwise indicated in the processes described herein, protecting group P^1 and any P^2 groups that are present can be removed simultaneously or in any order.

In one embodiment of the invention, the processes described herein further comprise the step of forming a pharmaceutically-acceptable salt of the compound of formula (I).

In another embodiment of the invention, the processes described herein further comprise the following steps in any order:

(i) optionally separating an enantiomer from a mixture of enantiomers; and

(ii) optionally converting the product to a corresponding salt or solvate thereto;

In other embodiments, this invention is directed to the other processes described herein; and to the product prepared by any of the processes described herein.

The invention further provides a compound of formula (III), and a compound of formula (IV).

Further details regarding specific reaction conditions and other procedures for preparing representative compounds of the invention or intermediate thereto are described in the Examples below.

Pharmaceutical Compositions

The invention also provides pharmaceutical compositions comprising a compound of the invention. Accordingly, the compound, preferably in the form of a pharmaceutically-acceptable salt, can be formulated for any suitable form of administration, such as oral or parenteral administration, or administration by inhalation.

By way of illustration, the compound can be admixed with conventional pharmaceutical carriers and excipients and used in the form of powders, tablets, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions will contain from about 0.05 to about 90% by weight of the active compound, and more generally from about 0.1 to about 30%. The pharmaceutical compositions may contain common carriers and excipients, such as cornstarch or gelatin, lactose, magnesium sulfate, magnesium stearate, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride, and alginic acid. Disintegrators commonly used in the formulations of this invention include croscarmellose, microcrystalline cellulose, cornstarch, sodium starch glycolate and alginic acid.

A liquid composition will generally consist of a suspension or solution of the compound or pharmaceutically-acceptable salt in a suitable liquid carrier(s), for example ethanol, glycerine, sorbitol, non-aqueous solvent such as polyethylene glycol, oils or water, optionally with a suspending agent, a solubilizing agent (such as a cyclodextrin), preservative, surfactant, wetting agent, flavoring or coloring agent. Alternatively, a liquid formulation can be prepared from a reconstitutable powder.

For example a powder containing active compound, suspending agent, sucrose and a sweetener can be reconstituted with water to form a suspension; a syrup can be prepared from a powder containing active ingredient, sucrose and a sweetener.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid compositions. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, microcrystalline cellulose and binders, for example polyvinylpyrrolidone. The tablet can also be provided with a color film coating, or color included as part of the carrier(s). In addition, active compound can be formulated in a controlled release dosage form as a tablet comprising a hydrophilic or hydrophobic matrix.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, for example by incorporation of active compound and

excipients into a hard gelatin capsule. Alternatively, a semi-solid matrix of active compound and high molecular weight polyethylene glycol can be prepared and filled into a hard gelatin capsule; or a solution of active compound in polyethylene glycol or a suspension in edible oil, for example liquid paraffin or fractionated coconut oil can be prepared and filled into a soft gelatin capsule.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, poly-vinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose. Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica.

Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used. Additionally, it may be desirable to add a coloring agent to make the dosage form more attractive in appearance or to help identify the product.

The compounds of the invention and their pharmaceutically-acceptable salts that are active when given parenterally can be formulated for intramuscular, intrathecal, or intravenous administration.

A typical composition for intra-muscular or intrathecal administration will consist of a suspension or solution of active ingredient in an oil, for example arachis oil or sesame oil. A typical composition for intravenous or intrathecal administration will consist of a sterile isotonic aqueous solution containing, for example active ingredient and dextrose or sodium chloride, or a mixture of dextrose and sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus dextrose injection, Normosol-M and dextrose, Isolyte E, acylated Ringer's injection, and the like. Optionally, a co-solvent, for example, polyethylene glycol; a chelating agent, for example, ethylenediamine tetraacetic acid; a solubilizing agent, for example, a cyclodextrin; and an anti-oxidant, for example, sodium metabisulphite, may be included in the formulation. Alternatively, the solution can be freeze dried and then reconstituted with a suitable solvent just prior to administration.

The compounds of this invention and their pharmaceutically-acceptable salts which are active on topical administration can be formulated as transdermal compositions or transdermal delivery devices ("patches"). Such compositions include, for example, a backing, active compound reservoir, a control membrane, liner and contact adhesive. Such transdermal patches may be used to provide continuous or discontinuous infusion of

the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, for example, U.S. Patent No. 5,023,252. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

One preferred manner for administering a compound of the invention is inhalation. Inhalation is an effective means for delivering an agent directly to the respiratory tract. There are three general types of pharmaceutical inhalation devices: nebulizer inhalers, dry powder inhalers (DPI), and metered-dose inhalers (MDI). Conventional nebulizer devices produce a stream of high velocity air that causes a therapeutic agent to spray as a mist which is carried into the patient's respiratory tract. The therapeutic agent is formulated in a liquid form such as a solution or a suspension of micronized particles of respirable size, where micronized is typically defined as having about 90 % or more of the particles with a diameter of less than about 10 μm.

A typical formulation for use in a conventional nebulizer device is an isotonic aqueous solution of a pharmaceutical salt of the active agent at a concentration of the active agent of between about 0.05 μg/mL and about 1 mg/mL. Suitable nebulizer devices are provided commercially, for example, by PARI GmbH (Starnberg, Germany). Other nebulizer devices have been disclosed, for example, in U.S. Patent 6,123,068.

DPI's typically administer a therapeutic agent in the form of a free flowing powder that can be dispersed in a patient's air-stream during inspiration. Alternative DPI devices which use an external energy source to disperse the powder are also being developed. In order to achieve a free flowing powder, the therapeutic agent can be formulated with a suitable excipient (e.g., lactose or starch). A dry powder formulation can be made, for example, by combining dry lactose particles with micronized particles of a suitable form, typically a pharmaceutically-acceptable salt, of a compound of the invention (i.e. the active agent) and dry blending. Alternatively, the agent can be formulated without excipients. The formulation is loaded into a dry powder dispenser, or into inhalation cartridges or capsules for use with a dry powder delivery device.

Examples of DPI delivery devices provided commercially include Diskhaler (GlaxoSmithKline, Research Triangle Park, NC) (see, e.g., U.S. Patent No. 5,035,237); Diskus (GlaxoSmithKline) (see, e.g., U.S. Patent No. 6,378,519; Turbuhaler (AstraZeneca, Wilmington, DE) (see, e.g., U.S. Patent No. 4,524,769); and Rotahaler (GlaxoSmithKline) (see, e.g., U.S. Patent No. 4,353,365). Further examples of suitable

DPI devices are described in U.S. Patent Nos. 5,415,162, 5,239,993, and 5,715,810 and references therein.

MDI's typically discharge a measured amount of therapeutic agent using compressed propellant gas. Formulations for MDI administration include a solution or suspension of active ingredient in a liquefied propellant. While chlorofluorocarbons, such as CCl_3F, conventionally have been used as propellants, due to concerns regarding adverse affects of such agents on the ozone layer, formulations using hydrofluoroalklanes (HFA), such as 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3,-heptafluoro-n-propane, (HFA 227) have been developed. Additional components of HFA formulations for MDI administration include co-solvents, such as ethanol or pentane, and surfactants, such as sorbitan trioleate, oleic acid, lecithin, and glycerin. (See, for example, U.S. Patent No. 5,225,183, EP 0717987 A2, and WO 92/22286.)

Thus, a suitable formulation for MDI administration can include from about 0.001 % to about 2 % by weight of a compound of the invention, from about 0 % to about 20 % by weight ethanol, and from about 0 % to about 5 % by weight surfactant, with the remainder being the HFA propellant. In one approach, to prepare the formulation, chilled or pressurized hydrofluoroalkane is added to a vial containing a compound of the invention, ethanol (if present) and the surfactant (if present). To prepare a suspension, the pharmaceutical salt is provided as micronized particles. The formulation is loaded into an aerosol canister, which forms a portion of an MDI device. Examples of MDI devices developed specifically for use with HFA propellants are provided in U.S. Patent Nos. 6,006,745 and 6,143,227.

In an alternative preparation, a suspension formulation is prepared by spray drying a coating of surfactant on micronized particles of a pharmaceutical salt of active compound. (See, for example, WO 99/53901 and WO 00/61108.) For additional examples of processes of preparing respirable particles, and formulations and devices suitable for inhalation dosing see U.S. Patent Nos. 6,268,533, 5,983,956, 5,874,063, and 6,221,398, and WO 99/55319 and WO 00/30614.

