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(54) **Title:** CORTICOSTEROID-BETA-AGONIST-MUSCARINIC ANTAGONIST COMPOUNDS FOR USE IN THERAPY

(57) **Abstract:** The instant invention relates to new chemical entities which comprise corticosteroids, phosphorylated β-agonists and muscarinic (M3) antagonists for use in therapy and compositions comprising and processes for preparing the same.

CORTICOSTEROID-BETA-AGONIST-MUSCARINIC ANTAGONIST COMPOUNDS FOR USE IN THERAPY

This application claims priority to US provisional patent application Serial No. 61/286657 filed 15 Dec 2009.

Field of the Invention

The instant invention relates to new chemical entities which comprise corticosteroids, phosphorylated β-agonists and muscarinic (M3) antagonists for use in therapy and compositions comprising and processes for preparing the same.

Background of the Invention

Asthma is a chronic inflammatory disease of the airways produced by the infiltration of pro-inflammatory cells, mostly eosinophils and activated T-lymphocytes (Poston, *Am. Rev. Respir. Dis.,* 145 (4 Pt 1), 918-921, 1992; Walker, *J. Allergy Clin. Immunol.,* 88 (6), 935-42, 1991) into the bronchial mucosa and submucosa. The secretion of potent chemical mediators, including cytokines, by these proinflammatory cells alters mucosal permeability, mucus production, and causes smooth muscle contraction. All of these factors lead to an increased reactivity of the airways to a wide variety of irritant stimuli (Kaliner, "Bronchial asthma, Immunologic diseases" E. M. Samter, Boston, Little, Brown and Company: 117-118. 1988).

Glucocorticoids, which were first introduced as an asthma therapy in 1950 (Carryer, *Journal of Allergy,* 21, 282-287, 1950), remain the most potent and consistently effective therapy for this disease, although their mechanism of action is not yet fully understood (Morris, *J. Allergy Clin. Immunol.,* 75 (1 Pt) 1-13, 1985). Unfortunately, oral glucocorticoid therapies are associated with profound undesirable side effects such as truncal obesity, hypertension, glaucoma, glucose intolerance, acceleration of cataract formation, bone mineral loss, and psychological effects, all of which limit their use as long-term therapeutic agents (Goodman and Gilman, 10th edition, 2001). A solution to systemic side effects is to deliver steroid drugs directly to the site of inflammation. Inhaled corticosteroids (ICS) have been developed to mitigate the severe adverse effects of oral steroids. While ICS are very effective in controlling inflammation in asthma, they too are not precisely delivered to the optimal site of action in the lungs and produce unwanted side effects in the mouth and pharynx (candidiasis, sore throat, dysphonia).

Combinations of inhaled ß$_2$-adrenoreceptor agonist bronchodilators such as formoterol or salmeterol with ICS's are also used to treat both the bronchoconstriction and the inflammation associated with asthma and COPD (Symbicort® and Advair®, respectively). However, these combinations have the side effects of both the ICS's and the ß$_2$-adrenoreceptor agonist because of systemic absorption (tachycardia, ventricular dysrhythmias, hypokalemia) primarily because neither agent is delivered exclusively to the optimal sites of action in the lungs. In consideration of all problems and disadvantages connected with the adverse side effect profile of ICS and of β-agonists it would be highly advantageous to provide a drug which masks the pharmacological properties of both steroids and β-agonists until such a drug reaches the optimal site of action.

Muscarinic acetylcholine receptor antagonists (hereinafter "muscarinic antagonists" or "M3 antagonists") have also been employed as bronchodilators for the treatment of respiratory disorders including asthma and chronic obstructive pulmonary disease. Examples of such compounds include ipratropium and tiotropium. Compositions which incorporate both β-agonists and muscarinic antagonists for the treatment of respiratory disorders are known in the art. See, for example, USPN 6433027. In addition, compounds having dual activity as both β-agonists and muscarinic antagonists have been disclosed. Examples of compounds having dual β-agonist and muscarinic antagonist activity can be found in, for example, PCT Publication Numbers WO07/1 7669, WO07/17670, WO08/01 7824, WO08/01 7827, WO08/096127, WO08/096129, WO08/1491 10, all to Argenta; WO05/1 11004 to Boehringer Ingelheim; WO07/090859 to GlaxoSmithKline; WO08/000483 to Novartis;

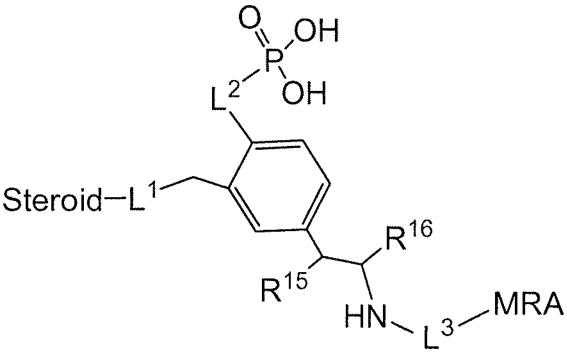
WO07/1 07828 and WO08/041 095 both to Pfizer; and WO04/0 74246, WO04/074812, WO04/089892, WO04/1 06333, WO05/051 946, WO05/080375, WO06/023454, WO06/023457, WO06/023460, WO07/127196 and WO07/1 27297 all to Theravance. The foregoing references also describe processes for making such dual active compounds and methods of treatment utilizing the same.

Certain phenylphosphate based mutual prodrugs of corticosteroids and β_2-agonists have been described by Baker in PCT Publication No. WO2006/1 38212. Certain mutual prodrugs of β_2-agonists and muscarinic antagonists have been described by Baker et al. in PCT Publication No. WO2008/076269. Certain mutual prodrugs of I¼-agonists and anti-inflammatory signal transduction modulators have been described by Baker et al., in PCT Publication No. WO2008/076265.

Despite these advances, there remains a need in the art for improved therapy for the treatment of respiratory disorders.

Summary of the Invention

As one aspect, the present invention provides compounds of Formula 1:



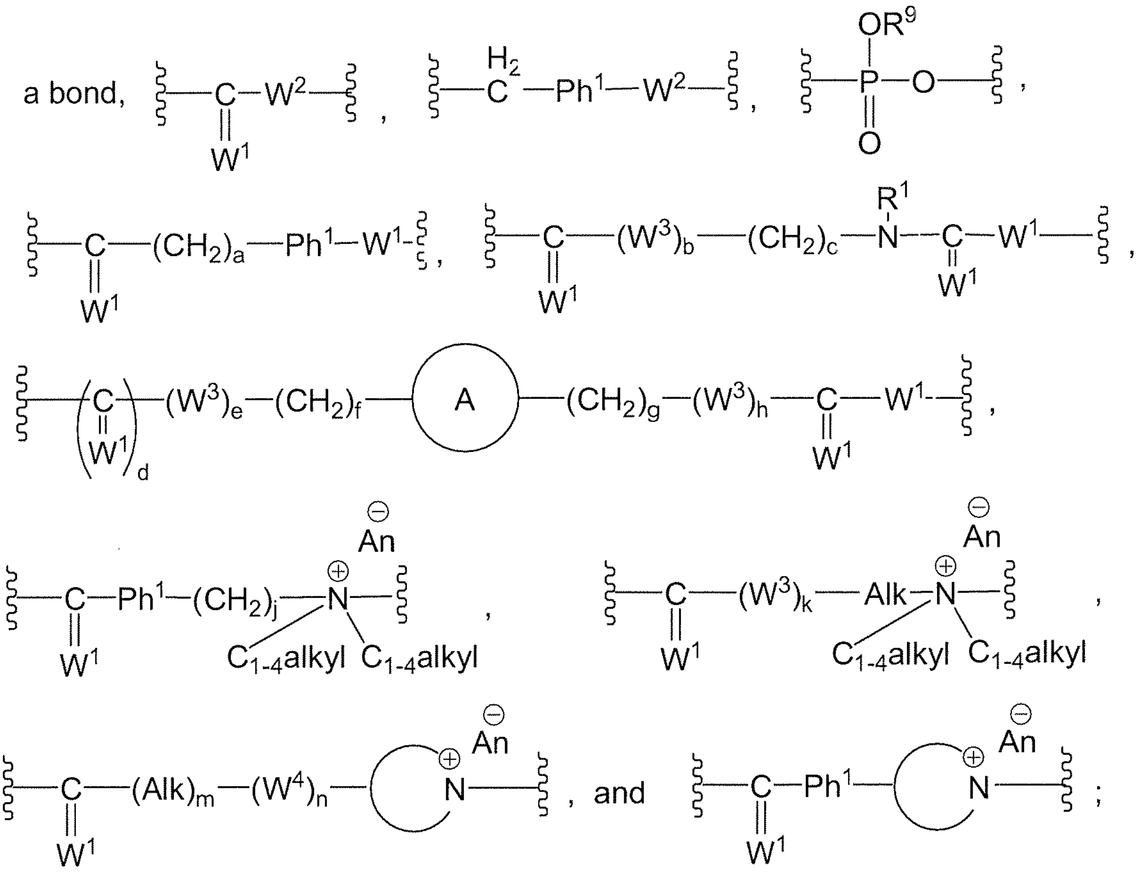
I

or a pharmaceutically acceptable salt thereof,

wherein:

Steroid is a corticosteroid moiety bound to L^1 through O;

L^1 is a selected from



wherein:

each W^1 is the same or different and is O or S;

W^2 is O, S or $N(R^1)$;

Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, $C_{1\text{-}4}$alkyl, OH, $C_{1\text{-}4}$alkoxyl, NH_2, $N(H)C_{1\text{-}4}$alkyl, and $N(C_{1\text{-}4}alkyl)_2$;

R^9 is H, $C_{1\text{-}4}$alkyl, or phenyl;

a is 0, 1, 2, 3, 4, 5 or 6;

each R^1 is the same or different and is independently H or $C_{1\text{-}4}$alkyl;

b is 0 and c is 1, 2, 3, 4, 5 or 6, or b is 1 and c is 2, 3, 4, 5 or 6;

each W^3 is the same or different and is independently -O- or $-N(R^1)-$;

d and e are both 0 and f is 1 or

d is 1, e is 0 or 1 and f is 0, 1, 2, 3, 4, 5 or 6;

Ring A is phenyl, pyridyl or pyrimidyl each optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, N(H)C_{1-4}alkyl, and N(C_{1-4}alkyl)$_2$;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0 or 1;

j is 0, 1, 2, 3, 4, 5 or 6;

k is 0 or 1;

each Alk is the same or different and is selected from

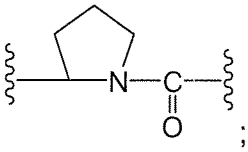
C_{1-6}alkylene or C_{1-6}alkenylene each optionally substituted on nonadjacent carbons by 1, 2 or 3 substituents, selected from halo, OH, C_{1-4}alkoxyl, NH_2, N(H)Ci$_{-4}$alkyl, or N(C_{1-} $_4$alkyl)$_{2-}$;

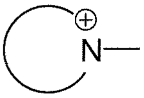
C_{3-6}cycloalkylene-Ci$_{-4}$alkylene; and

-CH(AA)- wherein AA is a proteinogenic amino acid side chain;

m is 0 or 1;

n is 0 or 1 and W^4 is -N(H)-C(O)-;

or $(Alk)_m$ and $(W^4)_n$ join to form:  ;

 is a quaternary N-heteroaryl having 5 or 6 ring atoms wherein one ring atom is a quaternary N and optionally one additional ring atom is N; or a quaternary N-heterocycle having 5 or 6 ring atoms wherein one ring atom is a quaternary N-methyl and optionally one additional ring atom is N, wherein said N-heteroaryl and said N-heterocycle are optionally substituted on any available ring atom with C_{1-4}alkyl;

each An® is a pharmaceutically acceptable counterion;

L^2 is a -O- or -O-CH $_2$-O-;

R^{15} is H, F, OH or methyl;

R^{16} is H, methyl or ethyl;

L^3 is selected from:

C_{4-12}alkylene, C_{4-12}alkenylene, or C_{4-12}alkynylene, each optionally substituted once or twice by a C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl or a

5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S;

C_{1-6}alkylene, C_2-6alkenylene, or C_{2-}6alkynylene wherein one carbon of said alkylene, alkenylene or alkynylene is *optionally* replaced by a Cs-ecycloalkylene, C 3-6cycloalkenylene, phenylene, or a 5-6 membered heterocyclene having 1 or 2 heteroatoms selected from N, O or S;

Alk^1-Q^1-Alk^2;

Alk^1-RG^1- Q^1-Alk^2

Alk^1-RG^1-Q^1-Alk^2-Q^1-Alk^3; and

Alk^1-Q^1-RG^1-Q^1-Alk^2;

wherein:

Alk^1 is C_{1-6}alkylene;

each Q^1 is the same or different and is -0-, -S-, -N(H)-, -N(Ci$_{-4}$alkyl)-, -C(0)N(H)-, -C(0)N(Ci $_{-4}$alkyl)-,-N(H)C(O)-, or -N(Ci $_{-4}$alkyl)C(O)-;

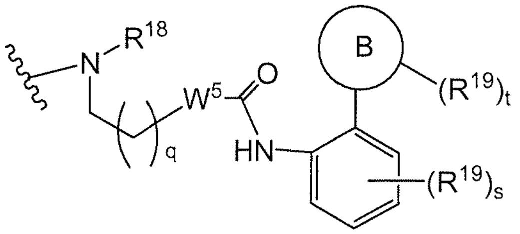
Alk^2 and Alk^3 are each the same or different and are Ci-6alkylene, C 2-6alkenylene, or C_{2-}6alkynylene;

RG^1 is phenylene or pyridylene each optionally substituted by 1, 2, 3 or 4 substituents selected from halo, C_1-ealkyl, C_{1-4}haloalkyl, OH, C_{1-4}alkylOH, O-Ci$_{-6}$alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl, N(Ci$_{-6}$alkyl)$_2$, and CN;

and

MRA is a moiety having muscarinic receptor antagonist activity.

In one embodiment, the compounds of Formula I are defined wherein MRA is selected from:

i) 

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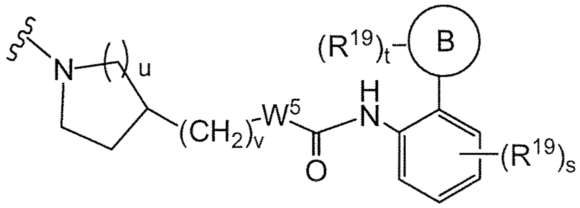

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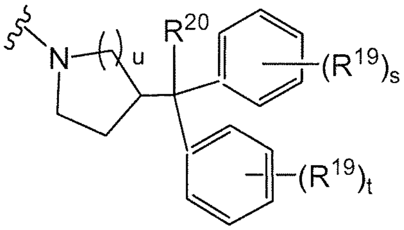
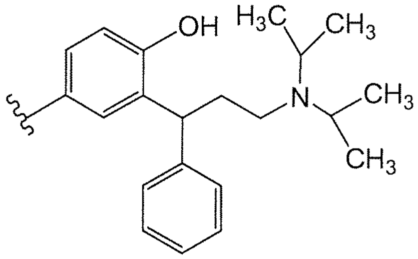


iii) , iv)



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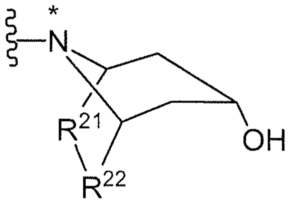
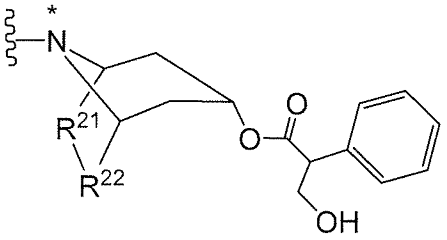


v) , vi)



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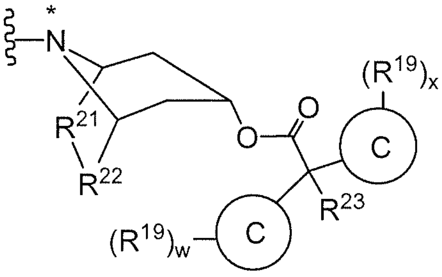
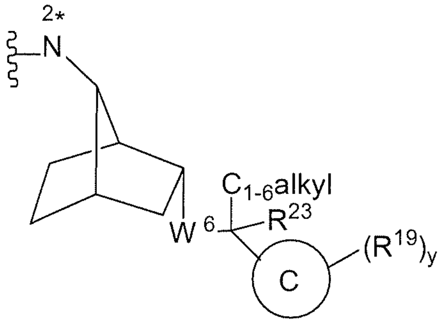


vii) , viii)



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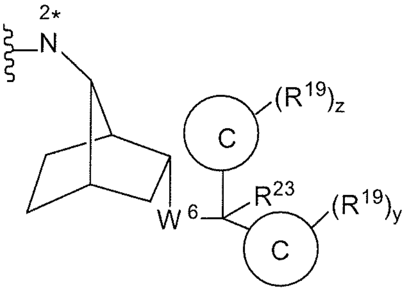
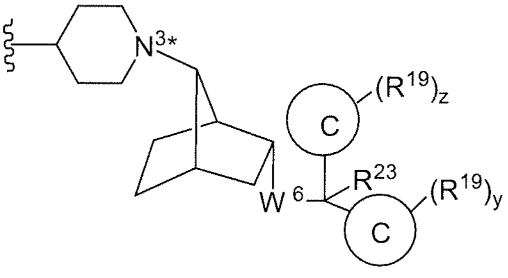


ix) x)



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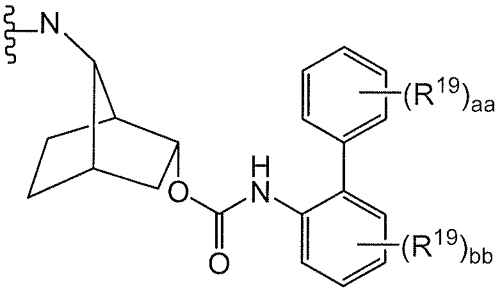
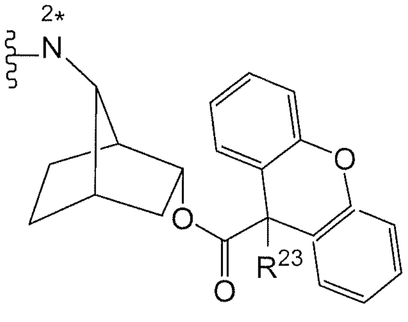


xi) , xii)



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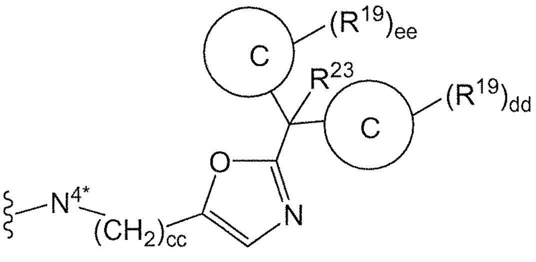
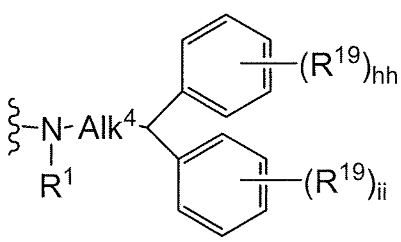
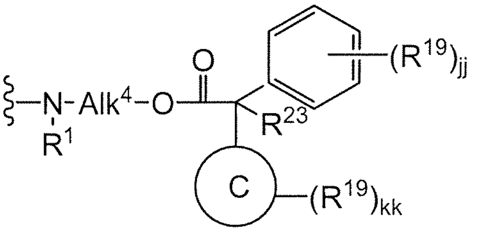
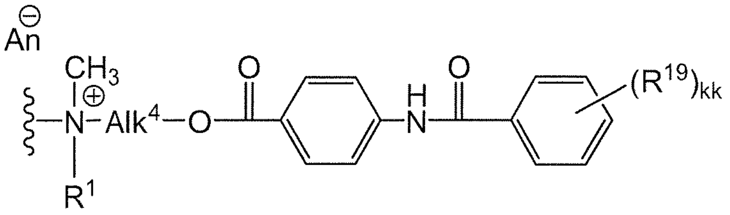
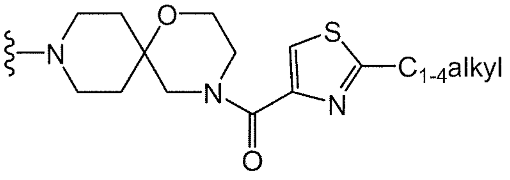
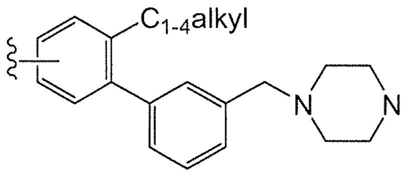
xiii)  , xiv)  ,

xv)  ,

xvi)  ,

xvii)  , and

xviii)  ;

wherein:

R^{18} is H, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, or $C_{3\cdot 6}$cycloalkyl;

q is 1, 2, 3, 4, 5, 6, or 7;

W^5 is O, NH, or N(Ci_{-6}alkyl);

each s, t, w, x, y, z, aa, bb, dd, ee, hh, ii, jj, and kk, is the same or different and is independently 0, 1, 2, or 3;

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, Ci_4haloalkyl, OH, O-C_{1-6}alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-Ci_{-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci_{-6}alkyl and N(C_{1-6}alkyl)$_2$ and CN;

each Ring B is phenyl or 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S;

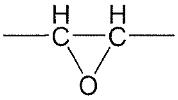
u is 1 or 2;

v is 0, 1, 2 or 3;

R^{20} is CN, $C0_2H$, CO_2C_{1-6}alkyl, $CONH_2$, $CON(H)C_{1-6}$alkyl, $CON(C_{1-6}alkyl)_2$, OH;

N^* is N, $(N^{\circledR}H)A\eta^{\ominus}$, $(N^{\circledR}-CH_3)An^{\ominus}$, or $(N^{\circledR}-CH(CH_3)_2)An^{\ominus}$;

R^{21} and R^{22} together are $-CH_2-CH_2-$, -CH=CH- or



;

each Ring C is the same or different and is selected from phenyl, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S;

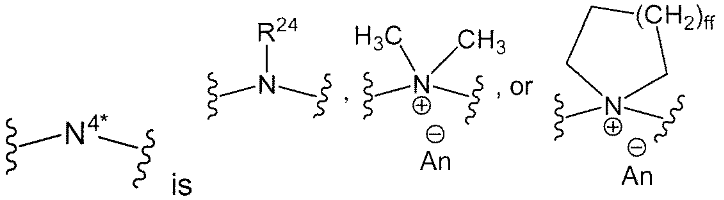
R^{23} is H or OH;

N^{2*} is $N(R^{24})$ or $(N^{\circledR}(CH_3)_2)An^{\ominus}$;

R^{24} is H or C_{1-6}alkyl;

W^6 is -O-C(=0)-, $-O-CH_2-$, or -N(H)C(=O)-;

N^{3*} is N, $(N^{\circledR}H)A\eta^{\theta}$, $N\Theta(CH_3)A\eta^{\theta}$, or $(N^{\circledR}-CH(CH_3)_2)An^{\ominus}$;



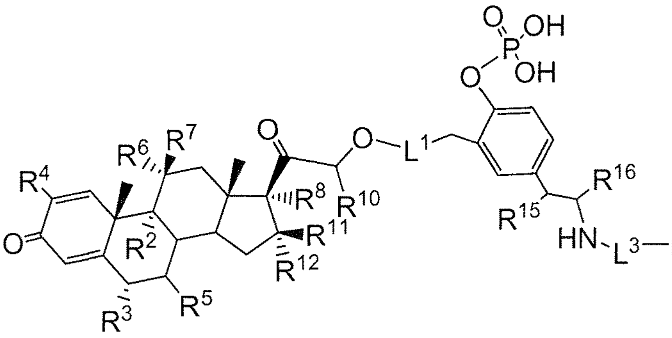
, wherein R^{24} is H or C_{1-6}alkyl, and ff is 1 or 2;

cc is 1, 2 or 3;

Alk^4 is C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene; and

$An^{\circledR}$ is a pharmaceutically acceptable counterion.

In one embodiment, the present invention provides compounds of Formula II:



II

and pharmaceutically acceptable salts thereof, wherein:

each R^2, R^3, R^4, and R^5 are the same or different and are independently H, C_{1-4}alkyl or halo;

R^6 and R^7 are the same or different and are independently H or OH; or R^6 and R^7 taken together with the carbon to which they are attached form a >C=O group;

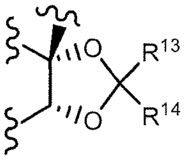
R^8 is H, OH, O(CO)C_{1-4}alkyl, or O(CO)OC_{1-4}alkyl;

each R^{10} and R^{11} is the same or different and is independently H or C_{1-4}alkyl;

R^{12} is H, OH, or C_{1-4}alkyl; or

R^{11} and R^{12} taken together with the carbon to which they are attached form a >=CH_2 group; or

R^{12} and R^8 taken together with the carbons to which they are attached form a 1,3-dioxolane ring represented by formula B:

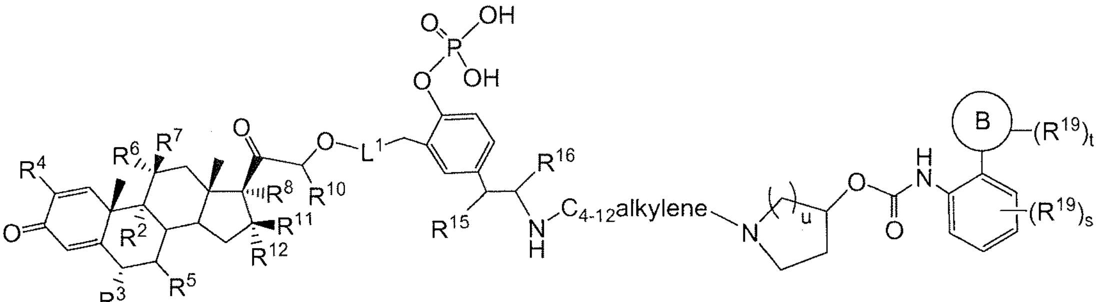


formula B;

wherein one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, C_{1-10}alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkenyl, or optionally substituted 5-6 ring atom heterocycle wherein 1 or 2 ring atoms are selected from N, O and S, and wherein said cycloalkyl, cycloalkenyl, and said heterocycle are each optionally substituted 1, 2 or 3 times with a substituent selected from halo, C_{1-4}alkyl, and O-C_{1-4}alkyl;

and all other variables are as defined above.

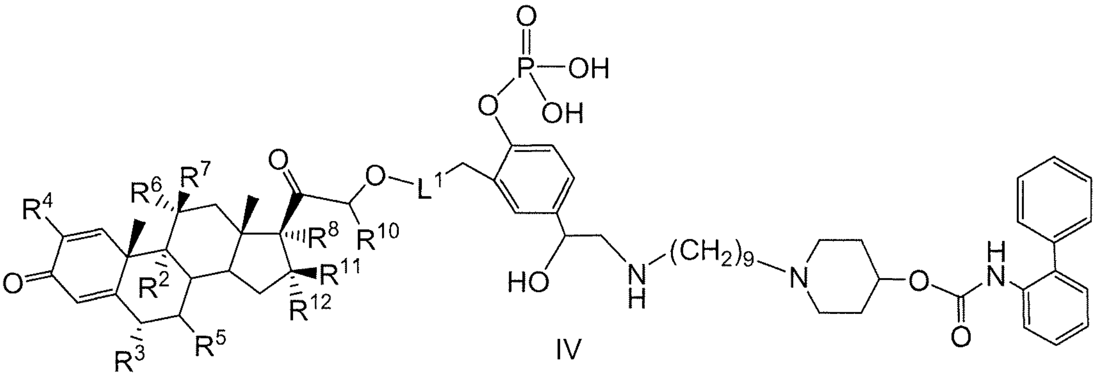
In another embodiment, the present invention provides compounds of Formula III:



III

and pharmaceutically acceptable salts thereof, wherein all variables are as defined above.

In another embodiment, the present invention provides compounds of Formula IV:



IV

and pharmaceutically acceptable salts thereof, wherein all variables are as defined above.

As another aspect, the present invention provides a composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, diluent or carrier.

As another aspect, the present invention provides a method for the treatment of pulmonary inflammation or bronchoconstriction in a human in need thereof. The method comprises administering to the human an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

As another aspect, the present invention provides a method for the treatment of a disease associated with reversible airway obstruction, asthma, COPD, bronchiectasis, or emphysema in a human in need thereof. The method comprises administering to the human an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

As another aspect, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the treatment of pulmonary inflammation or bronchoconstriction in a human.

As another aspect, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the treatment of a disease associated with reversible airway obstruction, asthma, COPD, bronchiectasis, or emphysema in a human.

As another aspect, the present invention provides use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of pulmonary inflammation or bronchoconstriction in a human.

As another aspect, the present invention provides use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a disease associated with reversible airway obstruction, asthma, COPD, bronchiectasis, or emphysema in a human.

As another aspect, the present invention provides a composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a medicament for the treatment of pulmonary inflammation or bronchoconstriction in a human.

As another aspect, the present invention provides a composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a medicament for the treatment of reversible airway obstruction, asthma, COPD, bronchiectasis, or emphysema in a human.

Detailed Description of the Invention

Headings are employed throughout the disclosure solely for ease of reference and are in no way to be construed as indicating that all subject matter in the passages below a particular heading constitute the sole disclosure relevant to the topic.

Definitions

When trade names are used herein, applicants intend to independently include the trade name product and the active pharmaceutical ingredient(s) of the trade name product.

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

"a compound of the invention" means a compound of Formula I, which includes compounds of formula II, III, and IV or a salt, particularly a pharmaceutically acceptable salt thereof.

"a compound of Formula I" means a compound having the structural formula designated herein as Formula I, including compounds of Formulas II, III and IV. Compounds of Formula I include solvates and hydrates as well as any amorphous and crystalline (polymorphic) forms thereof. In those embodiments wherein a compound of Formula I includes one or more chiral centers, the phrase is intended to encompass each individual stereoisomer including optical isomers (enantiomers and diastereomers) and geometric isomers (cis-/trans-isomerism) and mixtures of stereoisomers. Similarly, with respect to other compounds referred to herein, such as compounds of Formula II, III, IV and isolatable intermediates, the phrase "a compound of Formula (number)" means a compound of that formula and solvates and hydrates as well as amorphous and crystalline (polymorphic) forms thereof, and stereoisomers (where compounds include a chiral center) thereof.

"alkyl" as used herein refers to linear or branched hydrocarbon chains containing from 1 to 10 carbon atoms (*i.e.,* C_{1-10}alkyl), unless a different number of atoms is specified. Examples of "alkyl as used herein include but are not limited to methyl (Me), ethyl (Et), n-propyl (1-Pr, 1-propyl), isopropyl (i-Pr, 2-propyl), n-butyl (n-Bu, 1-butyl), isobutyl, (i-Bu, 2-methyl-1 -propyl), sec-butyl (s-Bu, 2-butyl), tert-butyl (t-butyl, t-Bu, 2-methyl-2-propyl), n-pentyl (1-pentyl), 2-pentyl, 3-pentyl $(-CH(CH_2CH_3)2)$, 2-methyl-2-butyl $(-C(CH_3)2CH2CH3)$, 3-methyl-2-butyl $(-CH(CH_3)CH(CH_3)_2)$, 3-methyl-1 -butyl $(-CH_2CH_2CH(CH_3)2)$, 2-methyl-1-butyl $(-CH_2CH(CH3)CH_2CH3)$, 1-hexyl, 2-hexyl, 3-hexyl $(-CH(CH_2CH3)(CH_2CH2CH3))$, 2-methyl-2-pentyl $(-C(CH3)2CH_2CH_2CH3)$, 3-methyl-2-pentyl $(-CH(CH_3)CH(CH_3)CH_2CH_3)$, 4-methyl-2-pentyl $(-CH(CH_3)CH_2CH(CH_3)_2)$, 3-methyl-3-pentyl $(-C(CH_3)(CH_2CH_3)2)$, 2-methyl-3-pentyl $(-CH(CH_2CH_3)CH(CH_3)_2)$, 2,3-dimethyl-2-butyl $(-C(CH_3)2CH(CH_3)2)$, 3,3-dimethyl-2-butyl $(-CH(CH_3)C(CH_3)_3$, and octyl $(-(CH_2)7CH_3)$. When the compound of Formula I includes more than one alkyl, the alkyls may be the same or different.

"alkoxyl" refers to linear or branched hydrocarbon chains containing from 1 to 10 carbon atoms (*i.e.,* C-i.-ioalkoxyl), unless a different number of atoms is specified, and an oxygen atom. Examples of alkoxyl groups include but are not limited to $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-CH_2-0-CH_3$, and the like.

"alkylene" refers to a linear or branched divalent hydrocarbon chain having from 1 to 12 carbon atoms (*i.e.,* Ci.^alkylene), unless a different number of carbon atoms is specified. Examples of "alkylene" as used herein include but are not limited to methylene, 1,1-ethyl $(-CH(CH_3)-)$, ethylene, propylene (1,3-propyl $(-CH_2CH_2CH_2-)$; 1,1-propyl $(-CH(CH_2CH_3)-)$, or 1,2-propyl $(-CH_2CH(CH_3)-)$) and butylene (1,4-butyl $(-CH2CH_2CH_2CH_2-)$), and the like. When the compound of Formula I includes more than one alkylene, the alkylenes may be the same or different.

"alkenyl" " as used herein refers to linear or branched hydrocarbon chains containing from 2 to 10 carbon atoms (*i.e.,* C_2-ioalkenyl), unless a different number of atoms is specified, and at least one carbon-carbon double bond. Examples of suitable alkenyl groups include, but are not limited to, ethenyl or vinyl $(-CH=CH_2)$, propenyl or allyl $(-CH_2CH=CH_2)$, and 5-hexenyl (-$CH_2CH_2CH_2CH_2CH=CH_2$). When the compound of Formula I includes more than one alkenyl, the alkenyls may be the same or different.

"alkenylene" refers to an unsaturated, linear or branched divalent hydrocarbon radical having at least one carbon-carbon double bond and from 2 to 12 carbon atoms ("C_{2-12} alkenylene"), unless the number of carbon atoms is specified. When the compound of Formula I includes more than one alkenylene the alkenylenes may be the same or different. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

"alkynyl" as used herein refers to linear or branched hydrocarbon chains containing from 2 to 10 carbon atoms *{i.e.,* C_{2-10}alkynyl), unless a different number of atoms is specified, and at least one carbon-carbon triple bond. Examples of alkynyl groups include, but are not limited to, ethynyl (-C≡CH), propargyl (-$CH_2C≡CH$), and the like. When the compound of Formula I includes more than one alkynyl, the alkynyls may be the same or different.

"alkynylene" refers to an unsaturated, linear or branched divalent hydrocarbon radical having at least one carbon-carbon triple bond and from 2 to 12 carbon atoms ("C_{2-i2} alkynylene"), unless the number of carbon atoms is specified. When the compound of Formula I includes more than one alkynylene the alkynylenes may be the same or different. Typical alkenylene radicals include, but are not limited to -C≡C-.

"halo" or "halogen" are synonymous and refer to fluoro, chloro, bromo, and iodo.

"haloalkyi" is linear or branched hydrocarbon chain of from 1 to 8 carbon atoms *{i.e.,* C_{1-8}haloalkyl), or typically, 1 to 6 carbon atoms *{i.e.,* C_{1-6}haloalkyl), unless the number of carbon atoms is otherwise specified, substituted by one or more halogens, fluoro, chloro, bromo and iodo. Haloalkyi include perhaloalkyls such as trifluoromethyl. When the compound of Formula I includes more than one haloalkyi, the haloalkyls may be the same or different. Examples of suitable haloalkyi groups include, but are not limited to, fluoromethyl, chloromethyl, trifluoromethyl, dichloromethyl, dichloroethyl, and the like.

"oxo" as used herein refers to the group =0 attached directly to a carbon atom of a hydrocarbon ring or a C, N or S of a heterocyclic ring to result in oxides, -N-oxides, sulfones and sulfoxides.

"Cycloalkyl" refers to a monocyclic saturated carbon ring having 3 to 10 carbon atoms, (C3 -iocycloalkyl) unless a different number of carbon atoms is specified. When the compound of Formula I includes more than one cycloalkyl, the cycloalkyl groups may be the same or different. Examples of specific cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In those embodiments wherein the compound of Formula I includes more than one cycloalkenyl, the cycloalkenyls may be the same or different.

"cycloalkylene" refers to a divalent cycloalkyl, as defined above.

"cycloalkenyl" refers to a monocyclic partially unsaturated, non-aromatic carbon ring having 3 to 10 carbon atoms, ($C_{3\text{-}10}$cycloalkenyl) unless a different number of carbon atoms is specified. In those embodiments wherein the compound of Formula I includes more than one cycloalkenyl, the cycloalkenyls may be the same or different.

"cycloalkenylene" refers to a divalent cycloalkenyl, as defined above.

"heterocycle" or "heterocyclyl" are synonymous and refer to monocyclic saturated or partially unsaturated, non-aromatic rings having the specified number of ring atoms (typically 5 or 6 ring atoms) wherein 1, 2, or 3 ring atoms is/are a heteroatom independently selected from N, O and S, unless a different number of heteroatoms is specified, and all other ring atoms are C. In all embodiments wherein the heterocycle includes 2 or more heteroatoms (N, O and S) the heteroatoms may be the same or different. In all embodiments wherein the compound of Formula I includes 2 or more heterocycles, the heterocycles may be the same or different. Examples of heterocycles include but are not limited to pyrrolinyl, pyrrolidinyl, dioxolanyi, oxazolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyranyl, dihydropyranyl, tetrahydropyranyl, dihydropyridyl, piperidyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, and the like.

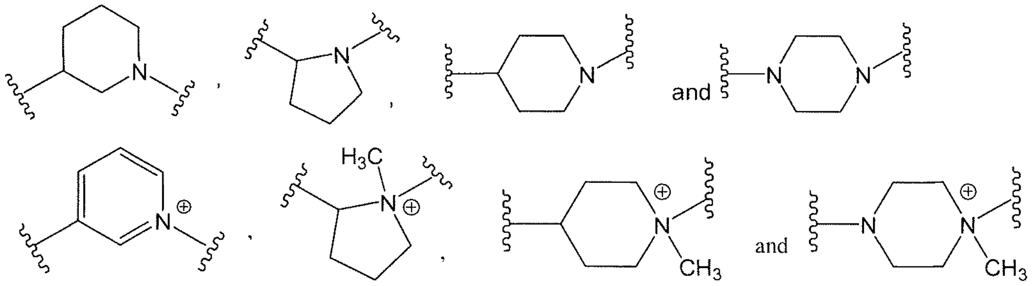
Heterocyclic groups may be bound through any available ring carbon or ring heteroatom, such as N.

“N-heterocycle" refers to monocyclic saturated or partially unsaturated, non-aromatic rings having the specified number of ring atoms (typically 5 or 6 ring atoms) including at least one N ring atom (which may be a quaternary N) and optionally 1 or 2 additional heteroatoms independently selected from N, O and S, unless a different number of heteroatoms is specified, and all other ring atoms are C. In all embodiments wherein the N-heterocycle includes 1 or more additional heteroatoms, the heteroatoms may be the same or different. In all embodiments wherein the compound of Formula I includes 2 or more N-heterocycles, the heterocycles may be the same or different. Examples of N-heterocycles include but are not limited to pyrrolinyl, pyrrolidinyl, oxazolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, dihydropyridyl, piperidyl, morpholinyl, thiomorpholinyl, piperazinyl, and the like. N-Heterocycles may be bound through any available ring carbon or through the N. N-heterocycles bound through the N of the heterocycle are sometimes referred to as "N-linked heterocycles."

"heteroaryl" refers to monocyclic aromatic rings having the specified number of ring atoms (typically 5 or 6 ring atoms) wherein 1, 2, 3 or 4 ring atoms is/are a heteroatom independently selected from N, O and S, unless a different number of heteroatoms is specified. In all embodiments wherein the heteroaryl includes 2 or more heteroatoms (N, O and S) the heteroatoms may be the same or different. In all embodiments wherein the compound of Formula I includes 2 or more heteroaryls, the heteroaryls may be the same or different. Non-limiting examples of heteroaryls include furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, and tetrazolyl, and the like. Heteroaryls may be bound through any available ring carbon or ring heteroatom, such as N.

“N-heteroaryl" refers to monocyclic aromatic rings having the specified number of ring atoms (typically 5 or 6 ring atoms) including at least one N ring atom (which may be a quaternary N) and optionally 1 or 2 additional heteroatoms independently selected from N, O and S, unless a different number of heteroatoms is specified, and all other ring atoms are C. In all embodiments wherein the N-heteroaryl includes 1 or more additional heteroatoms, the heteroatoms may be the same or different. In all embodiments wherein the compound of Formula I includes 2 or more N-heteroaryls, the heteroaryls may be the same or different. Examples of N-heteroaryls include pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, tetrazolyl, and the like. N-Heteroaryls may be bound through any available ring carbon or through the N. N-heteroaryls bound through the N of the heteroaryl are sometimes referred to as "N-linked heteroaryls."

"heterocyclene" refers to a bivalent heterocycle as defined herein. For example, heterocyclenes include:

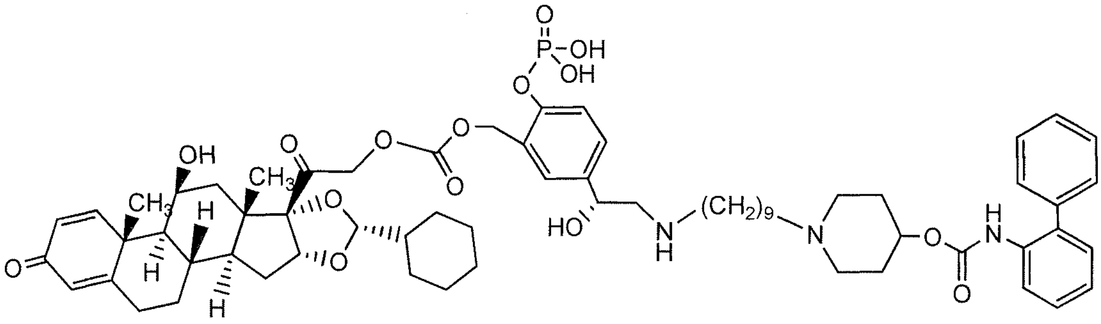


In those embodiments wherein the compounds of Formula I, include more than one heterocyclene, the heterocyclenes may be the same or different.

"optionally substituted" in reference to a particular moiety of the compound of Formula I (e.g., an optionally substituted phenyl) refers to that moiety having no substituents, and that moiety having the specified number of substituents; typically from 1 to 4 substituents unless otherwise indicated. Unless otherwise indicated, when the term "substituted" is used in conjunction with groups which have multiple available sites for substitution or two or more moieties capable of substitution, the substituents can be attached to any available C or heteroatom.

Compounds

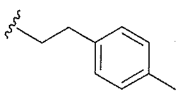
Throughout the description and examples, compounds are named using standard IUPAC naming principles where possible. The naming convention employed for the novel compounds are exemplified by the following name: "[(R)-1-[9-[2-[3-[illegible]11ß,16a]-[15,16-((R)-cyclohexylmethylene)bis(oxy)]-11-hydroxypregna-1,4-diene-3,20-dion-21-yl]oxycarbonyloxy]methyl]-4-(phosphonooxy)phenyl]-2-hydroxyethylamino]nonyl]piperidin-4-yl] (biphenyl-2-yl)carbamate" which corresponds to the structure shown below:



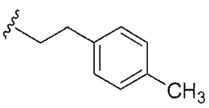
One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I should be selected in order to avoid embodiments which would be recognized by one of ordinary skill in the art as obviously inoperative.

In some chemical structure representations where carbon atoms do not have a sufficient number of variables attached to produce a valence of four, the remaining carbon substituents needed to provide a valence of four should be assumed to be hydrogen.