It will be understood that any form of the compounds of the invention, (i.e. free base, pharmaceutical salt, or solvate) that is suitable for the particular mode of administration, can be used in the pharmaceutical compositions discussed above.

The active compounds are useful as a β_2 adrenergic receptor agonist and therefore are useful for treating medical diseases or conditions mediated by β_2 adrenergic receptors

or associated with β_2 adrenergic receptor activity in a mammal, i.e. medical conditions which are ameliorated by treatment with a β_2 adrenergic receptor agonist. Such medical conditions include but are not limited to a pulmonary disease, such as asthma or chronic obstructive pulmonary disease, pre-term labor, a neurological disorder, a cardiac disorder, or inflammation.

The active compounds are effective over a wide dosage range and are generally administered in a therapeutically effective amount. It will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Suitable doses of the therapeutic agents for inhalation administration are in the general range of from about 0.05 μg/day to about 1000 μg/day, including from about 0.1 μg/day to about 500 μg/day. It will be understood that the fraction of active agent delivered to the lung characteristic of particular delivery devices is taken into account in determining suitable doses for inhalation administration.

A compound can be administered in a periodic dose: weekly, multiple times per week, daily, or multiple doses per day. The treatment regimen may require administration over extended periods of time, for example, for several weeks or months, or the treatment regimen may require chronic administration. Suitable doses for oral administration are in the general range of from about 0.05 μg/day to about 100 mg/day, such as from about 0.5 to about 1000 μg/day.

Among other properties, compounds of the invention are potent and selective agonists of the β_2 adrenergic receptor. In particular, compounds of the invention are selective for the β_2 adrenergic receptor as compared with the β_1 and β_3 adrenergic receptors.

The invention thus provides a method of treating a mammal having a disease or condition associated with β_2 adrenergic receptor activity, the method comprising administering to the mammal a therapeutically effective amount of a compound of the invention or of a pharmaceutical composition comprising a compound of the invention.

The present active agents can also be co-administered with one or more other therapeutic agents. For example, the present agents can be administered in combination with one or more therapeutic agents selected from anti-inflammatory agents (e.g. corticosteroids and non-steroidal anti-inflammatory agents (NSAIDs), antichlolinergic agents (particularly muscarinic receptor antagonists), other β_2 adrenergic receptor agonists, antiinfective agents (e.g. antibiotics or antivirals) or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of the invention together with one or more other therapeutic agents, for example, an anti-inflammatory agent, an antichlolinergic agent, another β_2 adrenergic receptor agonist, an antiinfective agent or an antihistamine, such as a corticosteroid, an anticholinergic agent, or a PDE4 inhibitor.

The other therapeutic agents can be used in the form of pharmaceutically-acceptable salts or solvates. As appropriate, the other therapeutic agents can be used as optically pure stereoisomers.

Further, the invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, a pharmaceutically-acceptable carrier, and a therapeutically effective amount of one or more other therapeutic agents, i.e., where the other therapeutic agent is selected from anti-inflammatory agents (e.g., corticosteroids and non-steroidal anti-inflammatory agents (NSAIDs)), anticholinergic agents (particularly muscarinic receptor antagonists), other β_2 adrenergic receptor agonists, antiinfective agents (e.g., antibiotics or antiviral), antihistamines, and a phosphodiesterase 4 (PDE4) inhibitor; such as an anti-inflammatory agent, an anticholinergic agent, another β_2 adrenergic receptor agonist, an antiinfective agent, or an antihistimine.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters

(e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester and 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, more preferably 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate; nedocromil sodium; phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors); leukotriene antagonists (e.g. monteleukast); inhibitors of leukotriene synthesis; iNOS inhibitors; protease inhibitors, such as tryptase and elastase inhibitors; beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists); cytokine antagonists (e.g. chemokine antagonists such as, an interleukin antibody (αIL antibody), specifically, an αIL-4 therapy, an αIL-13 therapy, or a combination thereof); or inhibitors of cytokine synthesis. Suitable other β_2-adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Also of interest is use of the present active agent in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. Representative phosphodiesterase-4 (PDE4) inhibitors or mixed PDE3/PDE4 inhibitors include, but are not limited to *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one; *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid and the like, or pharmaceutically-acceptable salts thereof. Other representative PDE4 or mixed PDE4/PDE3 inhibitors include AWD-12-281 (elbion); NCS-613 (INSERM); D-4418 (Chiroscience and Schering-Plough); CI-1018 or PD-168787 (Pfizer); benzodioxole compounds disclosed in WO99/16766 (Kyowa Hakko); K-34 (Kyowa Hakko); V-11294A (Napp); roflumilast

(Byk-Gulden); pthalazinone compounds disclosed in WO99/47505 (Byk-Gulden); Pumafentrine (Byk-Gulden, now Altana); arofylline (Almirall-Prodesfarma); VM554/UM565 (Vernalis); T-440 (Tanabe Seiyaku); and T2585 (Tanabe Seiyaku).

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M_1, M_2, or M_3 receptors, or of combinations thereof. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.

Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

Hyoscyamine (*d*, *l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt- CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine

with H_1-receptors. The majority of these inhibitors, mostly first generation antagonists, are characterized, based on their core structures, as ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic a tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chlorpheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically-acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a compound of the invention.

Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof and a corticosteroid. In particular, the invention provides a combination wherein the corticosteroid is fluticasone propionate or wherein the corticosteroid is 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester or 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof and a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof and an anticholinergic agent.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof and an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof together with a PDE4 inhibitor and a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof together with an anticholinergic agent and a corticosteroid.

As used in the embodiments described herein, the term, "a compound of formula (I)" includes a compound of formula (II) and preferred groups thereof, and any individually disclosed compound or compounds.

Accordingly, the pharmaceutical compositions of the invention can optionally comprise combinations of a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof with one or more other therapeutic agents, as described above.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical compositions. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art. Methods of treatment of the invention, therefore, include administration of the individual compounds of such combinations either sequentially or simultaneously in separate or combined pharmaceutical compositions.

Thus, according to a further aspect, the invention provides a method of treating a mammal having a disease or condition associated with β_2 adrenergic receptor activity, the method comprising administering to the mammal a therapeutically effective amount of a combination of a compound of formula (I) or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof with one or more other therapeutic agents.

Since compounds of the invention are β_2 adrenergic receptor agonists, such compounds are also useful as research tools for investigating or studying biological systems or samples having β_2 adrenergic receptors, or for discovering new β_2 adrenergic

receptor agonists. Moreover, since compounds of the invention exhibit selectivity for β_2 adrenergic receptors as compared with binding and functional activity at receptors of other β adrenergic subtypes, such compounds are also useful for studying the effects of selective agonism of β_2 adrenergic receptors in a biological system or sample. Any suitable biological system or sample having β_2 adrenergic receptors may be employed in such studies which may be conducted either *in vitro* or *in vivo*.

Representative biological systems or samples suitable for such studies include, but are not limited to, cells, cellular extracts, plasma membranes, tissue samples, mammals (such as mice, rats, guinea pigs, rabbits, dogs, pigs, etc.) and the like. The effects of agonizing the β_2 adrenergic receptor are determined using conventional procedures and equipment, such as radioligand binding assays and functional assays, for example the assay for ligand-mediated changes in intracellular cyclic adenosine monophosphate (cAMP) described below, or assays of a similar nature. A β_2 adrenergic receptor-agonizing amount of a compound of the invention will typically range from about 1 nanomolar to about 1000 nanomolar. When compounds of the invention are used as research tools for discovering new β_2 adrenergic receptor agonists, the invention also includes, as separate embodiments, both the generation of comparison data (using the appropriate assays) and the analysis of the test data to identify test compounds of interest.

Accordingly, the invention provides a method of studying a biological system or sample comprising a β_2 adrenergic receptor, the method comprising: (a) contacting the biological system or sample with a compound of formula (I); and (b) determining the effects caused by the compound on the biological system or sample.

The following non-limiting examples illustrate representative pharmaceutical compositions of the invention. Additional suitable carriers for formulations of the active compounds of the present invention can also be found in *Remington: The Science and Practice of Pharmacy, 20th Edition*, Lippincott Williams & Wilkins, Philadelphia, PA, 2000.

Formulation Example A

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Ingredient	1
Lactose, spray-dried	148
Magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

Formulation Example B

This example illustrates the preparation of another representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Ingredient	1
Cornstarch	50
Lactose	145
Magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

Formulation Example C

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention.

An oral suspension is prepared having the following composition.