Similarly, in some chemical structures where a bond is drawn without specifying the terminal group, such bond is indicative of a methyl group, as is conventional in the art. Thus,



is the same as



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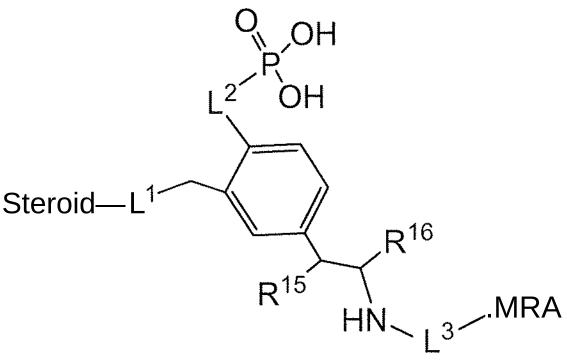
In one aspect, the invention comprises compounds of Formula I:



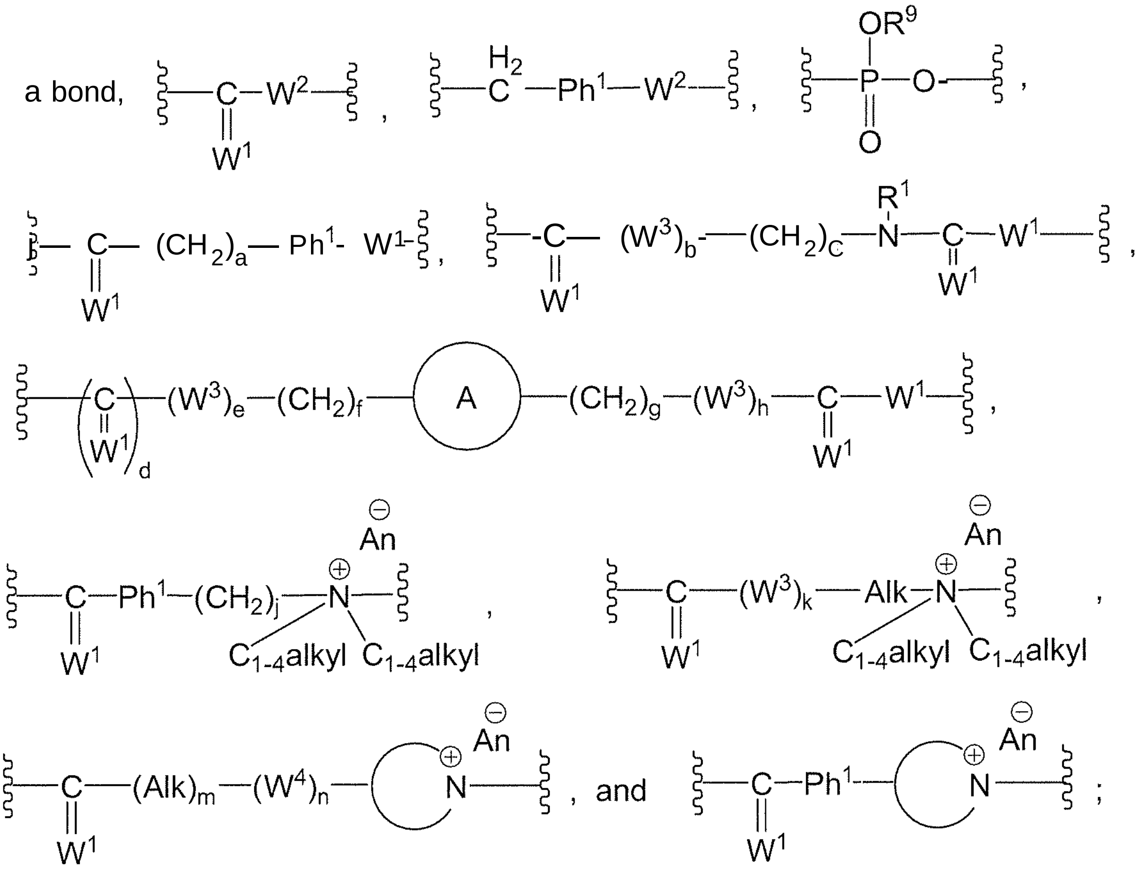
I

or a pharmaceutically acceptable salt thereof,

wherein:

Steroid is a corticosteroid moiety bound to L^1 through O;

L^1 is a selected from



wherein:

each W^1 is the same or different and is O or S;

W^2 is O, S or $N(R^1)$;

Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, c_{1-4}alkyl, **OH,** **C_{1-4}**alkoxyl, **NH_2,** **N(H)C_{1-4}**alkyl, and **N(C_{1-4}**alkyl$)_2$;

R^9 is **H,** **C_{1-4}**alkyl, or phenyl;

a is 0, 1, 2, 3, 4, 5 or 6;

each R^1 is the same or different and is independently **H** or **C_{1-4}**alkyl;

b is 0 and c is 1, 2, 3, 4, 5 or 6, or b is 1 and c is 2, 3, 4, 5 or 6;

each W^3 is the same or different and is independently **-O-** or -N(R ^{1})-;

d and e are both 0 and f is 1 or

d is 1, e is 0 or 1 and f is 0, 1, 2, 3, 4, 5 or 6;

Ring A is phenyl, pyridyl or pyrimidyl each optionally substituted on any available carbon with a substituent selected from halo, **C_{1-4}**alkyl, **OH,** **C_{1-4}**alkoxyl, **NH_2,** **N(H)C_{1-4}**alkyl, and **N(C_{1-4}**alkyl$)_2$;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0 or 1;

j is 0, 1, 2, 3, 4, 5 or 6;

k is 0 or 1;

each Alk is the same or different and is selected from

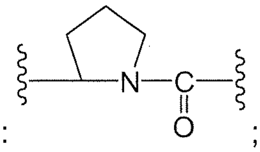
C_{1-6}alkylene or **C_{1-6}**alkenylene each optionally substituted on nonadjacent carbons by 1, 2 or 3 substituents, selected from halo, **OH,** **C_{1-4}**alkoxyl, **NH_2,** **N(H)Ci**$_{-4}$alkyl, or N(C_{1-4}alkyl$)_2$;

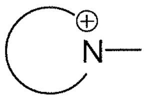
c_3-ecycloalkylene**-Ci**^alkylene; and

-CH(AA)- wherein AA is a proteinogenic amino acid side chain;

m is 0 or 1;

n is 0 or 1 and W^4 is **-N(H)-C(O)-;**

or $(Alk)_m$ and $(W^4)_n$ join to form:  ;

 is a quaternary N-heteroaryl having 5 or 6 ring atoms wherein one ring atom is a quaternary N and optionally one additional ring atom

is N; or a quaternary N-heterocycle having 5 or 6 ring atoms wherein one ring atom is a quaternary N-methyl and optionally one additional ring atom is N, wherein said N-heteroaryl and said N-heterocycle are optionally substituted on any available ring atom with **C**$_{1-4}$alkyl;

each An® is a pharmaceutically acceptable counterion;

L^2 is a -O- or -0-CH $_2$-0-;

R^{15} is H, F, OH or methyl;

R^{16} is H, methyl or ethyl;

L^3 is selected from:

C$_{4-12}$alkylene, C^-^alkenylene, or C$_{4-12}$alkynylene, each optionally substituted once or twice by a C$_{3-6}$cycloalkyl, C $_{3-6}$cycloalkenyl or a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S;

Ci$_{-6}$alkylene, C-2-6alkenylene, or C$_{2-}$6alkynylene wherein one carbon of said alkylene, alkenylene or alkynylene is *optionally* replaced by a **C**$_3$-ecycloalkylene, C 3.6cycloalkenylene, phenylene, or a 5-6 membered heterocyclene having 1 or 2 heteroatoms selected from N, O or S;

Alk^1-Q^1-Alk^2;

Alk^1-RG^1- Q^1-Alk^2

Alk^1-RG^1-Q^1-Alk^2-Q^1-Alk^3; and

Alk^1- Q^1-RG^1-Q^1-Alk^2;

wherein:

Alk^1 is **C**$_{1-6}$alkylene;

each Q^1 is the same or different and is -O-, -S-, -N(H)-, -N**(Ci**$_{-4}$alkyl)-, **-C(0)N(H)-,** -C(O)N **(Ci**$_{-4}$alkyl)-,-N(H)C(O)-, or -N(C $_{1-4}$alkyl)C(O)-;

Alk^2 and Alk^3 are each the same or different and are **C**$_{1-6}$alkylene, C$_{2-6}$alkenylene, or C$_{2-6}$alkynylene;

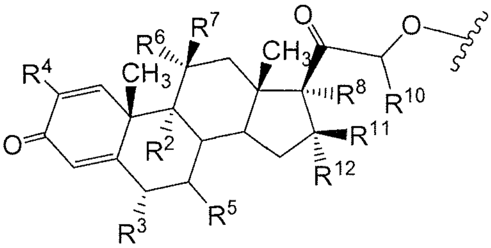
RG^1 is phenylene or pyridylene each optionally substituted by 1, 2, 3 or 4 substituents selected from halo, **C**$_{1-6}$alkyl, **C**$_{1-4}$haloalkyl, OH, **C**$_{1-4}$alkylOH, O-C$_{1-6}$alkyl, S-C$_{1-6}$alkyl, SO$_2$C$_{1-6}$alkyl, NH$_2$, N(H)C$_{1-6}$alkyl, N(C$_{1-6}$alkyl)$_2$, and CN;

and

MRA is a moiety having muscarinic receptor antagonist activity.

For the sake of brevity, the description of embodiments below may reference "compounds of Formula I". It should be understood that the definitions of variables and embodiments thereof apply equally to the same variable in compounds of Formula II, III and IV, as if the disclosure referenced all, since such compounds are also compounds of Formula I.

In one embodiment, the compounds of Formula I are defined wherein Steroid is a corticosteroid moiety of formula:



wherein:

each R^2, R^3, R^4, and R^5 are the same or different and are independently H, C_{1-4}alkyl or halo;

R^6 and R^7 are the same or different and are independently H or OH; or R^6 and R^7 taken together with the carbon to which they are attached form a >C=O group;

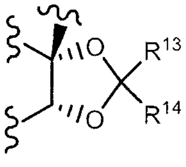
R^8 is H, OH, O(CO)C_{1-4}alkyl, or O(CO)OC_{1-4}alkyl;

each R^{10} and R^{11} is the same or different and is independently H or C_{1-4}alkyl;

R^{12} is H, OH, or C_{1-4}alkyl; or

R^{11} and R^{12} taken together with the carbon to which they are attached form a >=CH_2 group; or

R^{12} and R^8 taken together with the carbons to which they are attached form a 1,3-dioxolane ring represented by formula B:



formula B;

wherein one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkenyl, or optionally substituted 5-6 membered heterocycle wherein 1 or 2 ring atoms are selected from N, O and S, and wherein said cycloalkyl, cycloalkenyl, and said heterocycle are each optionally substituted 1, 2 or 3 times with a substituent selected from halo, C_{1-4}alkyl, and 0-C_{1-4}alkyl.

In one embodiment the compounds of the invention are defined wherein each of R^2, R^3, R^4, and R^5 are independently H, methyl, F or Cl, or any subset thereof. In one preferred embodiment R^2, R^3, R^4, and R^5 are H. In one embodiment R^4 and R^5 are H and R^2 and R^3 are H, F, Cl or methyl. In one embodiment R^4 and R^5 are H, R^2 is H, F or Cl and R^3 is H, F or methyl. In one particular embodiment R^4 and R^5 are H and R^2 and R^3 are H or F. In one particular embodiment R^4 and R^5 are H and R^2 and R^3 are F. In one particular embodiment R^4 and R^5 are H, R^2 is H and R^3 is F or R^2 is F and R^3 is H.

In one embodiment R^6 and R^7 taken together with the carbon to which they are attached form a >C=0 group. In one preferred embodiment R^6 is H and R^7 is OH.

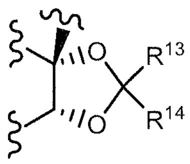
In one embodiment R^8 is H, OH, 0(CO)CH_2CH_3, 0(CO)OCH_3, or 0(CO)OCH_2CH_3, or any subset thereof.

In one embodiment R^{10} is H. In one particular embodiment R^{10} and R^{11} are H. In one embodiment R^{10} is H and R^{11} is methyl.

In one embodiment R^{12} is H, OH, or methyl. In one particular embodiment R^{12} is H or methyl, more particularly H.

In one embodiment R^{11} and R^{12} taken together with the carbon to which they are attached form a >=CH_2 group.

In one preferred embodiment R^{12} and R^8 taken together with the carbons to which they are attached form a 1,3-dioxolane ring represented by formula B:



formula B.

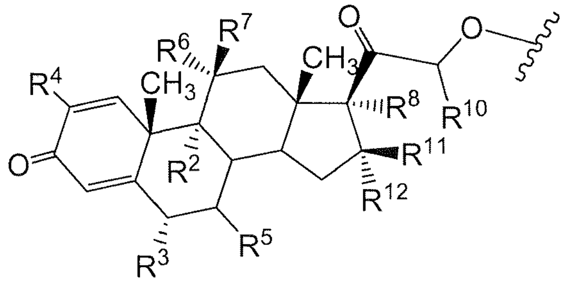
In one embodiment wherein R^{12} and R^{8} form a ring represented by formula **B**, one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, $\mathbf{C}_{1\text{-}10}$alkyl, $\mathbf{C}_{2\text{-}}$ioalkenyl, $\mathbf{C}_{2\text{-}}$ioalkynyl, optionally substituted $\mathbf{C}_{3\text{-}10}$cycloalkyl, optionally substituted $\mathbf{C}_{3\text{-}10}$cycloalkenyl, or optionally substituted 5-6 membered heterocycle wherein 1 or 2 ring atoms are selected from N, O and S, or any subset thereof, wherein the cycloalkyi, cycloalkenyl, and heterocycle are each optionally substituted 1, 2 or 3 times with a substituent selected from halo, $\mathbf{C}_{1\text{-}4}$alkyl, and 0 -$\mathbf{C}_{1\text{-}4}$alkyl.

In one embodiment wherein R^{12} and R^{8} form a ring represented by formula **B**, one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, $\mathbf{C}_{1\text{-}10}$alkyl, c 2-ioalkenyl, $\mathbf{C}_{2\text{-}}$ioalkynyl, or optionally substituted $\mathbf{C}_{3\text{-}}$iocycloalkyl, wherein the cycloalkyi is optionally substituted 1, 2 or 3 times with a substituent selected from halo, $\mathbf{C}_{1\text{-}4}$alkyl, and 0 -$\mathbf{C}_{1\text{-}4}$alkyl.

In one embodiment one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, c 1-10alkyl, or $\mathbf{C}_{3\text{-}}$iocycloalkyl, or any subset thereof. In one embodiment one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, $\mathbf{C}_{1\text{-}4}$alkyl, or $\mathbf{C}_{3\text{-}6}$cycloalkyl, or any subset thereof, more particularly cyclohexyl.

In one embodiment one of R^{13} and R^{14} is H or methyl, more particularly H, and the other is H, $\mathbf{C}_{1\text{-}4}$alkyl, or $\mathbf{C}_{3\text{-}6}$cycloalkyl, or any subset thereof, more particularly cyclohexyl. In one embodiment R^{13} and R^{14} are each methyl. In one embodiment R^{13} is H and R^{14} is propyl. In one preferred embodiment R^{13} is H and R^{14} is cyclohexyl.

In one preferred embodiment Steroid is a corticosteroid moiety of formula:



wherein:

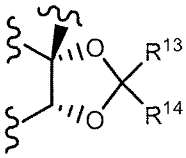
R^2, R^3, R^4, and R^5 are the same or different and are each independently H, methyl, F or Cl;

R^6 is H;

R^7 is OH;

R^{10} and R^{11} are H;

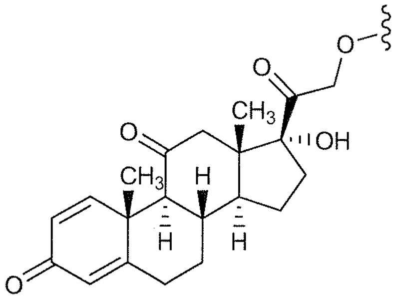
R^{12} and R^8 taken together with the carbons to which they are attached form a 1,3-dioxolane ring represented by formula B:



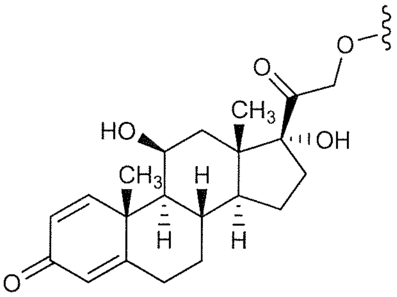
formula B;

one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, Ci-C-|$_0$alkyl, or C_3-C-io cycloalkyl, or any subset thereof.

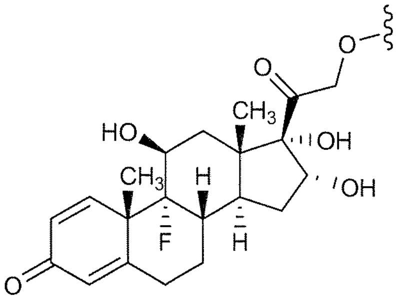
In one preferred embodiment Steroid is a corticosteroid moiety of formula:


O
O
CH3
OH
O
CH3
H
H
H
O

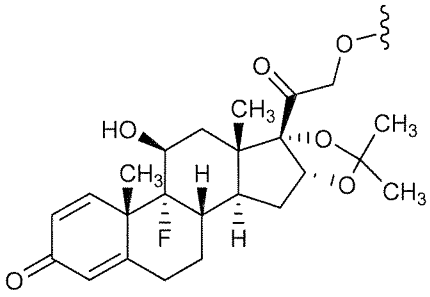
,


O
O
CH3
HO
OH
CH3
H
H
H
O

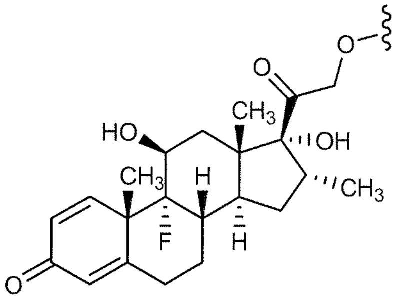
,


O
O
CH3
HO
OH
CH3
H
OH
F
H
O

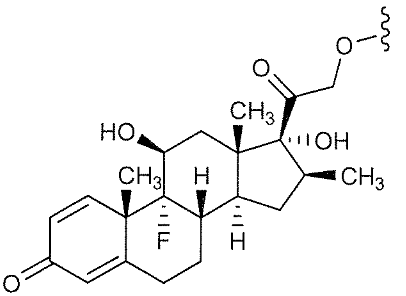
,


O
O
CH3
HO
O
CH3
CH3
H
O
CH3
F
H
O

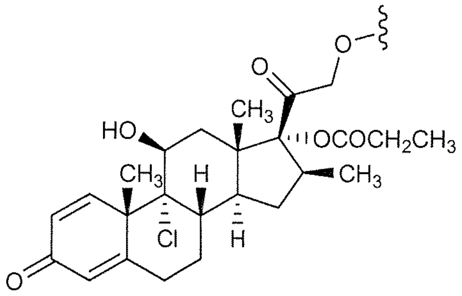
,


O
O
CH3
HO
OH
CH3
H
CH3
F
H
O

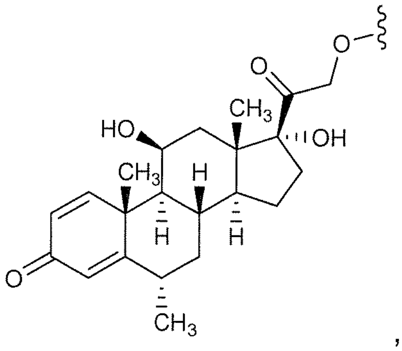
,


O
O
CH3
HO
OH
CH3
H
CH3
F
H
O

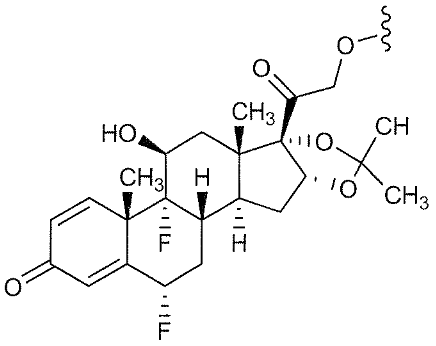
,


O
O
CH3
HO
OCOCH2CH3
CH3
H
CH3
Cl
H
O

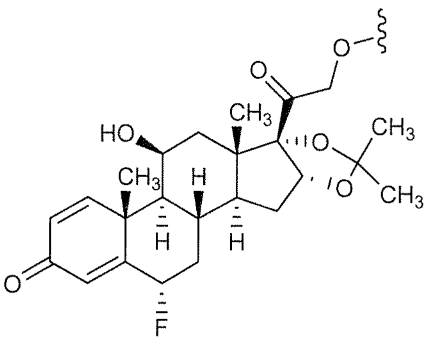
,


O
O
CH3
HO
OH
CH3
H
H
H
O
CH3

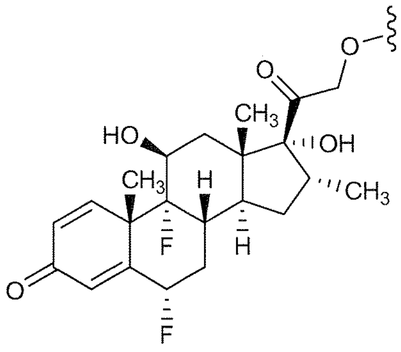
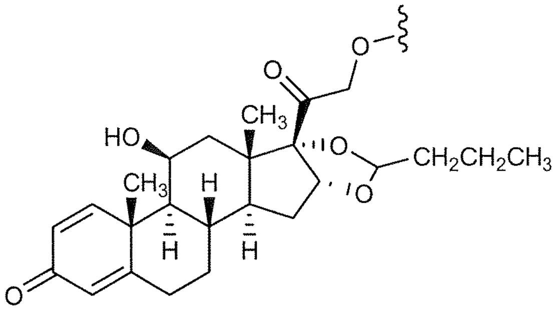
,

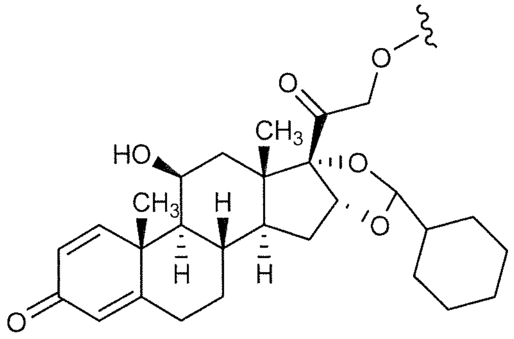

O
O
CH3
HO
O
CH
CH3
H
O
CH3
F
H
O
F

,

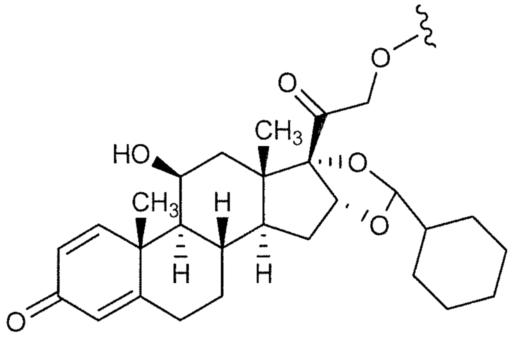

O
O
CH3
HO
O
CH3
CH3
H
O
CH3
H
H
O
F

,

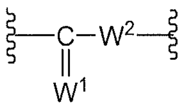

,

, or

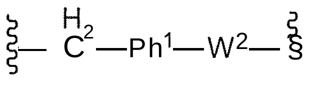

, or any subset thereof.

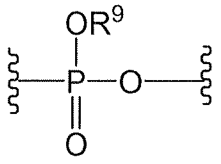
In one preferred embodiment Steroid is:


.

In one embodiment, the compounds of Formula I are defined wherein L^1 is selected from

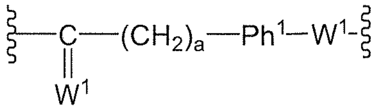
a) 
$-C(=W^1)-W^2-$, wherein W^1 is O, and W^2 is O, N(H), or $N(CH_3)$;

b) 
$-\overset{H_2}{C^2}-Ph^1-W^2-$, wherein Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo or methyl or twice with the same or different substituents selected from halo and methyl, and W^2 is O, N(H), or $N(CH_3)$;

c) 

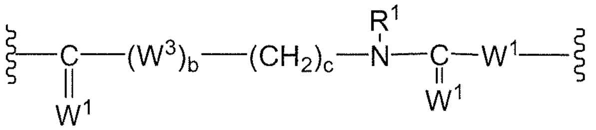
$-\overset{OR^9}{\underset{\|}{\overset{|}{P}}}-O-$ with $=O$ below P

, wherein R^9 is H;

d) 

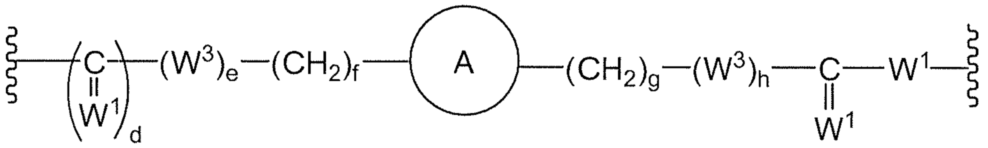
$-\underset{\underset{W^1}{\|}}{C}-(CH_2)_a-Ph^1-W^1-$

, wherein each W^1 is O, a is 1 or 2, and Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo or methyl or twice with the same or different substituents selected from halo and methyl;

e) 

$-\underset{\underset{W^1}{\|}}{C}-(W^3)_b-(CH_2)_c-\overset{R^1}{N}-\underset{\underset{W^1}{\|}}{C}-W^1-$

, wherein each W^1 is O, b is 0 and c is 1, 2 or 3, or b is 1, W^3 is N(H) and c is 2 or 3, and R^1 is H or CH_3;

f) 

$-\left(\underset{\underset{W^1}{\|}}{C}\right)_d-(W^3)_e-(CH_2)_f-(A)-(CH_2)_g-(W^3)_h-\underset{\underset{W^1}{\|}}{C}-W^1-$

,

wherein

d and e are both 0 and f is 1, or

d is 1, e is 1, $(W^3)_e$ is O, and f is 0, 1, 2 or 3, or

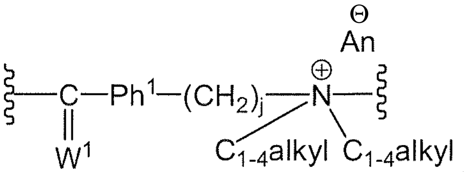
d is 1, e is 0 and f is 0, 1, 2 or 3,

Ring A is phenyl or pyridyl each optionally substituted once or twice with the same or different substituent selected from halo and methyl,

g is 0, 1 or 2,

h is 0 or h is 1 and $(W^3)_h$ is O, and

each W^1 is O;

g) 

$-\underset{\underset{W^1}{\|}}{C}-Ph^1-(CH_2)_j-\overset{\overset{\ominus}{An}}{\overset{\oplus}{N}}(C_{1\text{-}4}alkyl)(C_{1\text{-}4}alkyl)-$

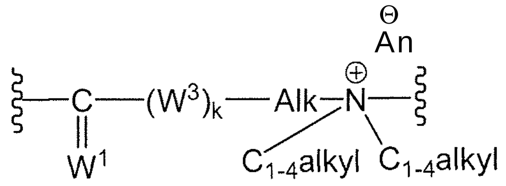
, wherejn

W^1 is O,

Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo or methyl or twice with the same or different substituents selected from halo and methyl, and

j is 1, 2 or 3;

h)

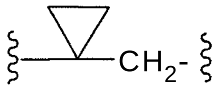


, wherein

W^1 is O,

k is 0, and

Alk is linear or branched C_{1-4}alkylene, -CH(NH$_2$)-(CH$_2$)$_4$-, -CH(AA)-, or



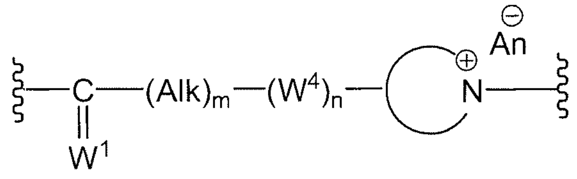
; or

W^1 is O,

k is 1 and W^3 is O or N(CH$_3$), and

Alk is linear or branched C-i$_{-4}$alkylene;

i)



, wherein

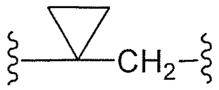
W^1 is O,

m and n are both 0,

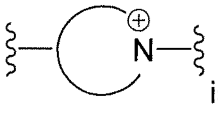
or m is 1 and n is 0,

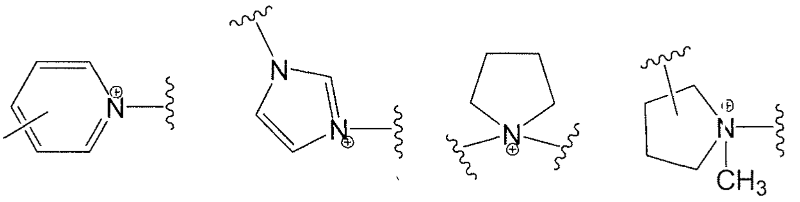
or m and n are both 1 and W^4 is N(H)C(O),

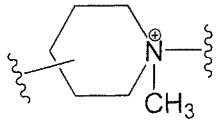
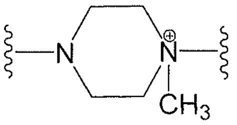
Alk is linear or branched C_{1-4}alkylene, -CH(NH$_2$)-(CH$_2$)4-, -CH(AA)-, or



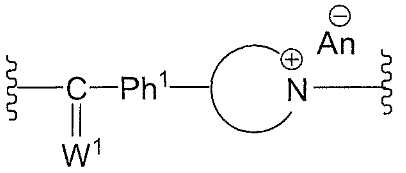
, and


is selected from



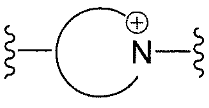

and


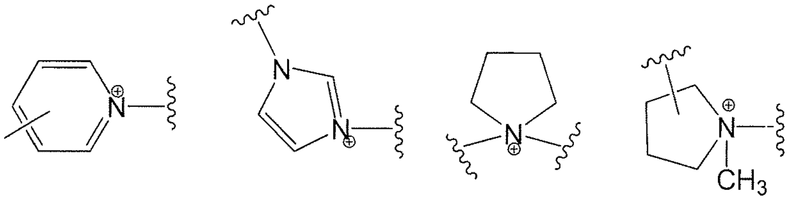
and

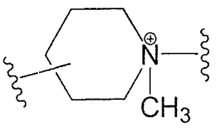
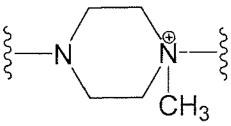
k)

, wherein

W^1 is O,

Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo or methyl or twice with the same or different substituents selected from halo and methyl, and


is selected from

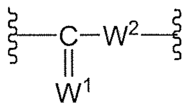



and


or any subset thereof.

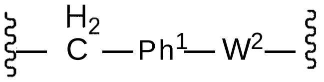
In one particular embodiment, L^1 is a bond.

In one preferred embodiment, L^1 is


$-C(=W^1)-W^2-$

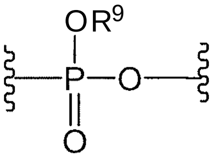
, W^1 is O or S, W^2 is O, S or N(R^1) and R^1 is H or Ci$_{_4}$alkyl. In one such embodiment, W^1 is O. In one such embodiment, W^2 is O, N(H), or N(CH_3), more particularly O or N(H).

In another particular embodiment, L^1 is


$-CH_2-Ph^1-W^2-$

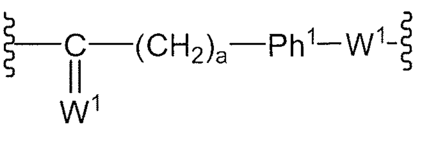
, wherein W^2 is O, S or N(R^1), or any subset thereof, wherein R^1 is H or $C_{1.4}$alkyl, and Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, $C_{1.4}$alkoxyl, NH_2, N(H)Ci$_{-4}$alkyl, and N(Ci$_{.4}$alkyl)$_2$, or any subset thereof. In one such embodiment Ph^1 is optionally substituted 1,2- or 1,4-phenyl. In one particular embodiment Ph^1 is optionally substituted 1,4-phenyl. In one embodiment, Ph^1 is unsubstituted phenyl or phenyl substituted with halo or methyl. In one particular embodiment, Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo (particularly F, or Cl) or methyl or twice with the same or different substituents selected from halo (particularly F, or Cl) and methyl. In one particular embodiment, Ph^1 is unsubstituted phenyl, particularly unsubstituted 1,4-phenyl. In one such embodiment, W^2 is O. In one such embodiment, W^2 is N(H).

In another particular embodiment, L^1 is

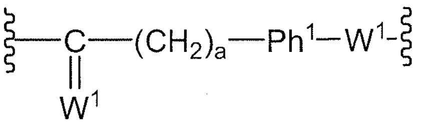

$-P(=O)(OR^9)-O-$

, wherein R^9 is H, $C_{1.4}$alkyl or phenyl. In one such embodiment, R^9 is H, CH_3, or phenyl. In one embodiment, R^9 is H.

In another particular embodiment, L^1 is


$-C(=W^1)-(CH_2)_a-Ph^1-W^1-$

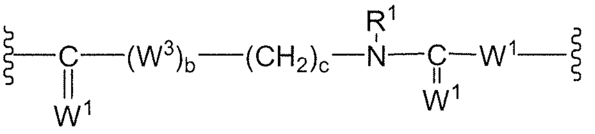
, wherein each W^1 is the same or different and is O or S; a is 0, 1, 2, 3, 4, 5 or 6, or any subset thereof; and Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, $N(H)C_{1-4}$alkyl, and $N(C_{1-4}alkyl)_2$, or any subset thereof. In one such embodiment, each W^1 is O. In one such embodiment, a is 1, 2, 3 or 4, particularly 1 or 2. In one particular embodiment, a is 1. In one such embodiment Ph^1 is optionally substituted 1,2- or 1,4-phenyl. In one particular embodiment Ph^1 is optionally substituted 1,4-phenyl. In one embodiment, Ph^1 is unsubstituted phenyl or phenyl substituted with halo or methyl. In one particular embodiment, Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo (particularly **F,** or Cl) or methyl or twice with the same or different substituents selected from halo (particularly **F,** or Cl) and methyl. In one particular embodiment, Ph^1 is unsubstituted phenyl, particularly unsubstituted 1,4-phenyl. In one particular embodiment, L^1 is



$$\sim\underset{\substack{\|\\W^1}}{C}-(CH_2)_a-Ph^1-W^1-\sim$$

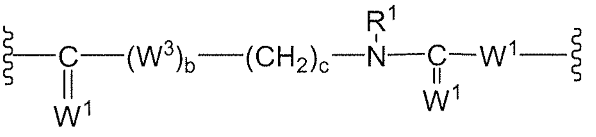
, wherein each W^1 is O, a is 1 or 2, and Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo (particularly **F,** or Cl) or methyl or twice with the same or different substituents selected from halo (particularly **F,** or Cl) and methyl.

In another particular embodiment, L^1 is



$$\sim\underset{\substack{\|\\W^1}}{C}-(W^3)_b-(CH_2)_c-\overset{\overset{R^1}{|}}{N}-\underset{\substack{\|\\W^1}}{C}-W^1-\sim$$

, wherein each W^1 is the same or different and is O or S; b is 0 and c is 1, 2, 3, 4, 5 or 6, or b is 1 and c is 2, 3, 4, 5 or 6; each W^3 is the same or different and is independently -O- or $-N(R^1)-$, and each R^1 is the same or different and is independently H or C_{1-4}alkyl. In one such embodiment, each W^1 is O. In one such embodiment, b is 0 and c is 1, 2 or 3. In one embodiment b is 1, W^3 is N(H), c is 2 or 3 and R^1 is H or CH_3. In one particular embodiment, L^1 is

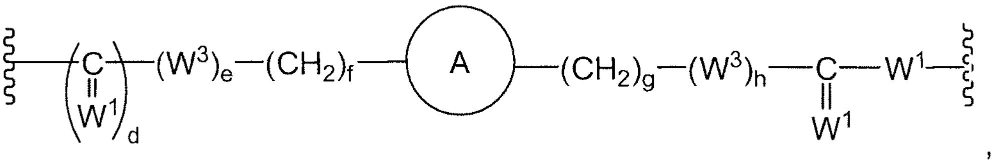


$$\sim\underset{\substack{\|\\W^1}}{C}-(W^3)_b-(CH_2)_c-\overset{\overset{R^1}{|}}{N}-\underset{\substack{\|\\W^1}}{C}-W^1-\sim$$

, wherein each W^1 is O, b is 0 and c

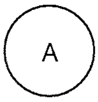
is 1, 2 or 3, or b is 1, W^3 is N(H) and c is 2 or 3, and R^1 is H or CH_3.

In another particular embodiment, L^1 is



,

wherein each W^1 is the same or different and is O or S; each W^3 is the same or different and is independently -O- or $-N(R^1)-$, wherein R^1 is H or C_{1-4}alkyl; d and e are both 0 and f is 1 or d is 1, e is 0 or 1 and f is 0, 1, 2, 3, 4, 5 or 6, or any subset thereof; Ring A is phenyl, pyridyl or pyrimidyl each optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, $N(H)C_{1-4}$alkyl, and $N(C_{1-4}alkyl)_2$, or any subset thereof; g is 0, 1, 2, 3, 4, 5 or 6, or any subset thereof; and h is 0 or 1.

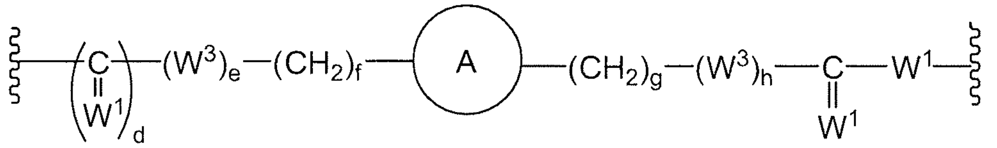


in the above group is referred to herein as "Ring A". In one such embodiment, Ring A is optionally substituted pyridyl. In another embodiment, Ring A is optionally substituted phenyl. In one embodiment, Ring A is unsubstituted phenyl or phenyl substituted once with halo (particularly F, or Cl) or methyl or twice with the same or different substituents selected from halo (particularly F, or Cl) and methyl. In one particular embodiment, Ring A is unsubstituted 1,4-phenyl. In one embodiment, Ring A is unsubstituted pyridyl or pyridyl substituted once with halo (particularly F, or Cl) or methyl or twice with the same or different substituents selected from halo (particularly F, or Cl) and methyl. In one embodiment, Ring A is unsubstituted pyridyl.

In one such embodiment, d and e are both 0 and f is 1. In one embodiment, d is 1, e is 0 and f is 0, 1, 2, 3, 4, 5 or 6, or any subset thereof, particularly f is 0, 1, 2 or 3. In one embodiment, d is 1, e is 1 and f is 0, 1, 2, 3, 4, 5 or 6, or any subset thereof, particularly f is 0, 1, 2 or 3. In one embodiment, d is 1, e is 0 and f is 1.

In one such embodiment, g is 0, 1, 2, 3 or 4, particularly 0, 1 or 2. In one particular embodiment, g is 0. In one embodiment, h is 0. In one embodiment, h is 1 and W^3 is O. In one embodiment, h is 1 and W^3 is N(H). In one embodiment, all W^1 are O.

In one particular embodiment, L^1 is



,

wherein

d and e are both 0 and f is 1, or

d is 1, e is 1, $(W^3)_e$ is O, and f is 0, 1, 2 or 3, or

d is 1, e is 0 and f is 0, 1, 2 or 3,

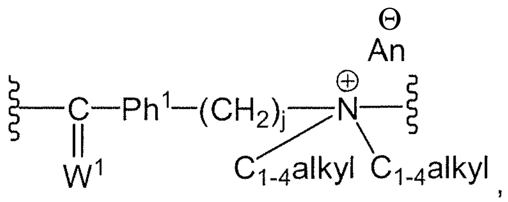
Ring A is phenyl or pyridyl each optionally substituted once or twice with the same or different substituent selected from halo (particularly F, or Cl) and methyl,

g is 0, 1 or 2,

h is 0 or h is 1 and $(W^3)_h$ is O, and

each W^1 is O.

In another particular embodiment, L^1 is



, wherejn

W^1 is O or S;

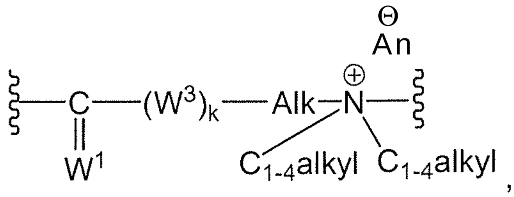
Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, N(H)Ci$_{-4}$alkyl, and $N(C_{1-4}alkyl)_2$;

j is 0, 1, 2, 3, 4, 5 or 6; and

$A\eta^{\theta}$ is a pharmaceutically acceptable counterion.

In one such embodiment, W^1 is O; Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo (particularly F or Cl) or methyl or twice with the same or different substituents selected from halo (particularly F or Cl) and methyl, and j is 1, 2 or 3. In one particular embodiment, Ph^1 is unsubstituted phenyl, particularly unsubstituted 1,4-phenyl. In one particular embodiment, each C_{1-4} alkyl on the quaternary N is the same, and particularly both C_{1-4} alkyl are the same and are either methyl or ethyl.

In another particular embodiment, L^1 is



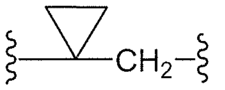
, wherein

W^1 is O or S;

k is 0 or 1, and when k is 0, W^3 is absent and when k is 1, W^3 is -O- or $-N(R^1)-$;

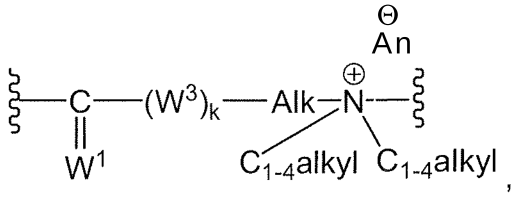
Alk is selected from a linear or branched C_{1-6}alkylene or C_{1-6}alkenylene each optionally substituted on nonadjacent carbons by 1, 2 or 3 substituents, selected from halo, OH, C_{1-4}alkoxyl, NH_2, $N(H)Ci_{-4}$alkyl, or $N(C_{1-4}alkyl)_2$; C_{3-6}cycloalkylene-Ci_{-4}alkylene; and -CH(AA)- wherein AA is a proteinogenic amino acid side chain, or any subset thereof; and

An® is a pharmaceutically acceptable counterion.

In one such embodiment, W^1 is 0. In one such embodiment, k is 0 and thus W^3 is absent. in one such embodiment, Alk is linear or branched C_{1-4}alkylene, $-CH(NH_2)-(CH_2)_4-$, -CH(AA)-, or , or any subset thereof.

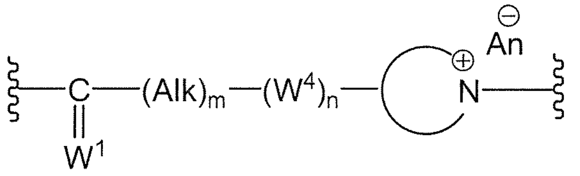
In one particular embodiment, each C_{1-4} alkyl on the quaternary N is the same, and particularly both C_{1-4} alkyl are the same and are either methyl or ethyl.

In a particular embodiment, L^1 is



, wherein w 1 is 0 ; k is 1 and W^3 is O or $N(CH_3)$, and Alk is linear or branched C_{1-4}alkylene; both C_{1-4} alkyl on the quaternary N are the same and are either methyl or ethyl and Aη$^{\theta}$ is a pharmaceutically acceptable counterion.

In another particular embodiment, L^1 is



, wherein

W^1 is O or S;

m is 0 or 1;

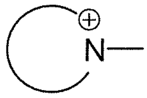
Alk is selected from

a linear or branched Ci^alkylene or C_{1-6}alkenylene each optionally substituted on nonadjacent carbons by 1, 2 or 3 substituents, selected from halo, OH, C_{1-4}alkoxyl, NH_2, N(H)Ci $_{-4}$alkyl, or $N(C_{1-4}alkyl)_2$;

Cs-ecycloalkylene-Ci^alkylene; and

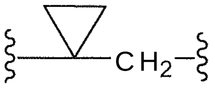
-CH(AA)- wherein AA is a proteinogenic amino acid side chain;

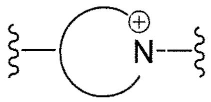
n is 0 or n is 1 and W^4 is -N(H)-C(O)-;



is a quaternary N-heteroaryl having 5 or 6 ring atoms wherein one ring atom is a quaternary N and optionally one additional ring atom is N; or a quaternary N-heterocycle having 5 or 6 ring atoms wherein one ring atom is a quaternary N-methyl and optionally one additional ring atom is N, wherein said N-heteroaryl and said N-heterocycle are optionally substituted on any available ring atom with C_{1-4}alkyl; and

each An® is a pharmaceutically acceptable counterion;

In one such embodiment, W^1 is O. In one such embodiment, m and n are both 0. In one such embodiment, m is 1 and n is 0. in one such embodiment, m and n are both 1. In one embodiment wherein m is 1, Alk is linear or branched Ci_{-4}alkylene, -CH(NH_2)-(CH_2)$_4$-, -CH(AA)-, , or any subset thereof. In one embodiment wherein n is 1, W^4 is N(H)C(0). In one such embodiment,



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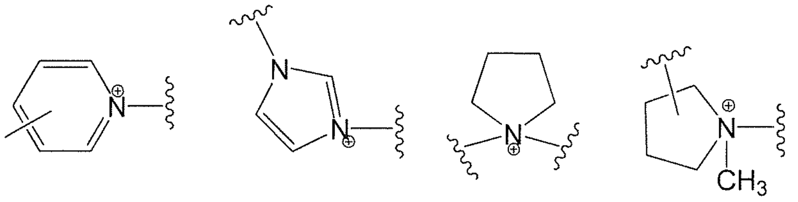

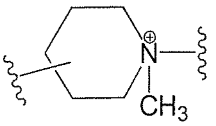

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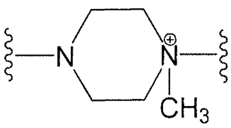
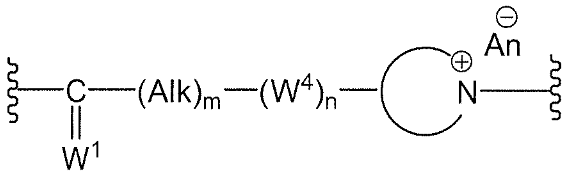


or any subset thereof.

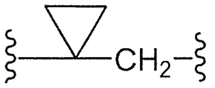
In one particular embodiment, L^1 is



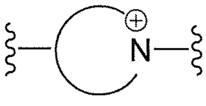
, wherein

W^1 is O, m and n are both 0 or m is 1 and n is 0 or m and n are both 1 and W^4 is N(H)C(0),

Alk is linear or branched $C_{1\text{-}4}$alkylene, -CH(NH_2)-(CH_2)$_4$-, -CH(AA)-, or



, or any subset thereof,



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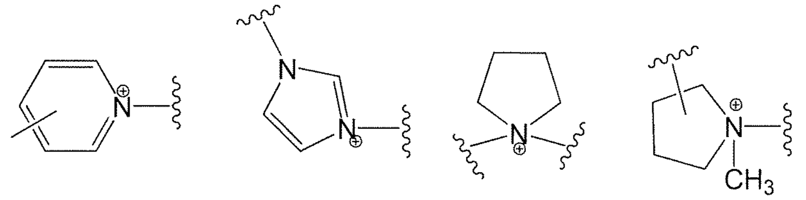

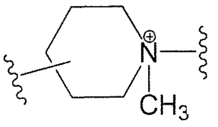

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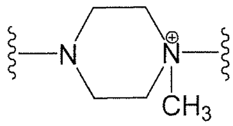
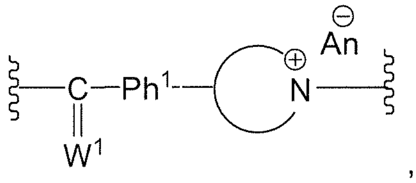


or any subset thereof, and

An$^{\ominus}$ is a pharmaceutically acceptable counterion;

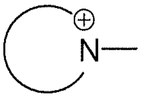
In another particular embodiment, L^1 is



, wherein

W^1 is O or S,

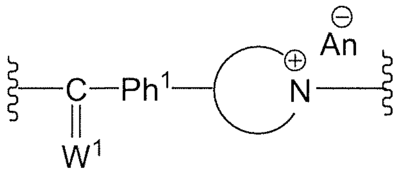
Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, N(H)C_{1-4}alkyl, and N(C_{1-4}alkyl)$_2$, or any subset thereof;



is a quaternary N-heteroaryl having 5 or 6 ring atoms wherein one ring atom is a quaternary N and optionally one additional ring atom is N; or a quaternary N-heterocycle having 5 or 6 ring atoms wherein one ring atom is a quaternary N-methyl and optionally one additional ring atom is N, wherein said N-heteroaryl and said N-heterocycle are optionally substituted on any available ring atom with C_{1-4}alkyl; and

An$^{\ominus}$ is a pharmaceutically acceptable counterion.

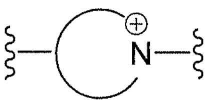
In one such embodiment, L^1 is



, wherein

W^1 is O;

Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo (particularly F or Cl) or methyl or twice with the same or different substituents selected from halo (particularly F or Cl) and methyl, and



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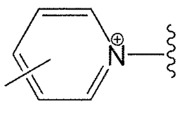

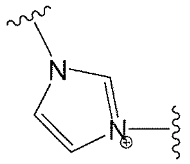

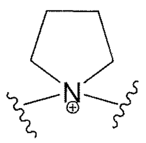

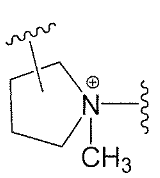

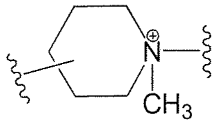

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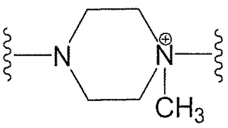


or any subset thereof; and

An® is a pharmaceutically acceptable counterion.

In one embodiment, L^2 is -0-CH $_2$-0-. In one preferred embodiment, L^2 is -0-.

In one preferred embodiment, R^{15} is OH.