Ingredients	
Active Compound	3 mg
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.1 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 mL
Colorings	0.5 mg
Distilled water	q.s. to 100 mL

Formulation Example D

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

An injectable preparation buffered to a pH of 4 is prepared having the following composition:

Ingredients	
Active Compound	0.1 mg
Sodium Acetate Buffer Solution (0.4 M)	2.0 mL
HCl (1N)	q.s. to pH 4
Water (distilled, sterile)	q.s. to 20 mL

Formulation Example E

This example illustrates the preparation of a representative pharmaceutical composition for injection of a compound of this invention.

A reconstituted solution is prepared by adding 20 mL of sterile water to 1 mg of the compound of this invention. Before use, the solution is then diluted with 200 mL of an intravenous fluid that is compatible with the active compound. Such fluids are chosen from 5% dextrose solution, 0.9% sodium chloride, or a mixture of 5% dextrose and 0.9% sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus 5% dextrose injection, Normosol-M and 5% dextrose, Isolyte E, and acylated Ringer's injection.

Formulation Example F

This example illustrates the preparation of a representative pharmaceutical composition for topical application of a compound of this invention.

Ingredients	grams
Active compound	0.2-10
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. to 100

All of the above ingredients, except water, are combined and heated to 60°C with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

Formulation Example G

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of the invention.

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

Formulation Example H

This example illustrates the preparation of a dry powder formulation containing a compound of the invention for use in inhalation cartridges.

Gelatin inhalation cartridges are filled with a pharmaceutical composition having the following ingredients:

Ingredients	mg/cartridge
Pharmaceutical salt of active compound	0.2
Lactose	25

The pharmaceutical salt of active compound is micronized prior to blending with lactose. The contents of the cartridges are administered using a powder inhaler.

Formulation Example I

This example illustrates the preparation of a dry powder formulation containing a compound of the invention for use in a dry powder inhalation device.

A pharmaceutical composition is prepared having a bulk formulation ratio of micronized pharmaceutical salt to lactose of 1:200. The composition is packed into a dry powder inhalation device capable of delivering between about 10 μg and about 100 μg of active drug ingredient per dose.

Formulation Example J

This example illustrates the preparation of a formulation containing a compound of the invention for use in a metered dose inhaler.

A suspension containing 5 % pharmaceutical salt of active compound, 0.5 % lecithin, and 0.5 % trehalose is prepared by dispersing 5 g of active compound as micronized particles with mean size less than 10 μm in a colloidal solution formed from 0.5 g of trehalose and 0.5 g of lecithin dissolved in 100 mL of demineralized water. The suspension is spray dried and the resulting material is micronized to particles having a mean diameter less than 1.5 μm. The particles are loaded into canisters with pressurized 1,1,1,2-tetrafluoroethane.

Formulation Example K

This example illustrates the preparation of a formulation containing a compound of the invention for use in a metered dose inhaler.

A suspension containing 5 % pharmaceutical salt of active compound and 0.1 % lecithin is prepared by dispersing 10 g of active compound as micronized particles with mean size less than 10 μm in a solution formed from 0.2 g of lecithin dissolved in 200 mL of demineralized water. The suspension is spray dried and the resulting material is micronized to particles having a mean diameter less than 1.5 μm. The particles are loaded into canisters with pressurized 1,1,1,2,3,3,3-heptafluoro-n-propane.

The following examples are offered to illustrate the invention, and are not to be construed in any way as limiting the scope of the invention.

Abbreviations

%Eff	% efficacy
ATCC	American Type Culture Collection
BSA	Bovine Serum Albumin
cAMP	Adenosine 3':5'-cyclic monophosphate
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl sulfoxide
EDTA	Ethylenediaminetetraacetic acid
Emax	maximal efficacy
FBS	Fetal bovine serum
Gly	Glycine
HEK-293	Human embryonic kidney - 293
PBS	Phosphate buffered saline
rpm	rotations per minute
Tris	Tris(hydroxymethyl)aminomethane

Biological Assays

The compounds of this invention, and their pharmaceutically-acceptable salts, exhibit biological activity and are useful for medical treatment. The ability of a compound to bind to the β_2 adrenergic receptor, as well as its selectivity, agonist potency, and intrinsic activity can be demonstrated using Tests A-C below, or can be demonstrated using other tests that are known in the art.

Membrane Preparation From Cells Expressing Human β_1 or β_2 Adrenergic Receptors

HEK-293 derived cell lines stably expressing cloned human β_1 or β_2 adrenergic receptors, respectively, were grown to near confluency in DMEM with 10% dialyzed FBS in the presence of 500 μg/mL Geneticin. The cell monolayer was lifted with Versene 1:5,000 (0.2 g/L EDTA in PBS) using a cell scraper. 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 preparation, cell pellets were resuspended in lysis buffer (10 mM Tris/HCL pH 7.4 @ 4°C, one tablet of "Complete Protease Inhibitor Cocktail Tablets with 2 mM EDTA" per 50 mL buffer (Roche cat.# 1697498, Roche Molecular Biochemicals, Indianapolis, IN)) and homogenized using a tight-fitting Dounce glass homogenizer (20 strokes) on ice. The homogenate was centrifuged at 20,000 x g, the pellet was washed once with lysis buffer by resuspension and centrifugation as above. The final pellet was resuspended in membrane buffer (75 mM Tris/HCl pH 7.4, 12.5mM $MgCl_2$, 1 mM EDTA @ 25°C). Protein concentration of the membrane suspension was determined by the method of Bradford (Bradford MM., *Analytical Biochemistry*, **1976**, *72*, 248-54). Membranes were stored frozen in aliquots at -80°C.

Test A

Radioligand Binding Assay on Human β_1 and β_2 Adrenergic Receptors

Binding assays were performed in 96-well microtiter plates in a total assay volume of 100 μL with 5 μg membrane protein for membranes containing the human β_2 adrenergic receptor, or 2.5 μg membrane protein for membranes containing the human β_1 adrenergic receptor in assay buffer (75 mM Tris/HCl pH 7.4 @ 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) at 10 different concentrations ranging from 0.01 nM – 200 nM. Displacement assays for determination of pK_i values of compounds were done with [^{3}H]dihydroalprenolol at 1 nM and 10 different concentrations of compound ranging from 40 pM – 10 μM. Compounds were dissolved to a concentration of 10 mM in dissolving buffer (25 mM Gly-HCl pH 3.0 with 50% DMSO), then diluted to 1 mM in 50 mM Gly-HCl pH 3.0, and from there serially diluted into assay buffer. Non-specific binding was determined in the presence of 10 μM unlabeled alprenolol. Assays were incubated for 90 minutes at room temperature, binding reactions were terminated by rapid filtration over GF/B glass fiber filter plates (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 @ 4°C, 12.5 mM $MgCl_2$, 1 mM EDTA) to remove unbound radioactivity. Plates were dried, 50 μL 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 alprenolol. K_i values for 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). The receptor subtype selectivity was calculated as the ratio of $K_i(\beta_1)/K_i(\beta_2)$. Compounds of the invention demonstrated greater binding at the β_2 adrenergic receptor than at the β_1 adrenergic receptor, i.e. $K_i(\beta_1)>K_i(\beta_2)$ with selectivity greater than about 10. In particular, the compound of Example 1 demonstrated greater binding at the β_2 adrenergic receptor than at the β_1 adrenergic receptor, i.e. $K_i(\beta_1)>K_i(\beta_2)$ with selectivity of about 18.

Test B

Whole-cell cAMP Flashplate Assays With Cell Lines Heterologously Expressing Human β_1 Adrenoceptor, β_2 Adrenoceptor, and β_3 Adrenoceptor, Respectively.

A HEK-293 cell line stably expressing cloned human β_1 adrenergic receptor (clone H34.1) was grown to about 70%-90% confluency in medium consisting of DMEM supplemented with 10% FBS and 500 μg/mL Geneticin. A HEK-293 cell line stably expressing cloned human β_2-adrenoceptor (clone H24.14) was grown in the same medium to full confluency. A CHO-K1 cell line stably expressing cloned human β_3-adrenoceptor was grown to about 70%-90% confluency in Ham's F-12 medium supplemented with 10% FBS and with 800 μg/mL Geneticin added to every fifth passage. The day before the assay, cultures were switched to the same growth-media without antibiotics.