In one embodiment R^{16} is H or methyl. In one preferred embodiment, R^{16} is H. In one embodiment, L^3 is a linear or branched $C_{4\text{-}12}$alkylene, c4.i$_2$alkenylene, or $C_{4\text{-}12}$alkynylene, each optionally substituted once or twice by a $C_{3\text{-}6}$cycloalkyl, $C_{3\text{-}6}$cycloalkene, or a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S. In one such embodiment, L^3 is a linear or branched $C_{4\text{-}12}$alkylene or $C_{4\text{-}12}$alkenylene, each optionally substituted once or twice by a c3-6cycloalkyl, c3-6cycloalkene, or a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S. In one such embodiment, L^3 is a linear or branched $C_{4\text{-}12}$alkylene optionally substituted once or twice by a $C_{3\text{-}6}$cycloalkyl, C_3_6cycloalkene, or a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S. In one such embodiment, L^3 is a linear or branched, unsubstituted C_4-i2alkylene. In one preferred embodiment, **L^3** is a linear unsubstituted C_{4-12}alkylene. In one particular embodiment, L^3 is a linear unsubstituted Cgalkylene.

In one embodiment, L^3 is a linear or branched **C_{1-6}**alkylene, C_{2-6}alkenylene, or C_2-6alkynylene wherein one carbon of said alkylene, alkenylene or alkynylene is *optionally* replaced by a C_{3-6}cycloalkylene, C_{3-}6cycloalkenylene, or a **5-6** membered heterocyclene having **1** or **2** heteroatoms selected from N, O or S. In one such embodiment, L^3 is a linear or branched **C_{1-6}**alkylene, C_{2-6}alkenylene, or C_2-6alkynylene wherein one carbon of said alkylene, alkenylene or alkynylene is replaced by a C_{3-}6cycloalkylene, C_{3-}6cycloalkenylene, or a **5-6** membered heterocyclene having **1** or **2** heteroatoms selected from N, O or S. In another such embodiment, L^3 is a linear or branched C_{2-6}alkylene, C_{2-}6alkenylene, or C_{2-6}alkynylene wherein one carbon of said alkylene, alkenylene or alkynylene is replaced by a C_{3-6}cycloalkylene, C_{3-6}cycloalkenylene, or a **5-6** membered heterocyclene having **1** or **2** heteroatoms selected from N, O or S.

In one embodiment, L^3 is Alk^1-Q^1-Alk^2, wherein Alk^1 is linear or branched C_{1-6}alkylene; Q^1 is **-0-,** -S-, -N(H)-, -N(C_{1-4}alkyl)-, -C(**0**)N(H)-, -C(**0**)N(C_{1-4}alkyl)-,-N(H)C **(0)-,** or - N(**Ci**$_{-4}$alkyl)C**(0)-;** and Alk^2 is linear or branched **Ci**$_{-6}$alkylene, C_{2-6}alkenylene, or $C_{2\cdot6}$alkynylene. In one such embodiment, Alk^1 is C_{1-2}alkylene, particularly -CH $_2$-. In one such embodiment, Q^1 is **-0-,** -C(**0**)N(H)-, or -N(H)C**(0)-,** more particularly Q^1 is **-0-.** In one such embodiment, Alk^2 is linear or branched C_{1-6}alkylene, more particularly linear or branched **C_{1-3}**alkylene.

In one embodiment, L^3 is Alk^1-RG^1- Q^1-Alk^2, wherein Alk^1 is linear or branched C_{1-6}alkylene; RG^1 is phenylene or pyridylene each optionally substituted by 1**, 2, 3** or **4** substituents selected from halo, **C_{1-6}**alkyl, **C_{1-4}**haloalkyl, OH, C_{1-4}alkylOH, O-C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl, N(C_{1-6}alkyl)$_2$, and **CN,** or any subset thereof; Q^1 is-O-, -S-, -N(H)-, **-N(Ci.**

$_4$alkyl)-, -C(0)N(H)-, -C(O)N(C$_{1\text{-}4}$alkyl)-,-N(H)C(O)-, or -N(C$_{1\text{-}4}$alkyl)C(0)-, or any subset thereof; and

Alk^2 is linear or branched C$_{1\text{-}6}$alkylene, C$_{2\text{-}6}$alkenylene, or C$_{2\text{-}6}$alkynylene, or any subset thereof.

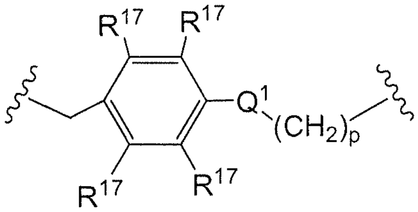
In one such embodiment, Alk^1 is C$_{1\text{.}2}$alkylene, particularly -CH$_2$-.

In one such embodiment, RG^1 is unsubstituted phenylene or unsubstituted pyridylene, particularly unsubstituted phenylene. In another such embodiment, RG^1 is phenylene or pyridylene each optionally substituted once or twice with the same or different substituents selected from halo, C-i$_{\text{-}6}$alkyl, Ci-$_4$haloalkyl, OH, 0-Ci$_{\text{-}6}$alkyl, S-C$_{1\text{-}6}$alkyl, S0$_2$C$_{1\text{-}6}$alkyl, NH$_2$, N(H)C$_{1\text{-}6}$alkyl, N(C$_{1\text{-}6}$alkyl)$_2$, and CN, or any subset thereof, or any subset thereof.

In one such embodiment, Q^1 is -0-, -C(0)N(H)-, or -N(H)C(0)-. In one particular embodiment, Q^1 is -0-.

In one such embodiment, Alk^2 is linear or branched C$_{1\text{-}6}$alkylene, more particularly linear C$_{1\text{-}6}$alkylene.

In one embodiment, L^3 is Alk^1-RG^1- Q^1-Alk^2, having the formula:



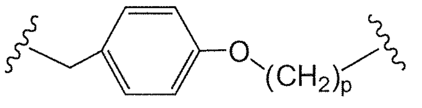
wherein:

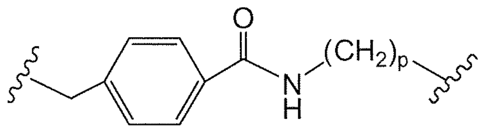
each R^{17} is the same or different and is independently selected from H, halo, C$_{1\text{-}6}$alkyl, C$_{1\text{-}4}$haloalkyl, OH, C$_{1\text{-}4}$alkylOH, O-Ci$_{\text{-}6}$alkyl, S-C$_{1\text{-}6}$alkyl, SO$_2$C$_{1\text{-}6}$alkyl, NH$_2$, N(H)C$_{1\text{-}6}$alkyl, N(C$_{1\text{-}6}$alkyl)$_2$, and CN, or any subset thereof;

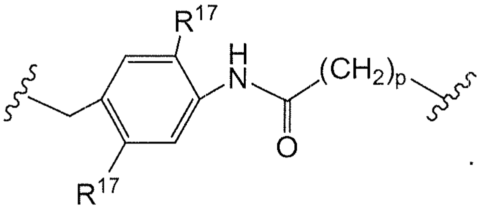
Q^1 is -O-, -C(O)N(H)- or -N(H)C(O)-, or any subset thereof; and

p is 1, 2, 3, 4, 5 or 6, or any subset thereof.

In one embodiment, L^3 is selected from the formula:

a)

,

b)

, or

c)

.

wherein:

each R^{17} is the same or different and is independently selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, OH, C_{1-4}alkylOH, O-C_{1-6}alkyl, S-Ci_{-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl, N(C_{1-6}alkyl)$_2$, and CN, or any subset thereof; and

p is 1, 2, 3, 4, 5 or 6, or any subset thereof.

In one such embodiment, L^3 is formula a) above, wherein p is 2, 3 or 4, more particularly 2 or 3, and particularly 3. In another such embodiment, L^3 is formula b) above, wherein p is 1 or 2, particularly 2. In another such embodiment, L^3 is formula c) above, wherein each R^{17} is the same or different and is halo (particularly **F** or Cl) , C_{1-6}alkyl, or O-C_{1-6}alkyl, more particularly **F,** Cl, CH_3, or OCH_3; and p is 1 or 2, particularly 2.

In one embodiment, L^3 is Alk^1-RG^1-Q^1-Alk^2-Q^1-Alk^3, wherein:

Alk^1 is linear or branched C_1-6alkylene;

RG^1 is phenylene or pyridylene each optionally substituted by 1, 2, 3 or 4 substituents selected from halo, C_{1-6}alkyl, C_{1-4}haloalkyl, OH, C_{1-4}alkylOH, O-C_{1-6}alkyl, S-C_{1-6}alkyl, SO2C_{1-6}alkyl, NH_2, N(H)Ci_{-6}alkyl, N(C_1-6alkyl)$_2$, and CN, or any subset thereof;

each Q^1 is the same or different and is -O-, -S-, -N(H)-, -N(C_{1-4}alkyl)-, -C(O)N(H)-, -C(O)N(C_{1-4}alkyl)-, -N(H)C(O)-, or -N(C_{1-4}alkyl)C(O)-, or any subset thereof; and

Alk^2 and Alk^3 are each the same or different and are linear or branched C-i-ealkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene, or any subset thereof.

In one such embodiment, Alk^1 is linear or branched Ci_{-4}alkylene, particularly $-C(CH_3)_2-CH_2-$.

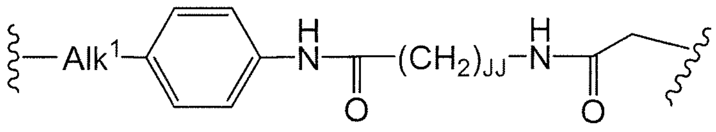
In one such embodiment RG^1 is unsubstituted phenylene or unsubstituted pyridylene, particularly unsubstituted phenylene. In another such embodiment, RG^1 is phenylene or pyridylene each optionally substituted once or twice with the same or different substituents selected from halo, C_{1-6}alkyl, C_{1-4}haloalkyl, OH, O-C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl, N(C_{1-6}alkyl$)_2$, and CN, or any subset thereof, or any subset thereof.

In one such embodiment, Q^1 is -O-, -C(O)N(H)-, or -N(H)C(O)-. In one particular embodiment, both Q^1 are the same. In one embodiment, both Q^1 are -N(H)C(O)-.

In one such embodiment, Alk^2 is a linear or branched C_{1-6}alkylene, more particularly a linear C_{1-6}alkylene, e.g., C_{2-3}alkylene.

In one such embodiment, Alk^3 is a linear or branched Ci^alkylene, more particularly a linear C_{1-6}alkylene, e.g., $-CH_2-$.

In one embodiment, L^3 is Alk^1-RG^1-Q^1-Alk^2-Q^1-Alk^3, having the formula:



, wherein Alk^1 is as defined above (including specific and preferred embodiments described above) and JJ is 0, 1, 2, 3 or 4, particularly 2, 3 or 4.

In one embodiment, L^3 is Alk^1- Q^1-RG^1-Q^1-Alk^2, wherein:

Alk^1 is linear or branched C_{1-6}alkylene;

each Q^1 is the same or different and is -0-, -S-, -N(H)-, -N(Ci$_{-4}$alkyl)-, -C(0)N(H)-, -C(O)N($C_{1\text{-}4}$alkyl)-, -N(H)C(0)-, or -N($C_{1\text{-}4}$alkyl)C(0)-, or any subset thereof;

RG^1 is phenylene or pyridylene each optionally substituted by 1, 2, 3 or 4 substituents selected from halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}4}$haloalkyl, OH, $C_{1\text{-}4}$alkylOH, O-$C_{1\text{-}6}$alkyl, S-Ci$_{-6}$alkyl, $SO_2C_{1\text{-}6}$alkyl, NH_2, N(H)$C_{1\text{-}6}$alkyl, N($C_{1\text{-}6}$alkyl)$_2$, and CN, or any subset thereof; and

Alk^2 is linear or branched $C_{1\text{-}6}$alkylene, $C_{2\text{-}}$6alkenylene, or c 2-6alkynylene, or any subset thereof.

In one such embodiment, Alk^1 is linear or branched $C_{1\text{-}4}$alkylene, particularly $-C(CH_3)_2-CH_2-$.

In one such embodiment, each Q^1 is -O-, -C(O)N(H)-, or -N(H)C(O)-. In one particular embodiment, both Q^1 are the same. In one embodiment, both Q^1 are -N(H)C(O)-. In one embodiment, both Q^1 are -O-.

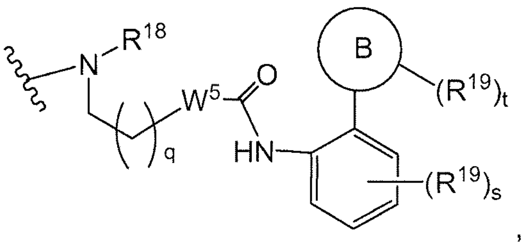
In one such embodiment RG^1 is unsubstituted phenylene or unsubstituted pyridylene, particularly unsubstituted phenylene. In another such embodiment, RG^1 is phenylene or pyridylene each optionally substituted once or twice with the same or different substituents selected from halo, Ci$_{-6}$alkyl, $C_{1\text{-}4}$haloalkyl, OH, O-$C_{1\text{-}6}$alkyl, S-$C_{1\text{-}6}$alkyl, $SO_2C_{1\text{-}6}$alkyl, NH_2, N(H)$C_{1\text{-}6}$alkyl, N($C_{1\text{-}6}$alkyl)$_2$, and CN, or any subset thereof, or any subset thereof.

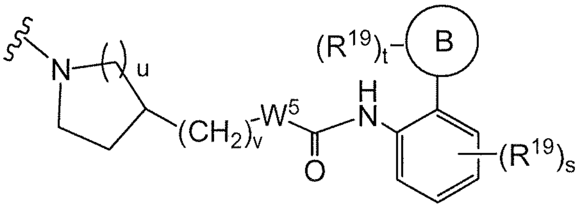
In one such embodiment, Alk^2 is a linear or branched $C_{1\text{-}6}$alkylene, more particularly a linear C_1^alkylene, e.g., $C_{2\text{-}3}$alkylene.

MRA in Formula I is a moiety having muscarinic receptor antagonist activity, and particularly M3 receptor antagonist activity. Muscarinic receptor antagonists constitute a well known and recognized class of therapeutically effective agents. Many examples of muscarinic receptor antagonists have been described in the patent and scientific literature. Examples of muscarinic receptor antagonists which have been marketed include ipratropium, tiotropium and scopolamine, among many others. Moieties having muscarinic receptor antagonist activity may be found in, for example, PCT Publication Numbers WO07/17669, WO07/17670, WO08/017824, WO08/017827, WO08/096127, WO08/096129, WO08/149110, all to Argenta; WO05/111004 to Boehringer Ingelheim; WO07/090859 to GlaxoSmithKline; WO08/000483 to Novartis; WO07/107828 and WO08/041095 both to Pfizer; and WO04/074246, WO04/074812, WO04/089892, WO04/106333, WO05/051946, WO05/080375, WO06/023454, WO06/023457, WO06/023460, WO07/127196 and WO07/127297 all to Theravance. The foregoing references also describe processes for making such moieties and compounds that incorporate such moieties.

Any compound having muscarinic receptor antagonist activity may be used as a template from which to form the MRA moiety of the compounds of the invention. In many cases, the muscarinic receptor antagonist will have an N which forms a suitable point of attachment for the group L^3 in Formula I. Thus, in one embodiment, the compounds of Formula I are defined wherein MRA is a moiety having muscarinic receptor antagonist activity which is bound to L^3 through an N of MRA. In one embodiment, the compounds of Formula I are defined wherein MRA is a moiety having muscarinic receptor antagonist activity which is bound to L^3 through a C or N or of a pyrrolidinyl or piperidinyl ring of MRA.

In one embodiment, MRA is a moiety selected from

i)  , ii)



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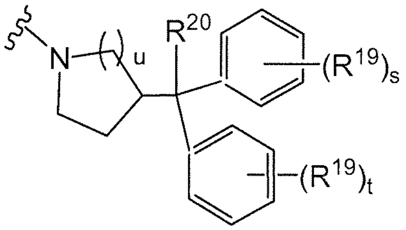
iii)



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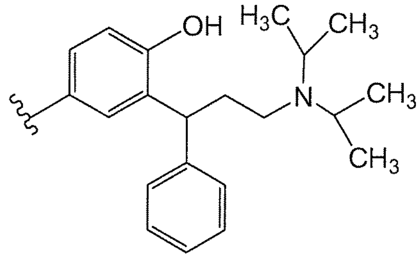

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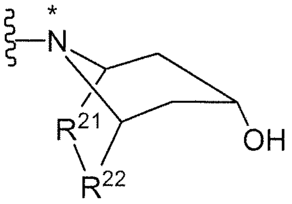

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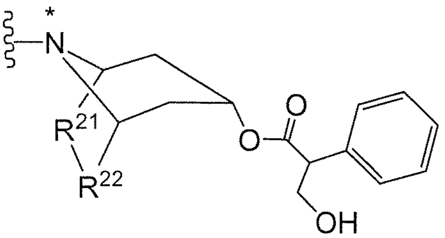

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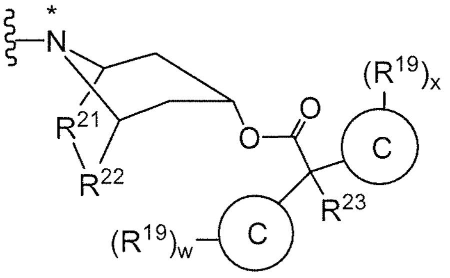

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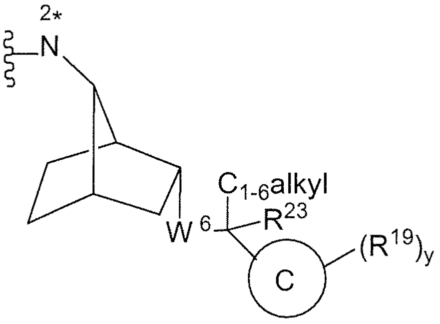

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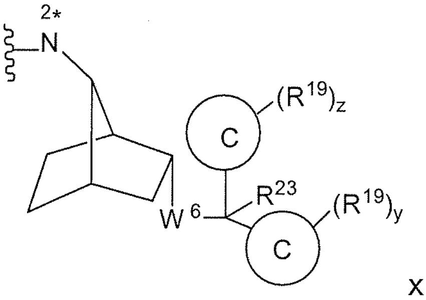

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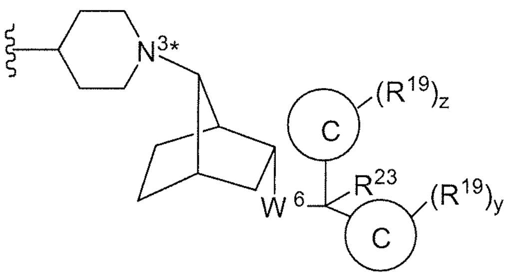

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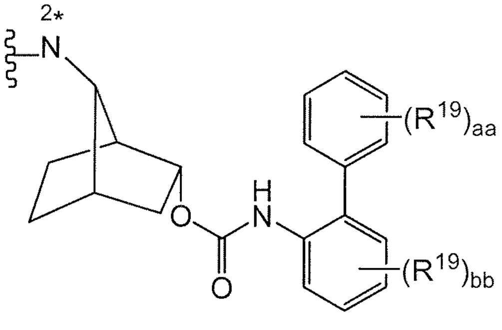

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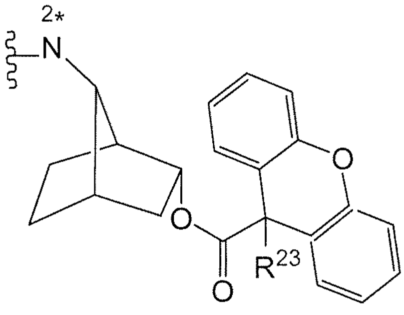

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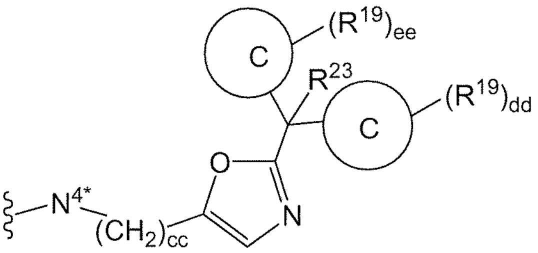
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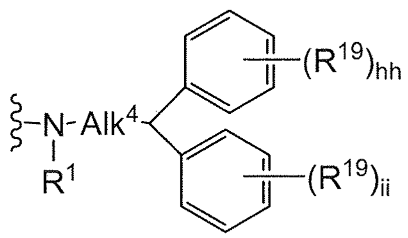
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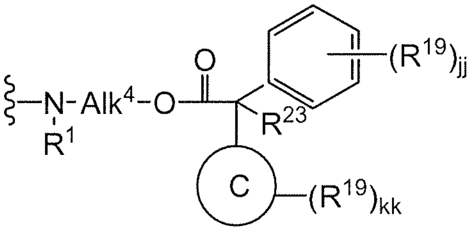
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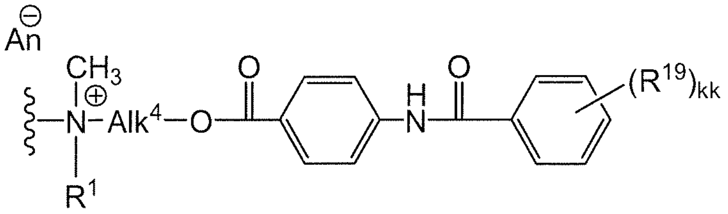
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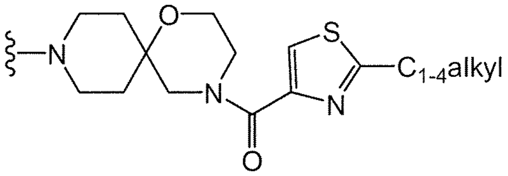
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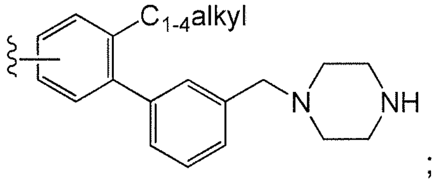

;

wherein:

R^{18} is H, Ci-6alkyl, c3-6alkenyl, C_{3-6}alkynyl, or C_{3-6}cycloalkyl;

q is 1, 2, 3, 4, 5, 6, or 7;

W^5 is O, NH, or N(C_{1-6}alkyl);

each s, t, w, x, y, z, aa, bb, dd, ee, hh, ii, jj, and kk, is the same or different and is independently 0, 1, 2, or 3;

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-}6alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-Ci $_{-6}$alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl and N(C_{1-6}alkyl)$_2$ and CN;

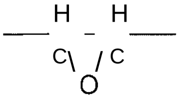
each Ring B is phenyl or 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S;

u is 1 or 2;

v is 0, 1, 2 or 3;

R^{20} is CN, $C0_2H$, $C0_2C_{1\text{-}6}$alkyl, $CONH_2$, CON(H)$C_{1\text{-}6}$alkyl, CON($C_{1\text{-}6}$alkyl)$_2$, OH;

N* is N, ($N^{®}H)A\eta^{\theta}$, ($N^{®}$-CH_3)$An^{\ominus}$, or ($N^{®}$-CH($CH_3)_2$)$An^{\ominus}$;

R^{21} and R^{22} together are -CH_2-CH_2-, -CH=CH- or ;

each Ring C is the same or different and is selected from phenyl, $C_{3\text{-}6}$cycloalkyl, and 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S;

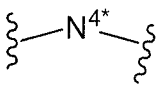
R^{23} is H or OH;

N^{2*} is N(R^{24}) or ($N^{®}(CH_3)_2$)$An^{\ominus}$;

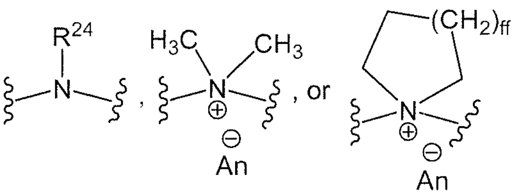
R^{24} is H or $C_{1\text{-}6}$alkyl;

W^6 is -O-C(=O)-, -O-CH_2-, or -N(H)C(=O)-;

N^{3*} is N, ($N^{®}H)A\eta^{\theta}$, $N\Theta(CH_3)A\eta^{\ominus}$, or ($N^{®}$-CH($CH_3)_2$)$An^{\ominus}$;



is

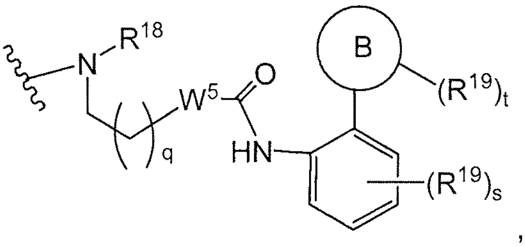


, wherein R^{24} is H or $C_{1\text{-}6}$alkyl, and ff is 1 or 2;

cc is 1, 2 or 3; and

Alk^4 is linear or branched $C_{1\text{-}6}$alkylene, $C_{2\text{-}6}$alkenylene or $C_{2\text{-}6}$alkynylene.

In one embodiment, MRA is

i) 

, wherein

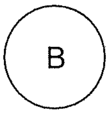
R^{18} is H, $C_{1\text{-}6}$alkyl, $C_{3\text{-}6}$alkenyl, $C_{3\text{-}6}$alkynyl, or $C_{3\text{-}6}$cycloalkyl, or any subset thereof;

q is 1, 2, 3, 4, 5, 6, or 7, or any subset thereof;

W^5 is O, NH, or N(Ci$_{-6}$alkyl), or any subset thereof;

s and t are the same or different and are independently 0, 1, 2, or 3, or any subset thereof;

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C 2-6alkenyl, C_{2-}6alkynyl, C_{3-}6cycloalkyl, C_{1-4}haloalkyl, OH, O-C^alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci$_{-6}$alkyl and N(Ci$_{-6}$alkyl)$_2$ and CN, or any subset thereof;

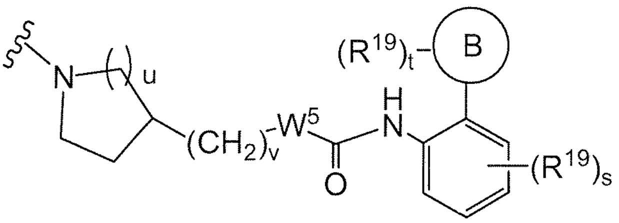


is referred to as "Ring B" and is phenyl or 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S, or any subset thereof.

In one embodiment, MRA is a moiety of formula i) above wherein R^{18} is H or C_{1-6}alkyl, or any subset thereof. In one embodiment, MRA is a moiety of formula i) above wherein q is 1, 2 or 3, particularly 1. In one embodiment, MRA is a moiety of formula i) above wherein W^5 is O, NH, or N(CH_3), particularly O. In one embodiment, MRA is a moiety of formula i) above wherein s and t are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, C $_{1-6}$alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-C_{1-6}alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci$_{-6}$alkyl and N(C_{1-6}alkyl)$_2$ and CN, or any subset thereof. In one particular embodiment, s and t are both 0. In one embodiment, MRA is a moiety of formula i) above wherein Ring B is phenyl, thiophenyl, pyridyl or thiazolyl. In one particular embodiment, Ring B is phenyl. In one particular embodiment, Ring B is thiophenyl.

In another embodiment, MRA is

ii)



, wherein

u is 1 or 2;

v is 0, 1, 2 or 3, or any subset thereof;

W^5 is O, NH, or N(C_{1-6}alkyl), or any subset thereof;

s and t are the same or different and are independently 0, 1, 2, or 3, or any subset thereof;

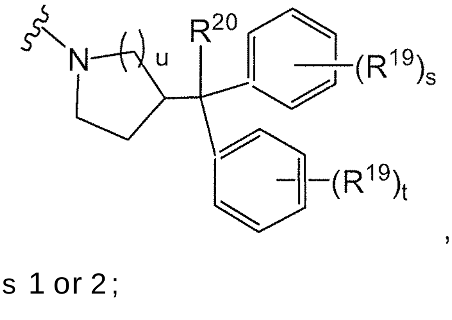
each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-C_{1-6}alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci$_{-6}$alkyl and N(Ci$_{-6}$alkyl)$_2$ and CN, or any subset thereof; and

Ring B is phenyl or 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S, or any subset thereof.

In one embodiment wherein MRA is a moiety of formula ii) above, u is 2. In one embodiment wherein MRA is a moiety of formula ii) above, v is 0. In one embodiment wherein MRA is a moiety of formula ii) above, W^5 is O, NH, or N(CH_3), particularly O. In one embodiment wherein MRA is a moiety of formula ii) above, s and t are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, Cs-ecycloalkyl, C_{1-4}haloalkyl, OH, O-C_{1-6}alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-Ci$_{-6}$alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl and N(C_{1-6}alkyl)$_2$ and CN, or any subset thereof. In one particular embodiment, s and t are both 0. In one embodiment, MRA is a moiety of formula i) above wherein Ring B is phenyl, thiophenyl, pyridyl or thiazolyl. In one particular embodiment, Ring B is phenyl. In one particular embodiment, Ring B is thiophenyl.

In another embodiment, MRA is

iii)



, wherein

u is 1 or 2;

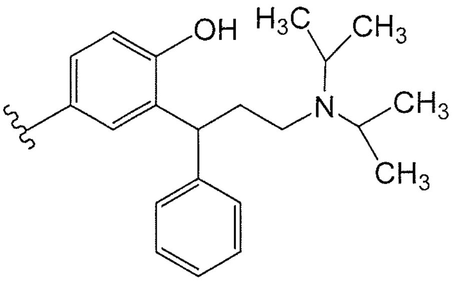
R^{20} is CN, $C0_2H$, $CO_2C_{1\text{-}6}$alkyl, $CONH_2$, $CON(H)C_{1\text{-}6}$alkyl, $CON(C_{1\text{-}6}alkyl)_2$, or any subset thereof;

s and t are the same or different and are independently 0, 1, 2, or 3, or any subset thereof; and

each R^{19} is the same or different and is independently selected from halo, C-i^alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}6}$cycloalkyl, $C_{1\text{-}4}$haloalkyl, OH, O-$C_{1\text{-}6}$alkyl, O-benzyl, CO_2H, $CO_2C_{1\text{-}6}$alkyl, S-$C_{1\text{-}6}$alkyl, $SO_2C_{1\text{-}6}$alkyl, NH_2, N(H)Ci $_{-6}$alkyl and N(Ci $_{-6}alkyl)_2$ and CN, or any subset thereof.

In one embodiment wherein MRA is a moiety of formula iii) above, u is 2. In one embodiment wherein MRA is a moiety of formula iii) above, R^{20} is $C0_2H$, $C0_2CH_3$, $CONH_2$, $CON(H)CH_3$, or $CON(CH_3)_2$, particularly $CONH_2$. In one embodiment wherein MRA is a moiety of formula iii) above, s and t are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}6}$cycloalkyl, $C_{1\text{-}4}$haloalkyl, OH, O-Ci $_{-6}$alkyl, O-benzyl, CO_2H, $CO_2C_{1\text{-}6}$alkyl, S-$C_{1\text{-}6}$alkyl, SO_2Ci $_{-6}$alkyl, NH_2, N(H)Ci $_{-6}$alkyl and $N(C_{1\text{-}6}alkyl)_2$ and CN, or any subset thereof. In one particular embodiment, s and t are both 0.

In one embodiment, MRA is

iv) 

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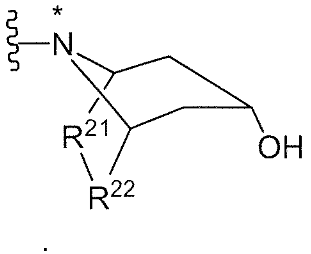
In one embodiment, MRA is

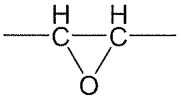
v) 

, and

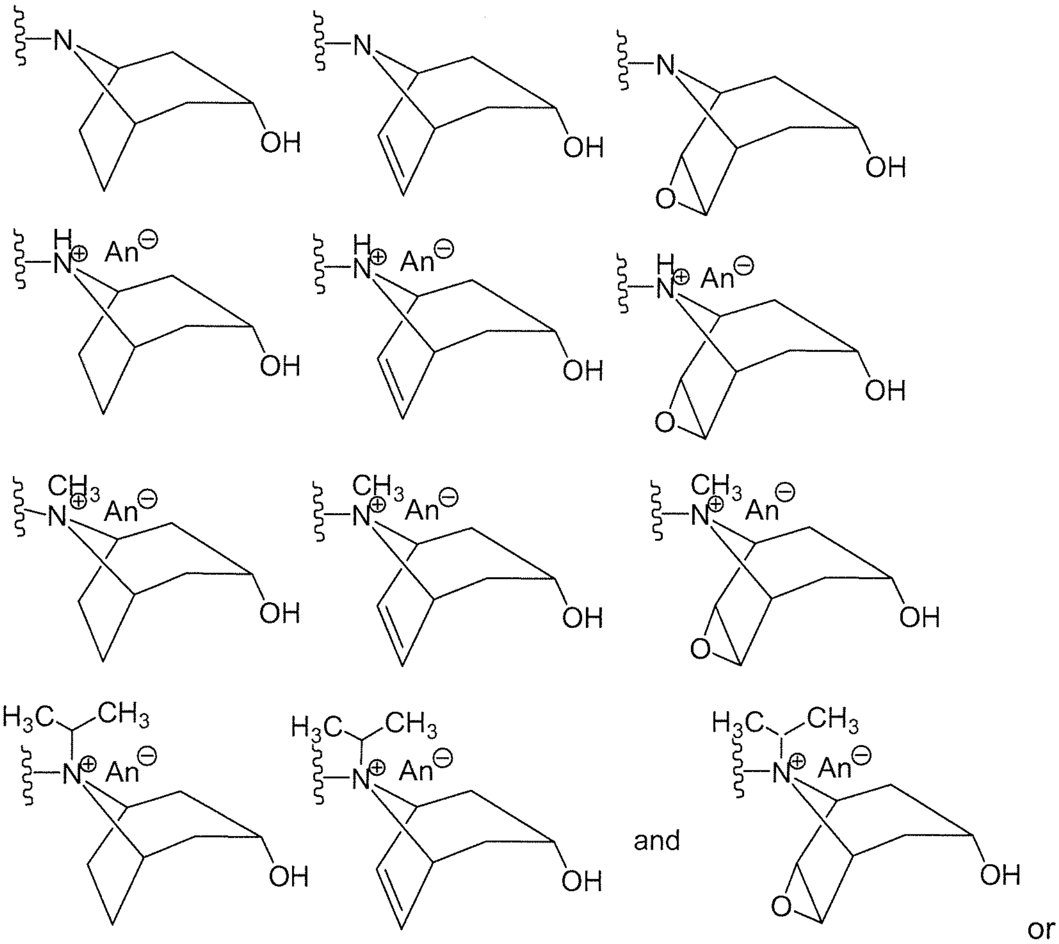
wherein

N* is N, $(N^{\oplus}H)A\eta^{\ominus}$, $(N^{®}\text{-}CH_3)An^{\ominus}$, or $(N^{\oplus}\text{-}CH(CH_3)_2)An^{\ominus}$;

$A\eta^{\theta}$ is a pharmaceutically acceptable counterion; and

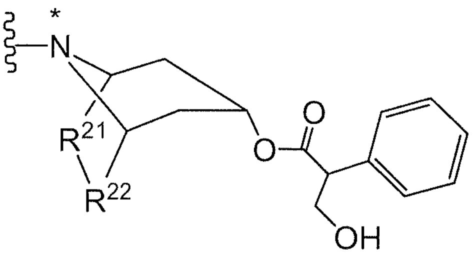
R^{21} and R^{22} together are $-CH_2\text{-}CH_2-$, $-CH=CH-$ or  .

Thus, according to this embodiment, MRA is selected from



or any subset thereof, wherein $An^{®}$ is a pharmaceutically acceptable counterion.

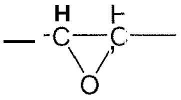
In one embodiment, MRA is

vi)  ,

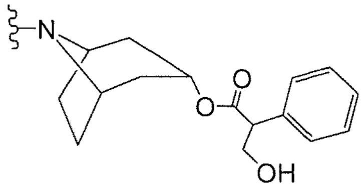
wherein

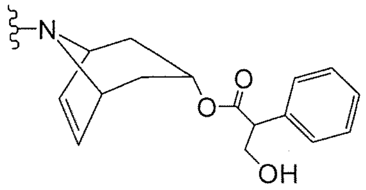
N* is N, $(N^{\circledR}H)A\eta^{\ominus}$, $(N^{\oplus}\text{-}CH_3)An^{\ominus}$, or $(N^{\oplus}\text{-}CH(CH_3)_2)A\eta^{\ominus}$;

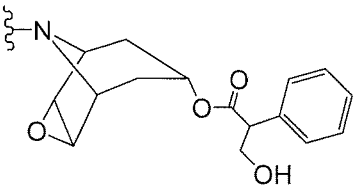
$A\eta^{\theta}$ is a pharmaceutically acceptable counterion; and

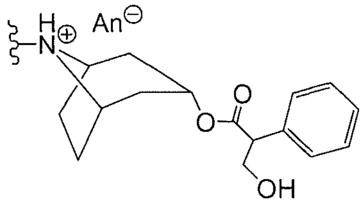
R^{21} and R^{22} together are $-CH_2\text{-}CH_2\text{-}$, $-CH{=}CH-$ or  .

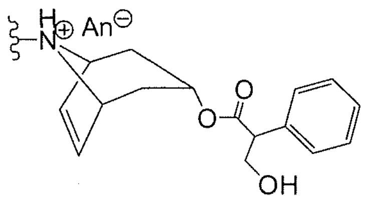
Thus, according to this embodiment, MRA is selected from

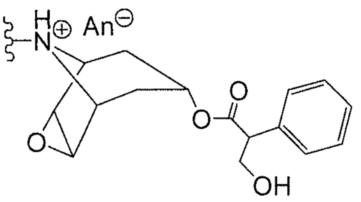


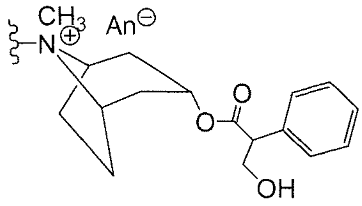


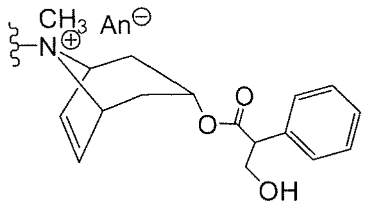


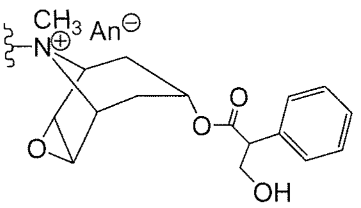


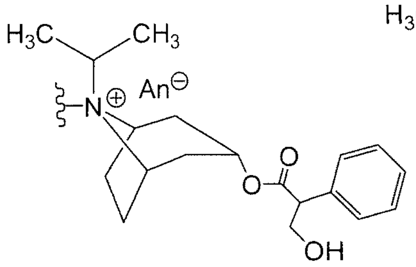


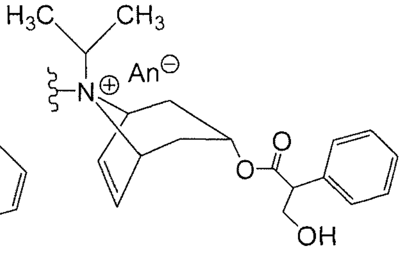




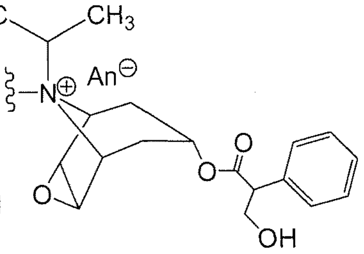






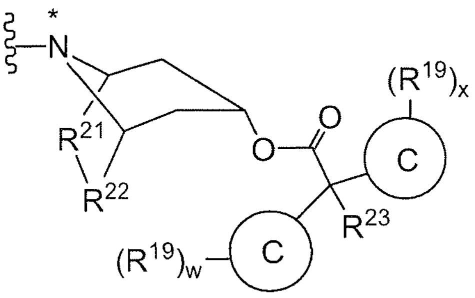


and



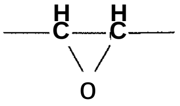
or any subset thereof.

In one embodiment, MRA is

vii)  , wherein

N* is N, $(N^{\oplus}H)An^{\ominus}$, $(N^{\oplus}\text{-}CH_3)An^{\ominus}$, or $(N^{\oplus}\text{-}CH(CH_3)_2)An^{\ominus}$;

$A\eta^{\theta}$ is a pharmaceutically acceptable counterion;

R^{21} and R^{22} together are $-CH_2-CH_2-$, $-CH=CH-$ or  $-\overset{H}{C}-\overset{H}{C}-$ (bridged by O) ;

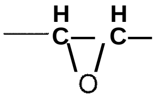
C is referred to as "Ring C" and is the same or different and is selected from phenyl, C3.6cycloalkyl, and 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S, or any subset thereof;

x and w are the same or different and are independently 0, 1, 2, 3 or 4, or any subset thereof;

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-}6alkenyl, C_{2-}6alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-C_{1-6}alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci $_{-6}$alkyl and N(C_{1-6}alkyl)$_2$ and CN, or any subset thereof; and

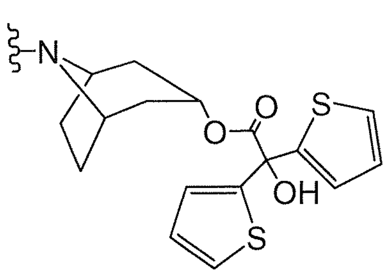
R^{23} is H or OH.

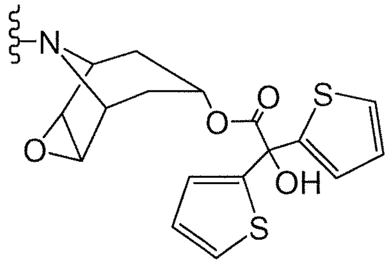
In one embodiment wherein MRA is a moiety of formula vii) above, N* is N, (N®H)$A\eta^{\ominus}$, or (N®-CH_3)An®. In one embodiment wherein MRA is a moiety of formula vii) above, R^{21} and R^{22} together are $-CH_2-CH_2-$. In one embodiment wherein MRA is a moiety of formula vii) above, R^{21} and R^{22} together are

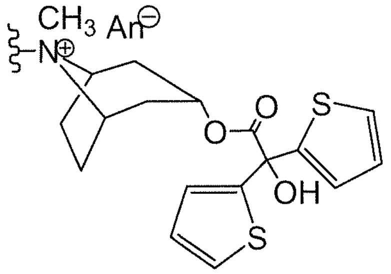

$-\overset{H}{C}-\overset{H}{C}-$ (bridged by O)

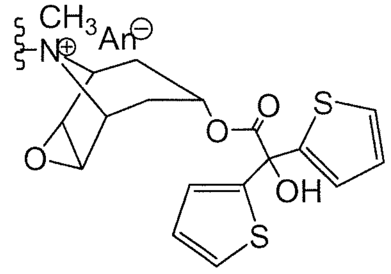
. In one embodiment wherein MRA is a moiety of formula vii) above, each Ring C is the same or different and is selected from phenyl, cyclohexyl, thiophenyl, thiazolyl, and pyridyl, or any subset thereof. In one particular embodiment, each Ring C is phenyl. In one particular embodiment, each Ring C is thiophenyl. In one embodiment wherein MRA is a moiety of formula vii) above, s and t are each 0 or 1, x and w are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, Ci-6alkyl, C_{2-}6alkenyl, C_{2-}6alkynyl, C3_6cycloalkyl, C_{1-4}haloalkyl, OH, O-Ci-6alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl and N(Ci $_{-}$6alkyl)$_2$ and CN, or any subset thereof. In one particular embodiment, x and w are both 0.

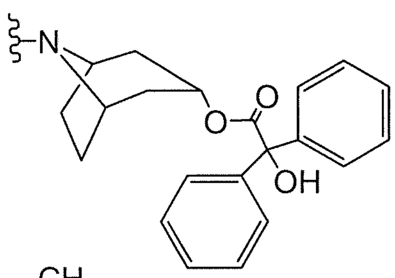
In one embodiment wherein MRA is a moiety of formula vii) above, R^{23} is OH. Specific examples of MRA moieties of formula vii) include

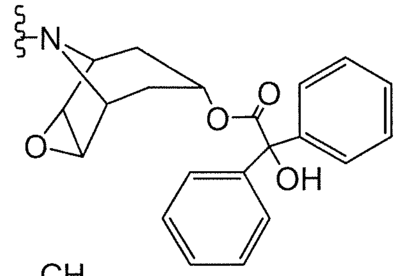


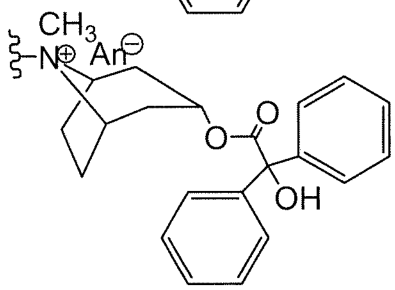




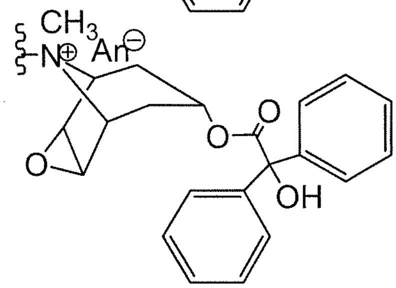






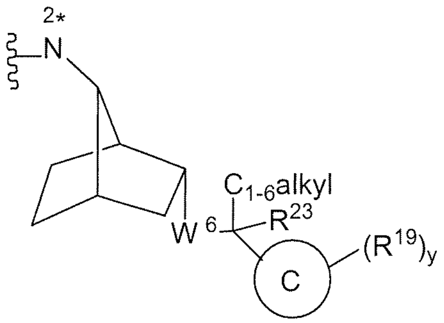


and



or any subset thereof.

In one embodiment, MRA is

viii)  , wherein

N^{2*} is N(R^{24}) or (N$^{®}$(CH$_3$)$_2$)An$^{\ominus}$, wherein R^{24} is H or C^alkyl;

An$^{®}$ is a pharmaceutically acceptable counterion;

W^6 is -0-C(=0)-, -O-CH2-, or -N(H)C(=O)-, or any subset thereof;

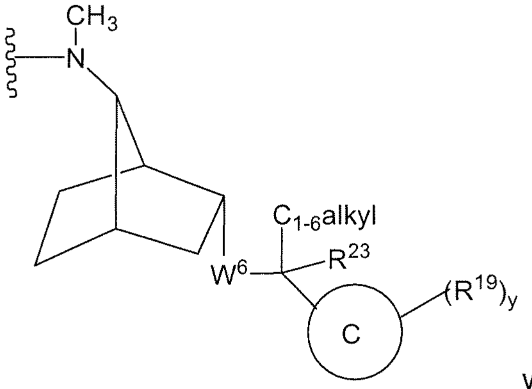
R^{23} is H or OH;

Ring C is the same or different and is selected from phenyl, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S, or any subset thereof;

y is 0, 1, 2, 3 or 4, or any subset thereof; and

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-C_{1-6}alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci $_{-6}$alkyl and N(C_{1-6}alkyl)$_2$ and CN, or any subset thereof.

In one such embodiment N^{2*} is N(CH_3) and MRA is a moiety of formula viii-a):

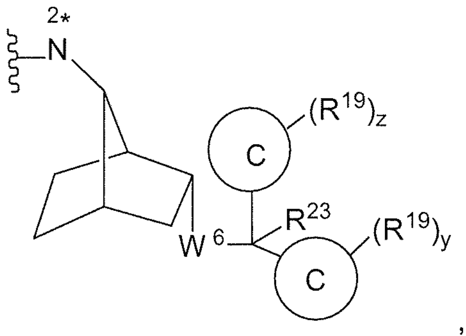


wherein all variables are as defined above.