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 once with PBS, lifted with Versene 1:5,000 (0.2 g/L EDTA in PBS) and counted. Cells were pelleted by centrifugation at 1,000 rpm and resuspended in stimulation buffer prewarmed to 37°C. For cells expressing the β_1-adrenoceptor, 10 nM ICI 118,551 were added to the stimulation buffer, and cells were incubated for 10 min at 37°C. Cells were used at final concentrations of 30,000, 40,000 and 70,000 cells / well for the β_1-adrenoceptor-, the β_2-adrenoceptor- and the β_3-adrenoceptor expressing cells, respectively. Compounds were dissolved to a concentration of 10 mM in DMSO, then diluted to 1 mM in 50 mM Gly-HCl pH 3.0, and from there serially diluted into assay buffer (75 mM Tris/HCl pH 7.4 @ 25°C, 12.5 mM $MgCl_2$, 1 mM EDTA, 0.2% BSA). Compounds were tested in the assay at 11 different concentrations, ranging from 10 μM to 9.5 pM. Reactions were incubated for 10 min at 37°C and stopped by addition of 100 μL 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 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) using the 3-parameter model for sigmoidal dose-response

(Hill slope = 1). Agonist potencies were expressed as pEC_{50} values. Functional β_2/β_1 selectivity was defined as the ratio $pEC_{50}(\beta_1)/EC_{50}(\beta_2)$, and correspondingly functional β_2/β_3 selectivity was defined as the ratio $pEC_{50}(\beta_3)/EC_{50}(\beta_2)$.

Compounds of the invention demonstrated potent activity at the β_2 adrenergic receptor in this assay, as evidenced by pEC_{50} values greater than about 7. In addition, the compounds tested demonstrated selectivity in functional activity at the β_2 receptor as compared with functional activity at the β_1 and β_3 receptors. In particular, compounds of the invention that were tested in this assay demonstrated $pEC_{50}(\beta_2)/pEC_{50}(\beta_1)$ ratios of greater than about 40 and $pEC_{50}(\beta_2)/pEC_{50}(\beta_3)$ ratios of greater than about 30.

Test C

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 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 resuspended in stimulation buffer prewarmed to 37°C at a final concentration of 600,000 cells / mL. Cells were used at a final concentration of 30,000 cells / well in the assay. Compounds were dissolved to a concentration of 10 mM in dissolving buffer (25 mM Gly-HCl pH 3.0 with 50% DMSO), then diluted to 1 mM in 50 mM Gly-HCl pH 3.0, and from there serially diluted into assay buffer (75 mM Tris/HCl pH 7.4 @ 25°C, 12.5 mM $MgCl_2$, 1 mM EDTA, 0.2% BSA).

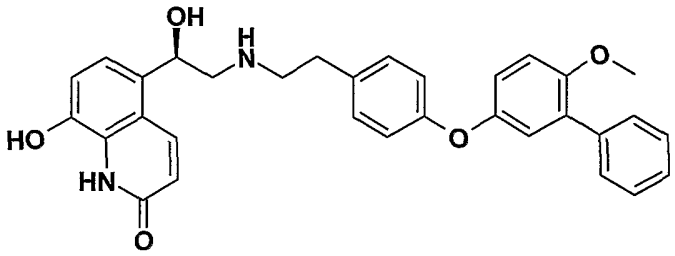
Compounds were tested in the assay at 10 different concentrations, ranging from 10 μM to 40 pM. Maximal response was determined in the presence of 10 μM Isoproterenol. Reactions were incubated for 10 min at 37°C and stopped by addition of 100 μl ice-cold detection buffer. Plates were sealed, incubated 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 with variable slope. Compound efficacy (%Eff) was calculated from the ratio of the observed Emax (TOP of the fitted curve) and the maximal response obtained for 10μM isoproterenol and was expressed as %Eff relative to isoproterenol. Compounds of the invention that were tested in this assay demonstrated a %Eff greater than about 50.

Examples

General: Unless noted otherwise, reagents, starting material and solvents were purchased from commercial suppliers, for example Sigma-Aldrich (St. Louis, MO), J. T. Baker (Phillipsburg, NJ), and Honeywell Burdick and Jackson (Muskegon, MI), and used without further purification; reactions were run under nitrogen atmosphere; reaction mixtures were monitored by thin layer chromatography (silica TLC), analytical high performance liquid chromatography (anal. HPLC), or mass spectrometry; reaction mixtures were commonly purified by flash column chromatography on silica gel, or by preparative HPLC using the general protocol described below; NMR samples were dissolved in deuterated solvent (CD_3OD, $CDCl_3$, or DMSO-*d*6), and spectra were acquired with a Varian Gemini 2000 instrument (300 MHz) under standard parameters; and mass spectrometric identification was performed by an electrospray ionization method (ESMS) with a Perkin Elmer instrument (PE SCIEX API 150 EX).

Example 1:

Synthesis of 8-Hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one



Step (a). Preparation of 6-Methoxybiphenyl-3-ol

A solution of 6-methoxybiphenyl-3-ylamine (3.4 g) in acetic acid (6 mL) was added to a mixture of concentrated sulfuric acid (1.4 mL) and ice (30 g). The slurry was cooled to 0 °C and a solution of sodium nitrite (1.24 g) in water (9 mL) was added slowly, maintaining the temperature below 5°C. The mixture was stirred at 0 °C for 0.5 h, then added via syringe under the surface of refluxing 2M sulfuric acid (150 mL). The reaction mixture was refluxed for 1 h, then allowed to cool to room temperature. The solution was extracted with dichloromethane (2 x 200 mL). The combined organics were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, dichloromethane) to afford the title intermediate (2.1 g) as a dark oil. *m/z*: [M^+] calcd for $C_{13}H_{12}O_2$ 200.1; found 200.1. ^{1}H NMR (300 MHz, DMSO-d_6): 8.92 (s, 1H), 7.32-7.16 (m, 5H), 6.78 (d, 1H, J=8.5Hz), 6.57 (m, 2H), 3.51 (s, 1H).

Step (b). Preparation of 2-[2-(4-Iodophenyl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione

A solution of 2-(4-iodophenyl)ethylamine (7.08 g) and phthalic anhydride (4.24 g) in acetic acid (100 mL) was refluxed for 4 h. The solvent was evaporated and the residue triturated with ethanol (100 mL). The solid was filtered to afford the title intermediate (7.0 g) as a white solid.

Step (c). Preparation of 2-{2-[4-(6-Methoxybiphenyl-3-yloxy)phenyl]ethyl}isoindole-1,3-dione

A slurry of the product of step (a) (400 mg) and cesium carbonate (652 mg) in *N*-methylpyrrolidinone (2 mL) was degassed by bubbling nitrogen gas through it for 10 minutes. To this slurry was then added copper (I) chloride (50 mg), 2,2,6,6-tetramethylheptane-3,5-dione (45 mg), and the product of step (b) (377 mg). The reaction mixture was warmed to 120 °C and stirred for 4 h before being allowed to cool to room

temperature. The solution was diluted with methyl-*tert*-butyl ether (20 mL), washed with 1M hydrochloric acid (20 mL) then 1M sodium hydroxide (20 mL), then dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 250:1:0.5 dichloromethane:methanol:acetic acid) to afford the title intermediate (170 mg) as a clear oil.

Step (d). Preparation of 2-[4-(6-Methoxybiphenyl-3-yloxy)phenyl]ethylamine

A solution of the product of step (c) (170 mg) and hydrazine (2 mL) in dichloromethane (10 mL) was stirred at room temperature for 3h then diluted with water (20 mL) and dichloromethane (50 mL). The organics were separated, washed with water (2 x 20 mL), dried over sodium sulfate and evaporated to afford the title intermediate (110 mg). *m/z*: $[M+H^+]$ calcd for $C_{21}H_{21}NO_2$ 320.2; found 320.3.

Step (e). Preparation of 8-Benzyloxy-5-((*R*)-1-(*tert*-butyldimethylsilanyloxy)-2-{2-[4-(6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one

A slurry of the product of step (d) (919 mg), 8-(benzyloxy)-5-[(*R*)-2-bromo-1-(*tert*-butyldimethylsilanyloxy)ethyl]-1*H*-quinolin-2-one (909 mg), potassium carbonate (771 mg) and sodium iodide (418 mg) in DMSO was heated at 90 °C for 5 h. The mixture was allowed to cool then diluted with water (10 mL). The solution was extracted with dichloromethane (2 x 30 mL). The combined organics were dried over sodium sulfate and the solvent removed *in vacuo*. The residue was purified by column chromatography (40:2:1 dichloromethane:methanol:acetic acid) to afford the title intermediate (1.0 g) as a clear oil. *m/z*: $[M+H^+]$ calcd for $C_{45}H_{50}N_2O_5Si$ 727.4; found 727.8.