In one embodiment wherein MRA is a moiety of formula viii) or viii-a) above, W^6 is -O-C(=O)-. In one embodiment wherein MRA is a moiety of formula viii) or viii-a) above, C_{1-6}alkyl is methyl or ethyl. In one embodiment wherein MRA is a moiety of formula viii) or viii-a) above, R^{23} is OH. In one embodiment wherein MRA is a moiety of formula viii) or viii-a) above, Ring C is selected from phenyl, cyclohexyl, thiophenyl, thiazolyl, and pyridyl, or any subset thereof. In one particular embodiment, Ring C is phenyl. In one particular embodiment, Ring C is thiophenyl. In one embodiment wherein MRA is a moiety of formula viii) or viii-a) above, y is 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, C_{1-6}alky!, C_{2-6}alkenyl, C2-6alkynyl, Cs-ecycloalkyl, $C_{1\text{-}4}$haloalkyl, **OH,** **O-C**$_{1\text{-}6}$alkyl, **O**-benzyl, **CO_2H,** **CO_2C**$_{1\text{-}6}$aikyl, **S-C**$_{1\text{-}6}$alkyl, **SO_2C**$_{1\text{-}6}$alkyl, **NH_2**, **N(H)C**$_{1\text{-}6}$alkyl and **N(C**$_{1\text{-}6}$alkyl)$_2$ and **CN,** or any subset thereof, or any subset thereof. In one particular embodiment, y is **0.**

In one embodiment, MRA is

ix)



, wherein

N^{2*} is **N**(R^{24}) or **($N^{\oplus}(CH_3)_2$)**$An^{\ominus}$, wherein R^{24} is **H** or **CH_3;**

Aη$^{\theta}$ is a pharmaceutically acceptable counterion;

W^6 is **-O-C(=O)-,** **-O-CH_2-,** or **-N(H)C(=O)-,** or any subset thereof;

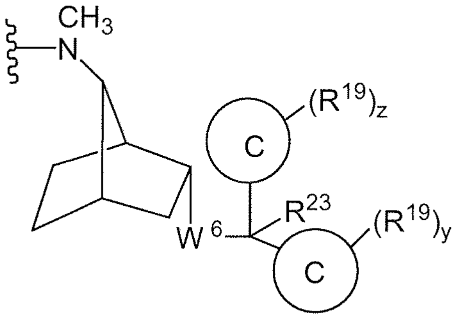
R^{23} is **H** or **OH;**

each Ring **C** is the same or different and is selected from phenyl, **$C_{3\text{-}6}$**cycloalkyl, and 5-6 membered heteroaryl having 1 or **2** heteroatoms selected from **N, O** and **S,** or any subset thereof;

y and z are the same or different and are independently **0, 1, 2, 3** or **4,** or any subset thereof; and

each R^{19} is the same or different and is independently selected from halo, **C**1_6alkyl, **C**$_{2\text{-}6}$alkenyl, **C**$_{2\text{-}6}$alkynyl, **C**$_{3\cdot 6}$cycloalkyl, **C**$_{1\text{-}4}$haloalkyl, **OH,** **O-C**$_{1\text{-}6}$alkyl, **O**-benzyl, **CO_2H,** **CO_2C**$_{1\text{-}6}$alkyl, S-**Ci**$_{\text{-}6}$alkyl, **SO_2C_1**$_{\text{-}6}$alkyl, **NH_2, N(H)Ci$_{\text{-}6}$alkyl** and **N(Ci**$_{\text{-}6}$alkyl)$_2$ and **CN,** or any subset thereof.

In one such embodiment **N^{2*}** is **N(CH_3)** and MRA is a moiety of formula ix-a):

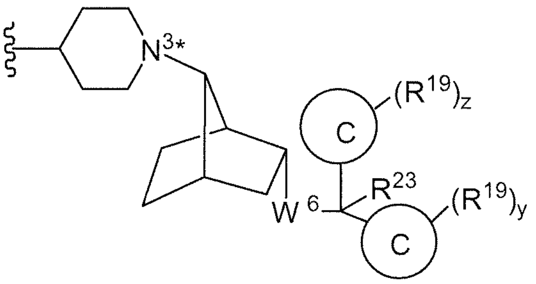


, wherein all variables are defined above.

In one embodiment wherein MRA is a moiety of formula ix) or ix-a) above, W^6 is -0-C(=0)-. In one embodiment wherein MRA is a moiety of formula ix) or ix-a) above, R^{23} is OH. In one embodiment wherein MRA is a moiety of formula ix) or ix-a) above, each Ring C is the same or different and is selected from phenyl, cyclohexyl, thiophenyl, thiazolyl, and pyridyl, or any subset thereof. In one particular embodiment, each Ring C is phenyl. In one particular embodiment, each Ring C is thiophenyl. In one embodiment wherein MRA is a moiety of formula ix) or ix-a) above, y and z are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, C_2-6alkynyl, $C_{3\text{-}}$6cycloalkyl, $C_{1\text{-}4}$haloalkyl, OH, O-Ci$_{\text{-}6}$alkyl, O-benzyl, CO_2H, CO2C$_{1\text{-}6}$alkyl, S-$C_{1\text{-}6}$alkyl, $SO_2C_{1\text{-}6}$alkyl, NH_2, N(H)$C_{1\text{-}6}$alkyl and N($C_{1\text{-}6}$alkyl)$_2$ and CN, or any subset thereof, or any subset thereof. In one particular embodiment, y and z are both 0.

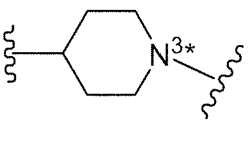
In one embodiment MRA is

x)

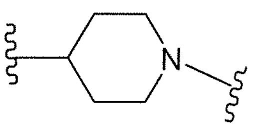


, wherein

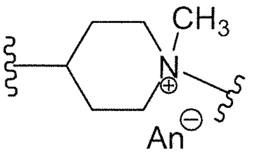
N^{3*} is N or N⊕(CH_3)An$^{\ominus}$, i.e.,



is



, or



;

$A\eta^{\theta}$ is a pharmaceutically acceptable counterion;

W^6 is -0-C(=0)-, -O-CH2-, or -N(H)C(=0)-;

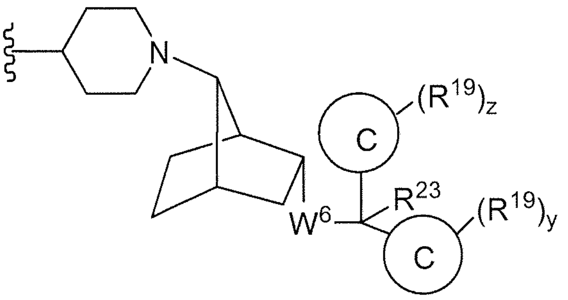
R^{23} is H or OH;

each Ring C is the same or different and is selected from phenyl, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S, or any subset thereof;

y and z are the same or different and are independently 0, 1, 2, 3 or 4, or any subset thereof; and

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-}6alkenyl, C2-6alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-Ci-ealkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-Ci $_{-6}$alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C-i $_{-6}$alkyl and N(Ci $_{-6}$alkyl)$_2$ and CN, or any subset thereof.

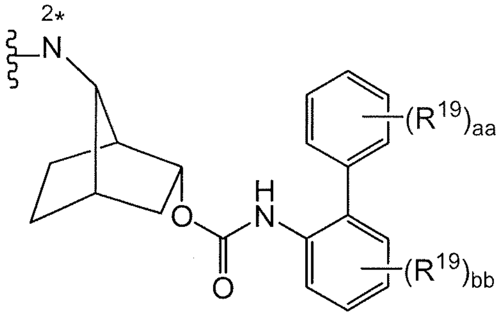
In one such embodiment N^{3*} is N and the MRA is a moiety of formula x-a):



.

In one embodiment wherein MRA is formula x) or x-a) above, W^6 is -O-C(=O)-. In one embodiment wherein MRA is formula x) or x-a) above, R^{23} is OH. In one embodiment wherein MRA is formula x) or x-a) above, each Ring C is the same or different and is selected from phenyl, cyclohexyl, thiophenyl, thiazolyl, and pyridyl, or any subset thereof. In one particular embodiment each Ring C is phenyl. In one embodiment wherein MRA is a moiety of formula x) or x-a) above, y and z are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, Chalky!, C_{2-}6alkenyl, C_{2-}6alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-C_{1-6}alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl and N(C_{1-6}alkyl)$_2$ and CN, or any subset thereof, or any subset thereof. In one particular embodiment, y and z are both 0.

In one embodiment MRA is

xi) 

, wherein

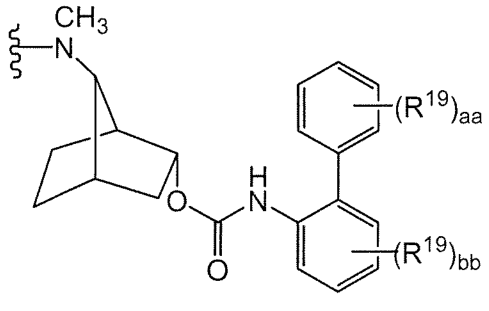
N^{2*} is **N**(**R**^{24}) or (N$^{\oplus}$(**CH** $_3$)$_2$)An$^{\ominus}$, where **R**^{24} is **H** or **CH**$_3$;

$A\eta^{\theta}$ is a pharmaceutically acceptable counterion;

aa and bb are the same or different and are independently 0, 1, 2, 3 or 4, or any subset thereof; and

each R^{19} is the same or different and is independently selected from halo, **C**$_{1\text{-}6}$alkyl, **C**$_{2\text{-}6}$alkenyl, **C**$_{2\text{-}6}$alkynyl, **C**$_{3\text{-}6}$cycloalkyl, c $_{1\text{-}4}$haloalkyl, **OH,** **O-C** $_{1\text{-}6}$alkyl, **O**-benzyl, **CO$_2$H, CO$_2$C**$_{1\text{-}6}$alkyl, S-**C**$_{1\text{-}6}$alkyl, **SO$_2$C**$_{1\text{-}6}$alkyl, **NH$_2$, N(H)Ci $_{-6}$alkyl** and **N(Ci** $_{-6}$alkyl)$_2$ and **CN,** or any subset thereof.

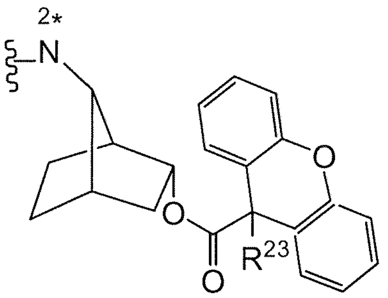
In one such embodiment N^{2*} is N(C**H$_3$)** and MRA is a moiety of formula xi-a):



, wherein all variables are defined above.

In one embodiment wherein MRA is a moiety of formula xi) or xi-a) above, aa and bb are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, **C**$_{1\text{-}6}$alkyl, **C**$_{2\text{-}6}$alkenyl, **C**$_{2\text{-}6}$alkynyl, **C**$_{3\text{-}6}$cycloalkyl, **C**$_{1\text{-}4}$haloalkyl, **OH, O-C**$_{1\text{-}6}$alkyl, **O**-benzyl, **CO$_2$H, CO$_2$C**$_{1\text{-}6}$alkyl, **S-Ci** $_{-6}$alkyl, **SO$_2$C**$_{1\text{-}6}$alkyl, **NH$_2$, N(H)Ci $_{-6}$alkyl** and **N(C**$_{1\text{-}6}$alkyl)$_2$ and **CN,** or any subset thereof. In one particular embodiment, aa and bb are both 0.

In one embodiment MRA is

xii) 

,

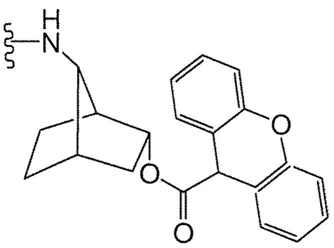
wherein

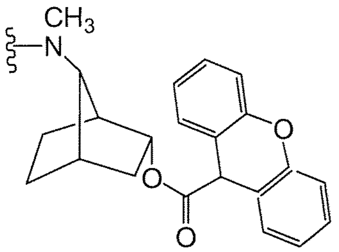
N^{2*} is $N(R^{24})$ or $(N^{\oplus}(CH_3)_2)An^{\ominus}$, where R^{24} is H or CH_3;

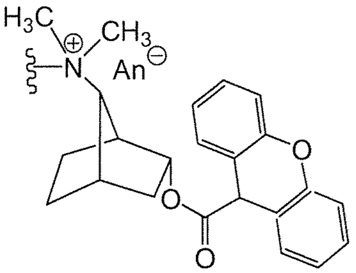
$A\eta^{\theta}$ is a pharmaceutically acceptable counterion;

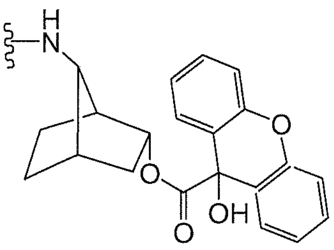
R^{23} is H or OH.

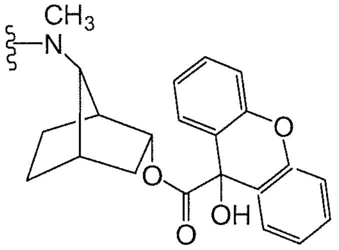
Thus, according to this embodiment, MRA is selected from



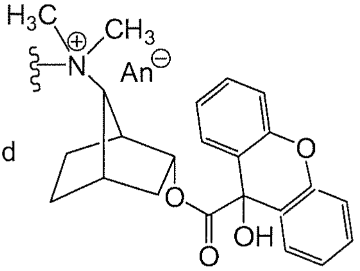






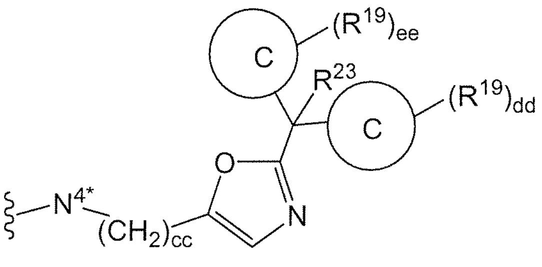


and

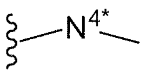
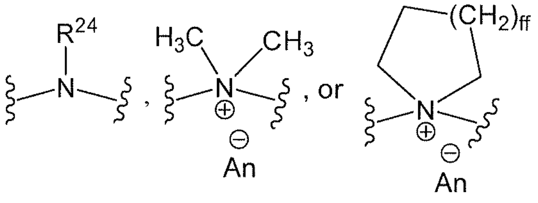


, or any subset thereof.

In one embodiment MRA is

xiii) 

, wherein

 is  , wherein ff is 1 or 2;

R^{24} is H or CH_3;

$A\eta^{\theta}$ is a pharmaceutically acceptable counterion;

cc is 1, 2 or 3;

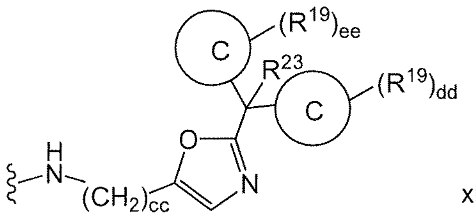
R^{23} is H or OH;

each Ring C is the same or different and is selected from phenyl, C_{3-} ecycloalkyl, and 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S, or any subset thereof;

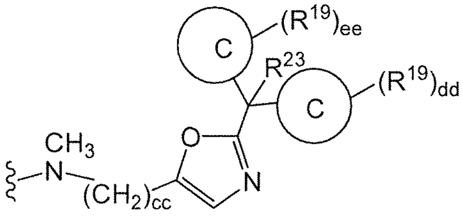
dd and ee are the same or different and are independently 0, 1, 2, 3 or 4, or any subset thereof; and

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-d-ealkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl and N(Ci $_{-6}$alkyl)$_2$ and CN, or any subset thereof.

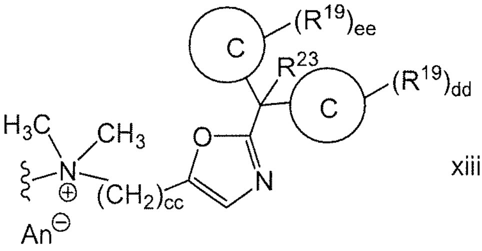
Thus, when MRA is a moiety of formula xiii), MRA is selected from xiii-a)



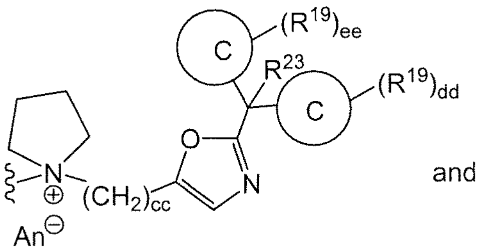
xiii-b)



xiii-c)

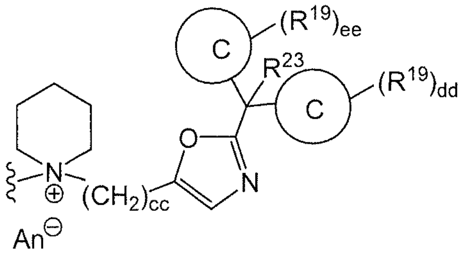


xiii-d)



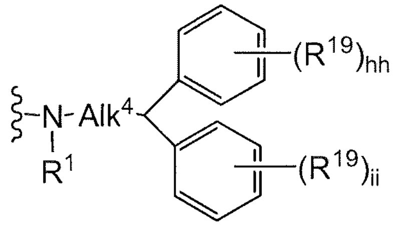
and

xiii-e)



In one embodiment wherein MRA is formula xiii), xiii-a), xiii-b), xiii-c), xiii-d) or xiii-e) above, cc is 1. In one embodiment wherein MRA is formula xiii), xiii-a), xiii-b), xiii-c), xiii-d) or xiii-e) above, each Ring **C** is the same or different and is selected from phenyl, cyclopentyl, cyclohexyl, thiophenyl, thiazolyl, and pyridyl, or any subset thereof. In one particular embodiment, each Ring **C** is the same or different and is selected from phenyl, cyclopentyl, cyclohexyl, and thiophenyl, or any subset thereof. In one particular embodiment, each Ring **C** is different and is selected from phenyl, cyclopentyl and cyclohexyl. In one embodiment wherein MRA is formula xiii), xiii-a), xiii-b), xiii-c), xiii-d) or xiii-e) above, dd and ee are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, **OH, O-**C_{1-6}alkyl, **O**-benzyl, CO_2H, CO_2C_{1-6}alkyl, **S-**C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, **N(H)**C_{1-6}alkyl and **N(Ci**$_{-6}$alkyl)$_2$ and **CN,** or any subset thereof. In one particular embodiment, dd and ee are both 0. In one embodiment wherein MRA is formula xiii), xiii-a), xiii-b), xiii-c), xiii-d) or xiii-e) above, R^{23} is **OH.**

In one embodiment MRA is



xiv) ,

wherein R^1 is H or CH_3;

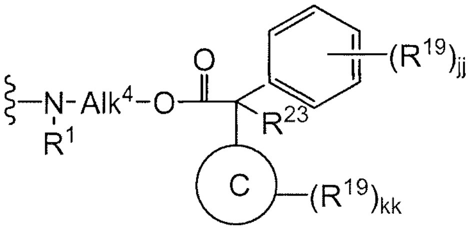
Alk^4 is linear or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene

hh and ii are the same or different and are independently 0, 1, 2, 3 or 4, or any subset thereof; and

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-d-ealkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci $_{-6}$alkyl and N(Ci $_{-6}$alkyl)$_2$ and CN, or any subset thereof.

In one embodiment wherein MRA is formula xiv), Alk^4 is C_{1-4}alkylene or C_{2-4}alkenylene. In one embodiment wherein MRA is formula xiv) above, hh and ii are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-Ci $_{-6}$alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci $_{-6}$alkyl and N(C_{1-6}alkyl)$_2$ and CN, or any subset thereof. In one particular embodiment, hh and ii are both 0.

In one embodiment MRA is



xv) ,

wherein:

R^1 is H or C_{1-4}alkyl;

Alk^4 is linear or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene;

R^{23} is H or OH;

each Ring C is the same or different and is selected from phenyl, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S, or any subset thereof;

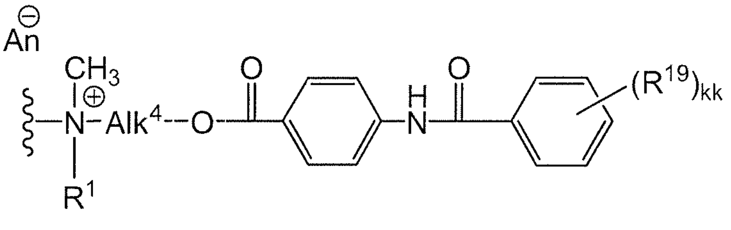
jj and kk are each the same or different and are independently 0, 1, 2, or 3, or any subset thereof;

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-C_{1-6}alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci $_{-6}$alkyl and N(C_{1-6}alkyl)$_2$ and CN, or any subset thereof; and

An® is a pharmaceutically acceptable counterion.

In one embodiment wherein MRA is formula xv), R^1 is H or CH_3. In one embodiment wherein MRA is formula xv), Alk^4 is C_{1-4}alkylene or C_{2-4}alkenylene, or any subset thereof. In one embodiment wherein MRA is formula xv), Ring C is C_{3-6}cycloalkyl. In one embodiment wherein MRA is formula xv), Ring C is cyclohexyl. In one embodiment wherein MRA is formula xv) above, jj and kk are each 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-Ci $_{-6}$alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2Ci $_{-6}$alkyl, NH_2, N(H)C_{1-6}alkyl and N(C_{1-6}alkyl)$_2$ and CN, or any subset thereof. In one particular embodiment, jj and kk are both 0.

In one embodiment MRA is

xvi) 

,

wherein:

R^1 is H or C_{1-4}alkyl;

Alk^4 is linear or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene;

An® is a pharmaceutically acceptable counterion;

kk is 0, 1, 2, or 3, or any subset thereof; and

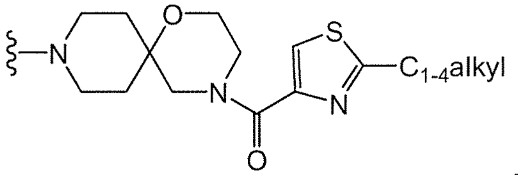
each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH,

0-C $_{1-6}$alkyl, **O**-benzyl, **CO$_2$H, C0** $_2$C$_{1-6}$alkyl, S-**C**$_{1-6}$alkyl, **S0** $_2$C$_{1-6}$alkyl, **NH$_2$, N(H)C**$_{1-6}$alkyl and **N(Ci** $_{-6}$alkyl)$_2$ and **CN,** or any subset thereof.

In one embodiment wherein MRA is formula xvi), R^1 is **H** or **CH$_3$.** In one embodiment wherein MRA is formula xvi), Alk^4 is **C**$_{1-4}$alkylene or **C$_{2-4}$**alkenylene, or any subset thereof. In one embodiment wherein MRA is formula xv) above, kk is 0 or 1, wherein each R^{19} is the same or different and is independently selected from halo, C$_{1-6}$alkyl, **C**$_{2-6}$alkenyl, **C**$_{2-6}$alkynyl, C$_{3-6}$cycloalkyl, C$_{1-4}$haloalkyl, **OH, O-C**$_{1-6}$alkyl, **O**-benzyl, **CO$_2$H, CO$_2$C**$_{1-6}$alkyl, S-**C**$_{1-6}$alkyl, **SO$_2$C**$_{1-6}$alkyl, **NH$_2$, N(H)C**$_{1-6}$alkyl and **N(Ci** $_{-6}$alkyl)$_2$ and **CN,** or any subset thereof. In one particular embodiment, kk is 0.