Step (f). Preparation of 8-Benzyloxy-5-((*R*)-1-hydroxy-2-{2-[4-(6-methoxy-biphenyl-3-yloxy)phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one

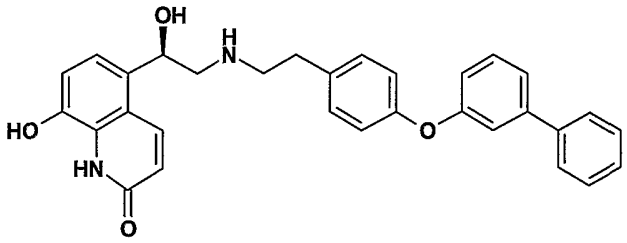
A solution of the product of step (e) (500 mg) and triethylamine trihydrofluoride (0.34 mL) in tetrahydrofuran (5 mL) was stirred at room temperature for 16 h. The solution was diluted with isopropyl acetate (20 mL) and sodium hydroxide (1M, 20 mL). The organics were separated, dried over sodium sulfate and evaporated to afford the title intermediate (200 mg) as a clear oil. *m/z*: $[M+H^+]$ calcd for $C_{39}H_{36}N_2O_5$ 613.3; found 613.5

Step (g). Synthesis of 8-Hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(6-methoxy-biphenyl-3-yloxy)phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one

A slurry of the product of step (g) (200 mg) and palladium hydroxide (20%w/w on carbon, 50 mg) in a solution of 1:1 dichloromethane:methanol (10 mL) was stirred under an atmosphere of hydrogen for 3 h. The catalyst was filtered off, the filtrate evaporated and the residue purified by reverse phase HPLC to afford the title compound (110 mg) in the form of a white solid as a trifluoroacetate salt. *m/z*: $[M+H^+]$ calcd for $C_{32}H_{30}N_2O_5$, 523.2; found 523.6. ^1H NMR (300 MHz, DMSO-d_6): 10.38 (d, 1H, J=19.3Hz), 8.57 (br s, 1H), 8.00 (d, 1H, J=9.9Hz), 7.35-7.16 (m, 6H), 7.11 (d, 2H, J=8.8Hz), 7.04-6.99 (m, 2H), 6.89-6.81 (m, 4H), 6.46 (d, 1H, J=8.3Hz), 6.06 (br s, 1H), 5.18 (d, 1H, J=9.1Hz), 3.63 (s, 3H), 3.07-2.78 (m, 7H).

Example 2

Synthesis of 5-((*R*)-2-{2-[4-(Biphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)- 8-hydroxy-1*H*-quinolin-2-one



Step (a). Preparation of 2-{2-[4-(3-Chlorophenoxy)phenyl]ethyl}isoindole-1,3-dione

A slurry of 3-chlorophenol (2.4 mL) and cesium carbonate (6.1 g) in *N*-methylpyrrolidinone (15 mL) was degassed by bubbling nitrogen gas through it for 10 minutes. Copper (I) chloride (462 mg), 2,2,6,6-tetramethylheptane-3,5-dione (425 mg), and the product of Example 1, step (b), 2-[2-(4-iodophenyl)ethyl]-1*H*-isoindole-1,3(2H)-dione (3.5 g) were then added to the slurry, which was then warmed to 120 °C and stirred for 3 h before being allowed to cool to room temperature. The solution was diluted with dichloromethane (100 mL), washed with 1 M hydrochloric acid (2 x 50 mL) then brine (2 x 50 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by reverse phase HPLC to afford the title intermediate (900 mg) as a clear oil. *m/z*: $[M+H^+]$ calcd for $C_{22}H_{16}ClNO_3$ 378.09; found 378.3.

Step (b). Preparation of 2-[4-(3-Chlorophenoxy)phenyl]ethylamine

A solution of the product of step (a) (900 mg) and hydrazine (4 mL) in dichloromethane (10 mL) was stirred at room temperature for 4 h. The mixture was diluted with water (20 mL) and dichloromethane (80 mL). The organic layer was separated, washed with water (2 x 20 mL) and brine (20ml), dried over sodium sulfate and evaporated to leave an oil/solid residue. The residue was taken up in methanol (20 mL) and filtered to remove solid material. The filtrate was evaporated to afford the title intermediate (470 mg) as a clear oil.

Step (c). Preparation of 8-Benzyloxy-5-((*R*)-1-(*tert*-butyldimethylsilanyloxy)-2-{2-[4-(3-chlorophenoxy)phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one

A slurry of the product of step (b) (1.39 g), 8-(benzyloxy)-5-[(*R*)-2-bromo-1-(*tert*-butyldimethylsilanyloxy)ethyl]-1*H*-quinolin-2-one (2.49g), sodium iodide (1.14 g) and potassium carbonate (2.11 g) in DMSO (7 mL) was heated at 90 °C for 5 h. The solution was allowed to cool, diluted with dichloromethane (60mL) and washed with water (4 x 30 mL) then brine (40 mL). The organics were dried over sodium sulfate, concentrated in vacuo and the residue purified by reverse phase HPLC to afford the title intermediate (1.85 g) as a clear oil. *m/z*: $[M+H^+]$ calcd for $C_{38}H_{43}ClN_2O_4Si$ 655.3; found 655.5.

Step (d). Preparation of 8-Benzyloxy-5-[(*R*)-2-{2-[4-(biphenyl-3-yloxy)phenyl]ethyl-amino}-1-(*tert*-butyldimethylsilanyloxy)ethyl]-1*H*-quinolin-2-one

A slurry of the product of step (c) (200 mg), phenylboronic acid (84 mg), sodium *tert*-butoxide (154 mg) and $[(tert\text{-butyl})_2P(OH)]_2PdCl_2$ (22 mg) in toluene (2 mL) was refluxed for 16 h. The mixture was allowed to cool, diluted with dichloromethane (10 mL) and washed with water (2 x 10 mL) then brine (10 mL). The organics were dried over sodium sulfate, concentrated *in vacuo* to yield the title intermediate (275 mg) which was used directly in the next step without further purification. *m/z*: $[M+H^+]$ calcd for $C_{44}H_{48}N_2O_4Si$ 697.4; found 697.5.

Step (e). Preparation of 8-Benzyloxy-5-[(*R*)-2-{2-[4-(biphenyl-3-yloxy)phenyl]ethyl-amino}-1-hydroxyethyl]-1*H*-quinolin-2-one

The product of step (d) (275 mg) and triethylamine trihydrofluoride (1.0 mL) in tetrahydrofuran (10 mL) was stirred at room temperature for 16 h. The solution was

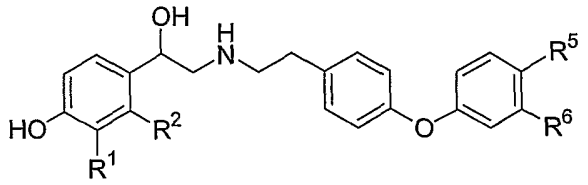
diluted with sodium hydroxide (0.5M, 10 mL), extracted with dichloromethane (2 x 10 mL) and the combined organics dried over sodium sulfate and evaporated to afford the title intermediate (105 mg), which was used directly in the next step without further purification.

Step (f). Synthesis of 8-Hydroxy-5-[(*R*)-2-{2-[4-(biphenyl-3-yloxy)phenyl]ethyl-amino}-1-hydroxyethyl]-1*H*-quinolin-2-one

A slurry of the the product of step (e) (105 mg) and palladium hydroxide (100 mg) in a solution of 1:1 acetic acid:tetrahydrofuran (10 mL) was stirred under an atmosphere of hydrogen for 24 h. The catalyst was filtered off, the filtrate evaporated and the residue purified by reverse phase HPLC to afford the title compound (16 mg) in the form of a white solid as a trifluoroacetate salt. *m/z*: [M+H$^+$] calcd for $C_{31}H_{28}N_2O_4$, 493.2; found 493.5. ^{1}H NMR (300 MHz, DMSO-d_6): 10.40 (d, 1H, J=20Hz), 8.60 (br s, 1H), 8.01 (d, 1H, J=8.8Hz), 7.49 (d, 2H, J=8.2Hz), 7.14-7.34 (m, 7H), 7.03 (d, 1H, J=7.4Hz), 6.93 (d, 2H, J=7.4Hz), 6.86-6.82 (m, 2H), 6.46 (d, 1H, J=9.9Hz), 6.07 (s, 1H), 5.18 (m, 1H), 3.19-2.82 (m, 6H).

Using procedures similar to those described in the Examples and General Synthetic Procedures section herein, and starting with the appropriate reagents, the following compounds listed in Table A can be prepared:

Table A



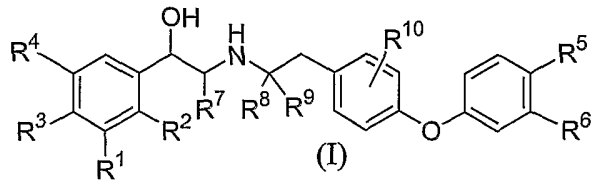
Ex.	R^1	R^2	R^5	R^6
3	-NHC(=O)CH=CH-		-O-$CH_2C(CH_3)_2NH_2$	-H
4	-NHC(=O)CH=CH-		-O-CH_3	-$(CH_2)_3NH_2$
5	-NHC(=O)CH=CH-		-O-$(CH_2)_2NH_2$	-CF_3
6	-NHC(=O)CH=CH-		-O-$(CH_2)_3NH_2$	-H
7	-NHC(=O)CH=CH-		-O-$(CH_2)_2O$-$(CH_2)_2$-NH_2	-H
8	-NHC(=O)CH=CH-		-O-$(CH_2)_2$-morpholin-4-yl	-H

Ex.	R^1	R^2	R^5	R^6
9	-NHC(=O)CH=CH-		-O-$(CH_2)_2$-piperazin-4-yl	-H
10	-NHC(=O)CH=CH-		-O-CH_3	-$(CH_2)_2N(CH_3)_2$
11	-NHC(=O)CH=CH-		-H	4-chlorophenyl
12	-NHC(=O)CH=CH-		-H	4-methoxyphenyl
13	-NHC(=O)CH=CH-		-H	3-cyanophenyl
14	-NHC(=O)CH=CH-		morpholin-4-yl	-H
15	-NHC(=O)CH=CH-		-O-CH_3	2-amino-3-ethyl-phenyl
16	-NHC(=O)CH=CH-		-O-CH_3	1-morpholin-4-yl-methylene
17	-NHCHO	H	-H	phenyl
18	-NHCHO	H	-O-$(CH_2)_2NH_2$	-H
19	-NHCHO	H	-O-CH_3	-$(CH_2)_2N(CH_3)_2$
20	-CH_2OH	H	-H	phenyl
21	-CH_2OH	H	-O-CH_3	2-amino-3-ethyl-phenyl
22	-CH_2OH	H	morpholin-4-yl	-H
23	-NHC(=O)CH=CH-		-O-CH_3	3-chlorophenyl
24	-NHC(=O)CH=CH-		-O-CH_3	3-cyanophenyl
25	-NHC(=O)CH=CH-		-O-CH_3	3-aminomethyl-phenyl
26	-NHC(=O)CH=CH-		-O-CH_3	4-aminomethyl-phenyl
27	-NHCHO	H	-O-CH_3	3-chlorophenyl
28	-NHCHO	H	-O-CH_3	3-cyanophenyl
29	-NHCHO	H	-O-CH_3	3-aminomethyl-phenyl
30	-NHCHO	H	-O-CH_3	4-aminomethyl-phenyl
31	-CH_2OH	H	-O-CH_3	3-chlorophenyl
32	-CH_2OH	H	-O-CH_3	3-cyanophenyl
33	-CH_2OH	H	-O-CH_3	3-aminomethyl-phenyl
34	-CH_2OH	H	-O-CH_3	4-aminomethyl-phenyl

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto. Additionally, all publications, patents, and patent documents cited hereinabove are incorporated by reference herein in full, as though individually incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein:

each of R^1, R^2, R^3, and R^4 is independently selected from hydrogen, hydroxy, amino, halo, -CH_2OH and -NHCHO, or R^1 and R^2 taken together are selected from -NHC(=O)CH=CH-, -CH=CHC(=O)NH-, -NHC(=O)S-, and –SC(=O)NH-;

R^5 and R^6 are independently selected from hydrogen, hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, -O-C_{1-6}alkylenyl-NR^aR^b; -O-C_{1-4}alkylenyl-O-C_{1-4}alkylenyl-NR^aR^b, -$SO_2NR^aR^b$, -NR^cR^d, phenyl, and heteroaryl; provided that R^5 and R^6 are not both hydrogen; wherein each phenyl is optionally substituted with 1 or 2 substituents selected from R^f; each heteroaryl is optionally substituted with 1 or 2 substituents selected from R^g; and each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

R^7 is hydrogen or C_{1-6}alkyl;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is hydrogen or C_{1-6}alkyl;

R^{10} is selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, aryl, heteroaryl, cycloalkyl, and heterocyclyl; or R^9 together with R^{10} is -CH_2- or -CH_2CH_2-;

R^a, R^b, R^c, R^d, and R^e are each independently hydrogen or C_{1-6} alkyl, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from hydroxy, C_{1-6}alkoxy, and amino; or R^a and R^b, or R^c and R^d together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclic ring having from 4 to 7 ring atoms, and containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

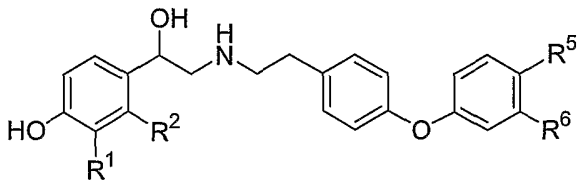
R^f is selected from hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -C(=O)OH, -CN, -NO_2, -C(=O)R^e, -SO_2-C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, and -C(=O)NR^aR^b, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino; and

R^g is C_{1-6}alkyl or oxo, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

2. The compound of Claim 1, wherein R^7 is hydrogen.

3. The compound of Claim 2, which is a compound of formula (II):



(II)

wherein:

R^1 is $-CH_2OH$ or –NHCHO, and R^2 is hydrogen; or R^1 and R^2 taken together are -NHC(=O)CH=CH-, -CH=CHC(=O)NH-, -NHC(=O)S-, or –SC(=O)NH-;

R^5 and R^6 are each independently selected from hydrogen, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, -O-C_{1-6}alkylenyl-NR^aR^b; -NR^cR^d, phenyl, and heteroaryl; provided that R^5 and R^6 are not both hydrogen; wherein each phenyl is optionally substituted with 1 or 2 substituents selected from R^f; each heteroaryl is optionally substituted with 1 or 2 substituents selected from R^g; and each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

R^a, R^b, R^c, R^d, and R^e are each independently hydrogen or C_{1-6} alkyl, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from hydroxy, C_{1-6}alkoxy, and amino; or R^a and R^b, or R^c and R^d together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclic ring having from 4 to 7 ring atoms, and containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R^f is selected from hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, -C(=O)OH, -CN, $-NO_2$, -C(=O)R^e, -C_{1-6}alkylenyl-NR^aR^b, and -C(=O)NR^aR^b; wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino; and

R^g is selected from C_{1-6}alkyl, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

4. The compound of Claim 3, wherein R^1 is $-CH_2OH$, and R^2 is hydrogen.

5. The compound of Claim 3, wherein R^1 is –NHCHO, and R^2 is hydrogen.

6. The compound of Claim 3, wherein R^1 and R^2 taken together are -NHC(=O)CH=CH-, or -CH=CHC(=O)NH-.

7. The compound of Claim 3, wherein R^5 and R^6 are each independently selected from hydrogen, hydroxy, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, -O-C_{1-6}alkylenyl-NR^aR^b, and -NR^cR^d; wherein for R^5 and R^6 each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino.

8. The compound of Claim 7, wherein:

one of R^5 and R^6 is selected from $-O(CH_2)_2NH_2$, $-O(CH_2)_3NH_2$, $-OCH_2C(CH_3)_2NH_2$, $-O(CH_2)_4NH_2$, $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, $-CH_2C(CH_3)_2NH_2$, $-(CH_2)_2N(CH_3)_2$, 4-morpholinylethoxy, and 4-piperazinylethoxy;

and the other of R^5 *and* R^6 *is selected from* hydrogen, methoxy, ethoxy, $-CF_3$, and methyl.

9. The compound of Claim 3, wherein:

R^5 is selected from hydrogen, hydroxy, methoxy, ethoxy, methyl, and ethyl; and

R^6 is selected from phenyl, furyl, thienyl, pyrrolyl, and pyridyl; wherein phenyl is optionally substituted with 1 or 2 substituents selected from R^f; and furyl, thienyl, pyrrolyl, and pyridyl are optionally substituted with 1 or 2 substituents selected from R^g.

10. The compound of Claim 9, wherein

R^5 is hydrogen, methoxy or ethoxy;

and R^6 is phenyl optionally substituted with 1 or 2 substituents selected from R^f.

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

8-hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(6-methoxybiphenyl-3-yloxy)phenyl]-ethylamino}ethyl)-1*H*-quinolin-2-one;

5-((*R*)-2-{2-[4-(biphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[4-(2-amino-2-methylpropoxy)phenoxy]phenyl}ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[3-(3-aminopropyl)-4-methoxyphenoxy]phenyl}ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[4-(2-aminoethoxy)-3-trifluoromethylphenoxy]phenyl}-ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[4-(3-aminopropoxy)phenoxy]phenyl}ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-{(*R*)-2-[2-(4-{4-[2-(2-aminoethoxy)ethoxy]phenoxy}phenyl)ethylamino]-1-hydroxyethyl}-8-hydroxy-1*H*-quinolin-2-one;

8-hydroxy-5-[(*R*)-1-hydroxy-2-(2-{4-[4-(2-morpholin-4-ylethoxy)-phenoxy]phenyl}ethylamino)ethyl]-1*H*-quinolin-2-one;

8-hydroxy-5-[(*R*)-1-hydroxy-2-(2-{4-[4-(2-piperazin-1-ylethoxy)phenoxy]-phenyl}ethylamino)ethyl]-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[3-(2-dimethylaminoethyl)-4-methoxyphenoxy]phenyl}-ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

5-((*R*)-2-{2-[4-(4'-chlorobiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

8-hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(4'-methoxybiphenyl-3-yloxy)-phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one;

3'-(4-{2-[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]ethyl}phenoxy)biphenyl-3-carbonitrile;

8-hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(4-morpholin-4-yl-phenoxy)-phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one;

5-[(*R*)-2-(2-{4-[3'-(2-aminoethyl)-6-methoxybiphenyl-3-yloxy]phenyl}-ethylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one;

8-hydroxy-5-((*R*)-1-hydroxy-2-{2-[4-(6-methoxy-3'-morpholin-4-ylmethylbiphenyl-3-yloxy)phenyl]ethylamino}ethyl)-1*H*-quinolin-2-one;

N-[5-((*R*)-2-{2-[4-(biphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

N-{5-[(*R*)-2-(2-{4-[4-(2-aminoethoxy)phenoxy]phenyl}ethylamino)-1-hydroxyethyl]-2-hydroxyphenyl}formamide;

N-{5-[(*R*)-2-(2-{4-[3-(2-dimethylaminoethyl)-4-methoxyphenoxy]phenyl}-ethylamino)-1-hydroxyethyl]-2-hydroxyphenyl}formamide;

4-((*R*)-2-{2-[4-(biphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-2-hydroxymethylphenol;

4-((*R*)-2-{2-[4-(2'-amino-3'-ethyl-6-methoxybiphenyl-3-yloxy)phenyl]-ethylamino}-1-hydroxyethyl)-2-hydroxymethylphenol;

2-hydroxymethyl-4-((*R*)-1-hydroxy-2-{2-[4-(4-morpholin-4-ylphenoxy)-phenyl]ethylamino}ethyl)phenol;

5-(2-{2-[4-(3'-chloro-6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

5'-(4-{2-[2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl-amino]ethyl}phenoxy)-2'-methoxybiphenyl-3-carbonitrile;

5-(2-{2-[4-(3'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]ethyl-amino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

5-(2-{2-[4-(4'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]ethyl-amino}-1-hydroxyethyl)-8-hydroxy-1*H*-quinolin-2-one;

N-[5-(2-{2-[4-(3'-chloro-6-methoxybiphenyl-3-yloxy)phenyl]ethyl-amino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

N-[5-(2-{2-[4-(3'-cyano-6-methoxybiphenyl-3-yloxy)phenyl]ethyl-amino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

N-[5-(2-{2-[4-(3'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]-ethylamino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

N-[5-(2-{2-[4-(4'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]-ethylamino}-1-hydroxyethyl)-2-hydroxyphenyl]formamide;

4-(2-{2-[4-(3'-chloro-6-methoxybiphenyl-3-yloxy)phenyl]ethylamino}-1-hydroxyethyl)-2-hydroxymethylphenol;

5'-(4-{2-[2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethylamino]-ethyl}phenoxy)-2'-methoxybiphenyl-3-carbonitrile;

4-(2-{2-[4-(3'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]ethyl-amino}-1-hydroxyethyl)-2-hydroxymethylphenol; and

4-(2-{2-[4-(4'-aminomethyl-6-methoxybiphenyl-3-yloxy)phenyl]ethyl-amino}-1-hydroxyethyl)-2-hydroxymethylphenol.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of Claims 1 to 11 and a pharmaceutically-acceptable carrier.

13. The pharmaceutical composition of Claim 12, wherein the composition futher comprises a therapeutically effective amount of one or more other therapeutic agents.

14. A combination comprising the compound of any one of Claims 1 to 11 and one or more other therapeutic agents.

15. A compound as claimed in any one of Claims 1 to 11 for use in therapy.

16. Use of a compound of any one of Claims 1 to 11 or of a combination of Claim 14 in the manufacture of a medicament.

17. The use of Claim 16 wherein the medicament is for the treatment of a mammal having a disease or condition associated with β_2 adrenergic receptor activity.

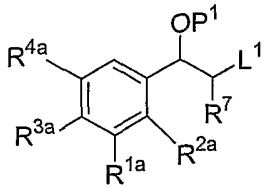
18. The use of Claim 17 wherein the disease or condition is a pulmonary disease or condition.

19. The use of Claim 18 wherein the medicament is suitable for administration by inhalation.

20. Use of a compound of any one of Claims 1 to 11 in the manufacture of a medicament for administration in combination with one or more therapeutic agents for the treatment of a mammal having a disease or condition associated with β_2 adrenergic receptor activity.

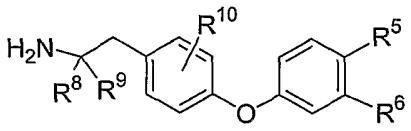
21. A process for preparing the compound of Claim 1, the process comprising:

(a) reacting a compound of formula (i):



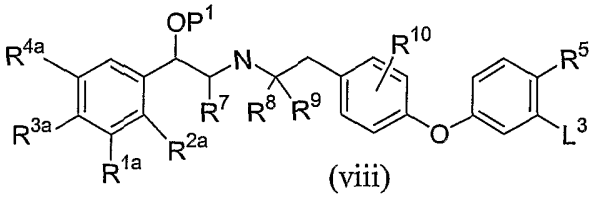
(i)

with a compound of formula (ii):



(ii) ;

(b) for a compound of formula (I) wherein R^6 is phenyl or heteroaryl, reacting a compound of formula (viii):



(viii)

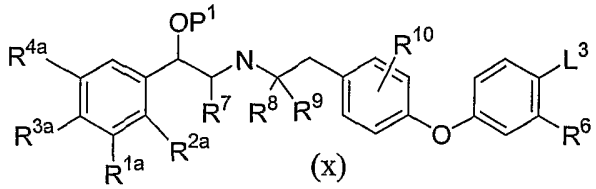
with a compound of formula (ix):

$Y^1–R^6$

(ix)

in the presence of a transition metal catalyst;

(c) for a compound of formula (I) wherein R^5 is phenyl or heteroaryl, reacting a compound of formula (x):



(x)

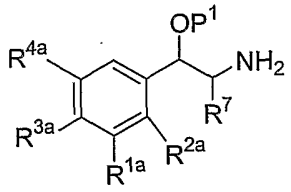
with a compound of formula (xi):

$Y^2–R^5$

(xi)

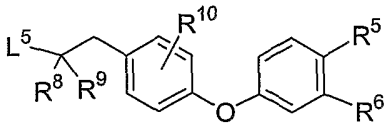
in the presence of a trasition metal catalyst;

(d) reacting a compound of formula (xv):



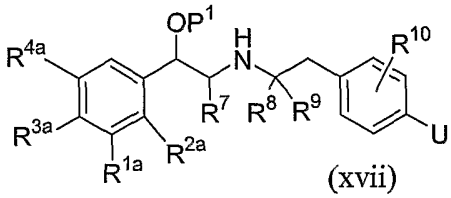
(xv) ;

with a compound of formula (xvi):



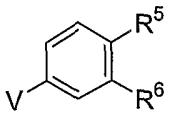
(xvi) ; or

(e) reacting a compound of formula (xvii):



(xvii)

with a compound of formula (xviii):



(xviii)

wherein:

P^1 is a hydroxy-protecting group;

each of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is the same as R^1, R^2, R^3, and R^4, or one or more of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is independently $-OP^2$, wherein P^2 is a hydroxy-protecting group;

L^1 is a leaving group;

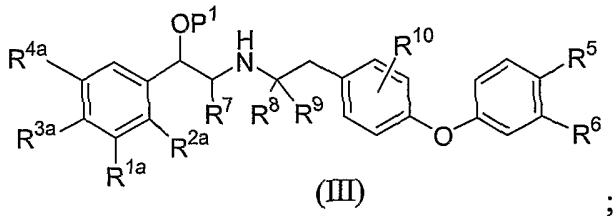
L^3 is a leaving group;

L^5 is a leaving group;

one of U and V is a leaving group, and the other of U and V is a hydroxy group; and

Y^1-R^6 and Y^2-R^5 are independently selected from phenyl- or heteroaryl-boronic acid, phenyl- or heteroaryl-trialkyl-tin, phenyl or heteroaryl zinc halide, and phenyl or heteroaryl magnesium halide;

to provide a compound of formula (III):



(III)

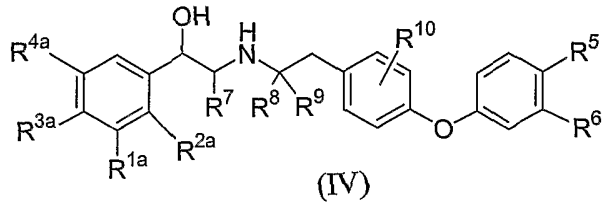
; and

removing the protecting group P^1 and any P^2 protecting groups that are present;

to provide a compound of formula (I), or a salt thereof.

22. A process for preparing the compound of Claim 1, the process comprising:

deprotecting a compound of formula (IV):



(IV)

wherein at least one or more of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is $-OP^2$, wherein P^2 is a hydroxy-protecting group; and the others of R^{1a}, R^{2a}, R^{3a}, and R^{4a} are R^1, R^2, R^3, and R^4;

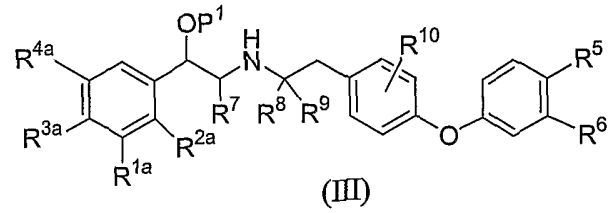
by removing the protecting groups P^2;

to provide a compound of formula (I), or a salt thereof.

23. The product prepared by the process of Claim 21.

24. The product prepared by the process of Claim 22.

25. A compound of formula (III):



(III)

wherein

P^1 is a hydroxy-protecting group;

each of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is independently selected from hydrogen, hydroxy, amino, halo, $-CH_2OH$, -NHCHO, and $-OP^2$, wherein P^2 is a hydroxy-protecting group; or

R^{1a} and R^{2a} taken together are selected from -NHC(=O)CH=CH-, -CH=CHC(=O)NH-, -NHC(=O)S-, and –SC(=O)NH-;

R^5 and R^6 are independently selected from hydrogen, hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, -O-C_{1-6}alkylenyl-NR^aR^b; -O-C_{1-4}alkylenyl-O-C_{1-4}alkylenyl-NR^aR^b, -$SO_2NR^aR^b$, -NR^cR^d, phenyl, and heteroaryl; provided that R^5 and R^6 are not both hydrogen; wherein each phenyl is optionally substituted with 1 or 2 substituents selected from R^f; each heteroaryl is optionally substituted with 1 or 2 substituents selected from R^g; and each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

R^7 is hydrogen or C_{1-6}alkyl;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is hydrogen or C_{1-6}alkyl;

R^{10} is selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, aryl, heteroaryl, cycloalkyl, and heterocyclyl; or R^9 together with R^{10} is -CH_2- or -CH_2CH_2-;

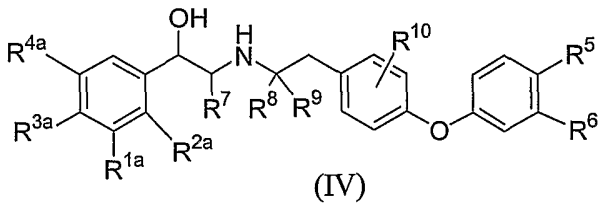
R^a, R^b, R^c, R^d, and R^e are each independently hydrogen or C_{1-6} alkyl, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from hydroxy, C_{1-6}alkoxy, and amino; or R^a and R^b, or R^c and R^d together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclic ring having from 4 to 7 ring atoms, and containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R^f is selected from hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -C(=O)OH, -CN, -NO_2, -C(=O)R^e, -SO_2-C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, and -C(=O)NR^aR^b, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino; and

R^g is C_{1-6}alkyl or oxo, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

or a salt or solvate or stereoisomer thereof.

26. A compound of formula (IV):



(IV)

wherein

each of R^{1a}, R^{2a}, R^{3a}, and R^{4a} is independently selected from hydrogen, hydroxy, amino, halo, -CH_2OH, -NHCHO, and -OP^2, wherein P^2 is a hydroxy-protecting group; or R^{1a} and R^{2a} taken together are selected from -NHC(=O)CH=CH-, -CH=CHC(=O)NH-, -NHC(=O)S-, and –SC(=O)NH-;

R^5 and R^6 are independently selected from hydrogen, hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, -O-C_{1-6}alkylenyl-NR^aR^b; -O-C_{1-4}alkylenyl-O-C_{1-4}alkylenyl-NR^aR^b, -$SO_2NR^aR^b$, -NR^cR^d, phenyl, and heteroaryl; provided that R^5 and R^6 are not both hydrogen; wherein each phenyl is optionally substituted with 1 or 2 substituents selected from R^f; each heteroaryl is optionally substituted with 1 or 2 substituents selected from R^g; and each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

R^7 is hydrogen or C_{1-6}alkyl;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is hydrogen or C_{1-6}alkyl;

R^{10} is selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, aryl, heteroaryl, cycloalkyl, and heterocyclyl; or R^9 together with R^{10} is -CH_2- or -CH_2CH_2-;

R^a, R^b, R^c, R^d, and R^e are each independently hydrogen or C_{1-6} alkyl, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from hydroxy, C_{1-6}alkoxy, and amino; or R^a and R^b, or R^c and R^d together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclic ring having from 4 to 7 ring atoms, and containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R^f is selected from hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -C(=O)OH, -CN, -NO_2, -C(=O)R^e, -SO_2-C_{1-6}alkyl, -C_{1-6}alkylenyl-NR^aR^b, and -C(=O)NR^aR^b, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino; and

R^g is C_{1-6}alkyl or oxo, wherein each C_{1-6}alkyl is optionally substituted with 1 to 3 substituents selected from halo, hydroxy, C_{1-6}alkoxy, and amino;

or a salt or solvate or stereoisomer thereof.

27. A method of treating a mammal having a disease or condition associated with β_2 adrenergic receptor activity, the method comprising administering to the mammal a therapeutically effective amount of a compound of any one of Claims 1 to 11.

28. The method of Claim 27 further comprising administering a therapeutically effective amount of one or more other therapeutic agents.

29. A method of studying a biological system or sample comprising a β_2 adrenergic receptor, the method comprising:

(a) contacting the biological system or sample with a compound of any one of Claims 1 to 11; and

(b) determining the effects caused by the compound on the biological system or sample.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/025690

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/26 C07C233/25 A61K31/4704 A61K31/167 A61P11/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 670 376 B1 (MORAN EDMUND J ET AL) 30 December 2003 (2003-12-30) column 1, line 36 - column 4, line 15	1-29
Y	ALIKHANI V ET AL: "Long-chain formoterol analogues: an investigation into the effect of increasing amino-substituent chain length on the .beta.2-adrenoceptor activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, no. 18, 2004, pages 4705-4710, XP002323505 ISSN: 0960-894X compound 12A	1-29

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2005	27/10/2005

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/025690

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/016601 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; CUENOUD, BERNARD; FAIRHURST, ROBIN,) 26 February 2004 (2004-02-26) page 17, line 8 - page 17, line 21; claim 1	1-29

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/025690

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

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

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

Although claims 27-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

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

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

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

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/025690

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6670376 B1	30-12-2003	US 2003229058 A1	11-12-2003
		US 2004063755 A1	01-04-2004
WO 2004016601 A	26-02-2004	AU 2003255400 A1	03-03-2004
		BR 0313723 A	02-08-2005
		CA 2493765 A1	26-02-2004
		EP 1529038 A1	11-05-2005