In one embodiment MRA is

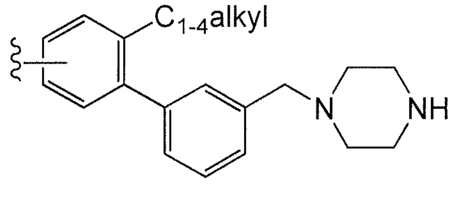
xvii)



. In one particular embodiment wherein MRA is formula xvii), **C**$_{1-4}$alkyl is methyl, ethyl, isopropyl or t-butyl.

In one embodiment MRA is

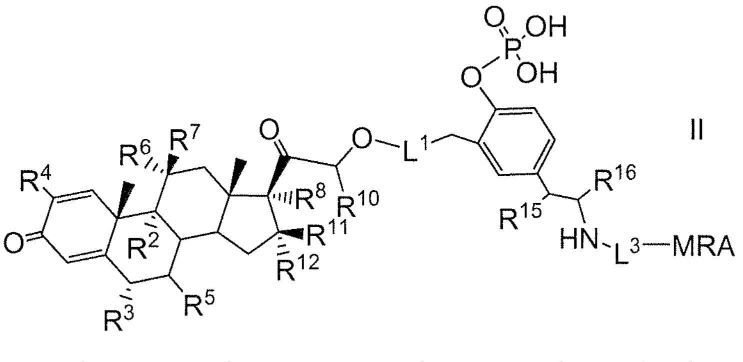
xviii)



. In one particular embodiment wherein MRA is formula xviii), **C**$_{1-4}$alkyl is methyl, ethyl, isopropyl or t-butyl.

The counterion, An®, is typically an anion of a pharmaceutically acceptable inorganic acid addition salt, such as chloride, bromide, iodide, hydroxide, sulfate, phosphate, or an anion from a salt derived from pharmaceutically acceptable organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, succinic acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, isethionic acid, lactobionic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, naphthalene-1 ,5-disulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, 1-hydroxy-2-naphthoate (xinafoate), pamoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, lactic acid, ethanesulfonic acid, lysine, arginine, glutamic acid, glycine, serine, threonine, alanine, isoleucine, leucine and the like. In one embodiment, the counterion Aη$^{\ominus}$ is selected from chloride, bromide, sulfate, phosphate, acetate, tartrate, fumarate, or xinafoate, or any subset thereof. Preferred anions include those from inorganic or organic acid salts which are either acceptable for use in inhaled products and/or known or believed to minimize pulmonary irritation. In one embodiment, Aη$^{\ominus}$ is selected from chloride, bromide, sulfate, acetate, tartrate, fumarate and xinafoate, or any subset thereof. In one particular embodiment, An$^{\ominus}$is chloride. In one particular embodiment, Aη$^{\theta}$ is sulfate. In one particular embodiment, An® is acetate. In one particular embodiment, An$^{\ominus}$ is tartrate. In one particular embodiment, An® is fumarate. In one particular embodiment, An® is xinafoate. In one particular embodiment, An® is succinate. In certain instances, there may be more than one counterion associated with a given compound according to the invention inasmuch as the compounds of the invention contemplate and include compounds which may have two or more quaternary nitrogens.

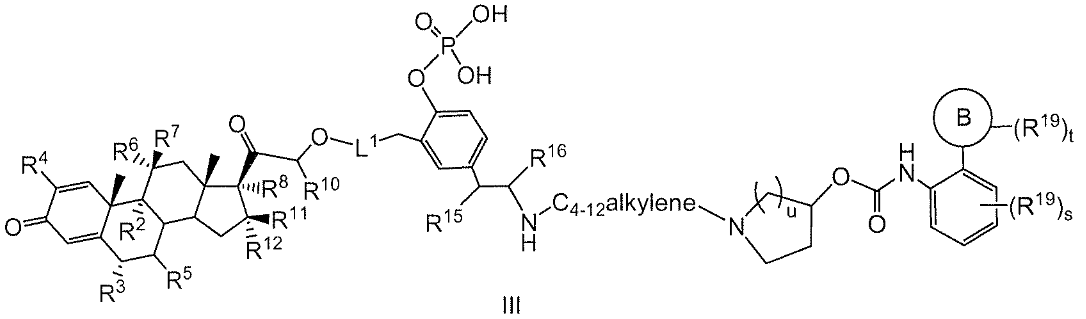
In one embodiment, the invention provides compounds of Formula II:



II

and pharmaceutically acceptable salts thereof, wherein all variables are as defined above, including all embodiments of each variable as described hereinabove. For the sake of brevity, the disclosure of those embodiments, including particular and preferred embodiments is not repeated. Any of the previously disclosed embodiments, particular embodiments and preferred embodiments of each variable are contemplated for combination in the foregoing Formula II.

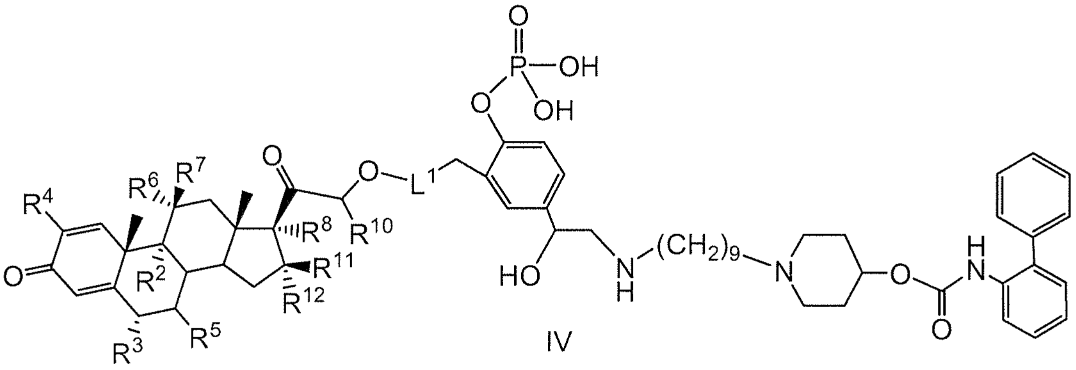
In one embodiment, the invention provides compounds of Formula III:



III

and pharmaceutically acceptable salts thereof, wherein all variables are as defined above, including all embodiments of each variable as described hereinabove. For the sake of brevity, the disclosure of those embodiments, including particular and preferred embodiments is not repeated. Any of the previously disclosed embodiments, particular embodiments and preferred embodiments of each variable are contemplated for combination in the foregoing Formula III.

In one embodiment, the invention provides compounds of Formula IV:



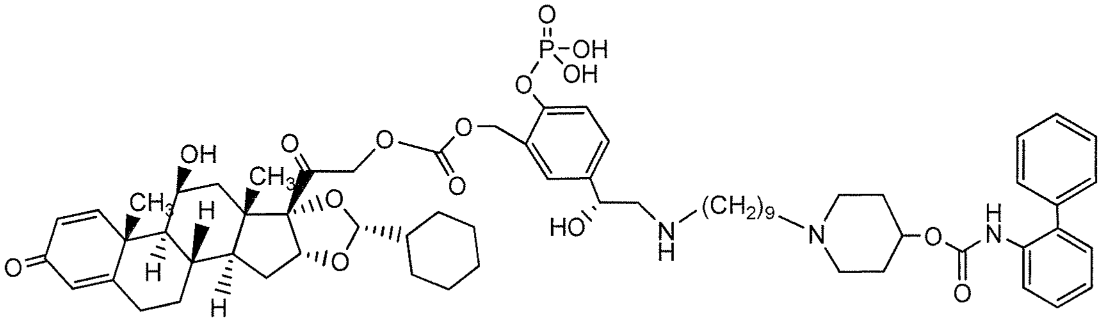
IV

and pharmaceutically acceptable salts thereof, or any subset thereof, wherein all variables are as defined above, including all embodiments of each variable as described hereinabove. For the sake of brevity, the disclosure of those embodiments, including particular and preferred embodiments is not repeated. Any of the previously disclosed embodiments, particular embodiments and preferred embodiments of each variable are contemplated for combination in the foregoing Formula IV.

It is to be understood that the present invention includes all combinations and subsets of the particular variable definitions defined hereinabove in the compounds of the invention.

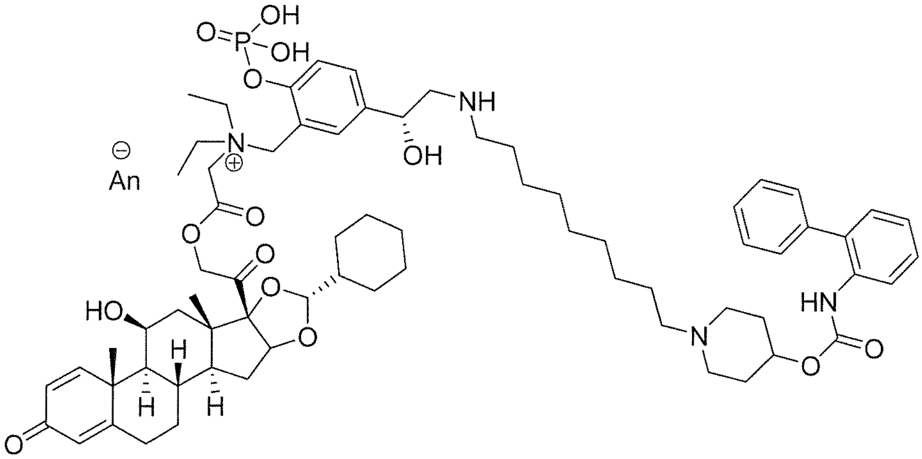
Specific examples of compounds of the invention include the compounds set forth in the examples below (and free base and pharmaceutically acceptable salt forms thereof).

One specific compound of the invention is



and pharmaceutically acceptable salts thereof.

Another specific compound of the invention is



and pharmaceutically acceptable salts thereof.

The compounds of Formula I, may be in the form of a salt, particularly a pharmaceutically acceptable salt. For a review of pharmaceutically acceptable salts see Berge et al., *J. Pharma Sci.* (1977) 66:1-19 and HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION, AND USE by Stahl and

Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Examples of pharmaceutically acceptable salts of the compounds of the Formula I include salts derived from an appropriate base, such as an alkali metal or an alkaline earth (for example, Na^+, Li^+, K^+, Ca^{2+} and Mg^{2+}), ammonium and $N(C_{1-4}alkyl)_4^+$. Pharmaceutically acceptable salts of a nitrogen atom or an amino group include (a) acid addition salts formed with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acids, phosphoric acid, nitric acid and the like; (b) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, isethionic acid, lactobionic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, naphthalene-1 ,5-disulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, 1-hydroxy-2-naphthoate pamoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, lactic acid, ethanesulfonic acid, lysine, arginine, glutamic acid, glycine, serine, threonine, alanine, isoleucine, leucine and the like; and (c) salts formed from elemental anions for example, chlorine, bromine, and iodine. In particular, compounds of Formula I which have a basic N can form quaternary ammonium salts with pharmaceutically acceptable counter-ions such as chlorine, bromine, acetate, formate, p-toluenesulfonate, succinate, hemi-succinate, naphthylene-bis sulfonate, methanesulfonate, xinafoate and the like. Zwitterionic compounds of Formula I, while not forming true stoichiometric salts may nonetheless form complexes with the pharmaceutically acceptable anions and cations mentioned above.

For therapeutic use, salts of active ingredients of the compounds of Formula I will be pharmaceutically acceptable, i.e. they will be salts derived from a pharmaceutically acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether or not derived from a pharmaceutically acceptable acid or base, are within the scope of the present invention.

Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

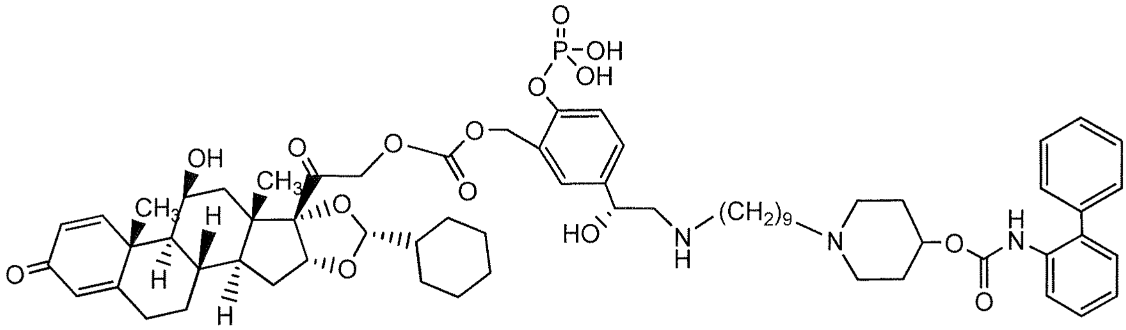
"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., MCGRAW-HILL DICTIONARY OF CHEMICAL TERMS (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., STEREOCHEMISTRY OF ORGANIC COMPOUNDS (1994) John Wiley & Sons, Inc., New York.

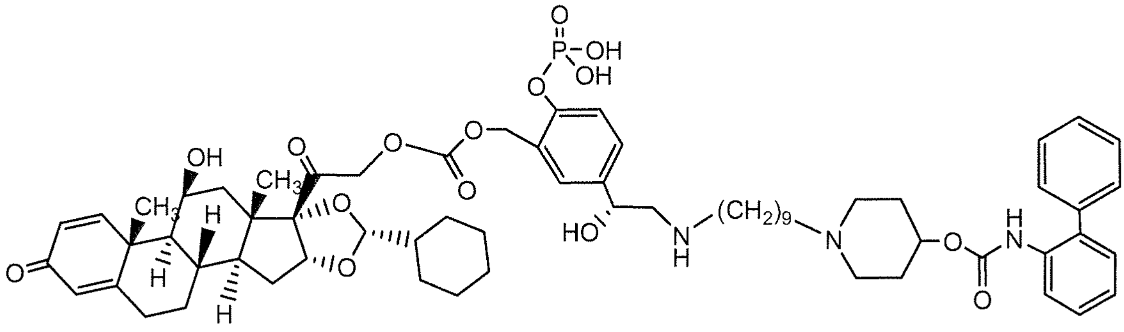
Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species.

It is to be noted that all enantiomers, diastereomers, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula I and pharmaceutically acceptable salts thereof are embraced by the present invention. All mixtures of such enantiomers and diastereomers, including enantiomerically enriched mixtures and diastereomerically enriched mixtures are within the scope of the present invention. Enantionmerically enriched mixtures are mixtures of enantiomers wherein the ratio of the specified enantiomer to the alternative enantiomer is greater than 50:50. More particularly, an enantiomerically enriched mixture comprises at least about 75% of the specified enantiomer, and preferably at least about 85% of the specified enantiomer. In one embodiment, the enantiomerically enriched mixture is substantially free of the other enantiomer. Similarly, diastereomerically enriched mixtures are mixtures of diastereomers wherein amount of the specified diastereomer is greater than the amount of each alternative diastereomer. More particularly, a diastereomerically enriched mixture comprises at least about 75% of the specified diastereomer, and preferably at least about 85% of the specified diastereomer. In one embodiment, the diastereomerically enriched mixture is substantially free of all other diastereomers.

For illustrative purposes, specific examples of enantiomers within the scope of the present invention include:

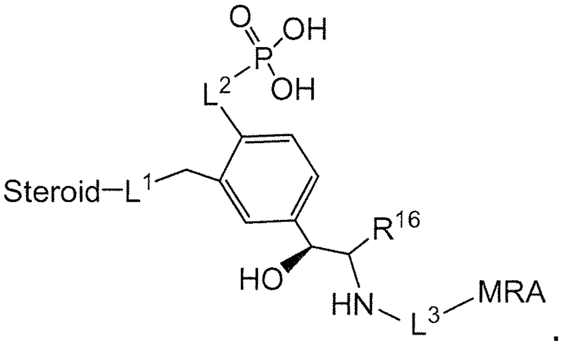


and



.

In one embodiment, the present invention provides an enantiomerically enriched mixture comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein R^{15} is OH and all other variables are as defined above, wherein the predominant enantiomer is represented by the formula:



A compound of Formula I and pharmaceutically acceptable salts thereof may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means the ability of a crystalline compound to exist in different crystal structures. The crystalline polymorphism may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). As used herein, crystalline pseudopolymorphism also includes the ability of a hydrate or solvate of a compound to exist in different crystal structures. The pseudopolymorphs of the instant invention may exist due to differences in crystal packing (packing pseudopolymorphism) or due to differences in packing between different conformers of the same molecule (conformational pseudopolymorphism). The instant invention comprises all polymorphs and pseudopolymorphs of the compounds of Formula I and pharmaceutically acceptable salts thereof.

A compound of Formula I and pharmaceutically acceptable salts thereof may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant invention. The instant invention comprises all amorphous forms of the compounds of Formula I and pharmaceutically acceptable salts thereof.

The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity).

Uses and Methods of Treatment

The compounds of the present invention are comprised of three chemically conjoined components. The linking groups between the respective active moieties are selected in order to be susceptible to enzymatic or metabolic cleavage *in vivo* in order to effect the release of the three components from the conjoined molecule. Thus, the utility and methods of using the compounds of the present invention are the same as the utility and methods of using the constituent components, namely the corticosteroids, selective β-agonists and muscarinic antagonists.

The compounds of the invention are useful as a medicament and more particularly, are useful for the treatment of clinical conditions for which a corticosteroid, selective β-agonists and particularly β_2-agonists, and/or muscarinic, particularly M3 antagonists, are indicated. Such conditions may involve pulmonary inflammation and/or bronchoconstriction, and include diseases associated with reversible or irreversible airway obstruction. More particularly, such conditions include asthma, chronic obstructive pulmonary diseases (COPD), chronic bronchitis, bronchiectasis, emphysema, respiratory tract infection and upper respiratory tract diseases (e.g., rhinitis, including seasonal and allergic rhinitis).

Accordingly, in one aspect, the present invention provides a method for the treatment of a condition in a mammal, such as a human, for which a corticosteroid, β-agonist, and/or muscarinic antagonist is indicated.

The terms "treating" and "treatment", as used herein refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition or one or more symptoms of such disorder or condition.

All therapeutic methods described herein are carried out by administering an effective amount of a compound of the invention, i.e., a compound of Formula I or a pharmaceutically acceptable salt thereof, to a subject (typically mammal and preferably human) in need of treatment.

In one embodiment the invention provides a method for the treatment of pulmonary inflammation and bronchoconstriction in a mammal, particularly a human, in need thereof. In one particular embodiment the present invention provides a method for the treatment of a condition associated with reversible airway obstruction in a mammal, particularly a human in need thereof. In one embodiment the invention provides a method for the treatment of asthma in a mammal, particularly a human, in need thereof. In one embodiment the invention provides a method for the treatment of chronic obstructive pulmonary disease in a mammal, particularly a human, in need thereof. With respect to treatments of COPD, the present invention also contemplates methods and uses for reducing the frequency, severity and/or duration of acute exacerbation of COPD.

In one embodiment the invention provides a method for the treatment of bronchitis, including chronic bronchitis in a mammal, particularly a human, in need thereof. In one embodiment the invention provides a method for the treatment of bronchiectasis in a mammal, particularly a human, in need thereof. In one embodiment the invention provides a method for the treatment of emphysema in a mammal, particularly a human in need thereof. In one embodiment the invention provides a method for the treatment of a respiratory tract infection or upper respiratory tract disease in a mammal, particularly a human in need thereof.

There is also provided a compound of the invention for use in medical therapy, particularly for use in the treatment of condition in a mammal, such as a human, for which a corticosteroid, β-agonist, and/or muscarinic antagonist is indicated. All therapeutic uses described herein are carried out by administering an effective amount of a compound of the invention to the subject in need of treatment. In one embodiment there is provided a compound of the invention for use in the treatment of pulmonary inflammation and bronchoconstriction in a mammal, particularly a human, in need thereof. In one particular embodiment there is provided a compound of the invention for use in the treatment of a condition associated with reversible airway obstruction in a mammal, particularly a human in need thereof. In one embodiment, there is provided a compound of the invention for use in the treatment of asthma in a mammal, particularly a human, in need thereof. In one embodiment there is provided a compound of the invention for use in the treatment of chronic obstructive pulmonary disease in a mammal, particularly a human, in need thereof. In one embodiment there is provided a compound for use in the treatment of bronchitis, including chronic bronchitis in a mammal, particularly a human, in need thereof. In one embodiment there is provided a compound for use in the treatment of bronchiectasis in a mammal, particularly a human, in need thereof. In one embodiment there is provided a compound for use in the treatment of emphysema in a mammal, particularly a human in need thereof. In one embodiment there is provided a compound of the invention for use in the treatment of a respiratory tract infection or upper respiratory tract disease in a mammal, particularly a human, in need thereof.

The present invention also provides the use of a compound of the invention in the manufacture of a medicament for the treatment of a condition in a mammal, such as a human, for which a corticosteroid, β-agonist, and/or muscarinic antagonist is indicated. In one embodiment is provided the use of a compound of the invention in the manufacture of a medicament for the treatment of pulmonary inflammation and bronchoconstriction in a mammal, particularly a human, in need thereof. In one particular embodiment is provided the use of a compound of the invention in the manufacture of a medicament for the treatment of a condition associated with reversible airway obstruction in a mammal, particularly a human in need thereof. In one embodiment is provided a compound of the invention in the manufacture of a medicament for the treatment of asthma in a mammal, particularly a human, in need thereof. In one embodiment is provided the use of a compound of the invention in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease in a mammal, particularly a human, in need thereof. In one embodiment is provided the use of a compound of the invention in the manufacture of a medicament for the treatment of bronchitis, including chronic bronchitis in a mammal, particularly a human, in need thereof. In one embodiment is provided the use of a compound of the invention in the manufacture of a medicament for the treatment of bronchiectasis in a mammal, particularly a human, in need thereof. In one embodiment is provided the use of a compound of the invention for the manufacture of a medicament for the treatment of emphysema in a mammal, particularly a human in need thereof. In one embodiment is provided the use of a compound of the invention for the manufacture of a medicament for the treatment of a respiratory tract infection or upper respiratory tract disease in a mammal, particularly a human in need thereof.

The term "effective amount", as used herein, is an amount of compound of the invention which is sufficient in the subject to which it is administered, to elicit the biological or medical response of a cell culture, tissue, system, mammal (including human) that is being sought, for instance by a researcher or clinician. The term also includes within its scope, amounts effective to enhance normal physiological function. In one embodiment, the effective amount is the amount needed to provide a desired level of drug in the secretions and tissues of the airways and lungs, or alternatively, in the bloodstream of a subject to be treated to give an anticipated physiological response or desired biological effect when such a composition is administered by inhalation. For example an effective amount of a compound of the invention for the treatment of a condition for which a corticosteroid and/or β-agonist is indicated is sufficient in the subject to which it is administered to treat the particular condition. In one embodiment an effective amount is an amount of a compound of the invention which is sufficient for the treatment of asthma, or COPD in a human.

The precise effective amount of the compounds of the invention will depend on a number of factors including but not limited to the species, age and weight of the subject being treated, the precise condition requiring treatment and its severity, the bioavailability, potency, and other properties of the specific compound being administered, the nature of the formulation, the route of administration, and the delivery device, and will ultimately be at the discretion of the attendant physician or veterinarian.

An estimated dose (for inhalation) of a compound of the invention for treatment of a 70 kg human may be in the range of from about 10 to about 5000pg. The selection of the specific dose for a patient will be determined by the attendant physician, clinician or veterinarian of ordinary skill in the art based upon a number of factors including those noted above. In one particular embodiment, the dose of a compound of the invention for the treatment of a 70 kg human will be in the range of from about 50 to about 2500 pg. In one preferred embodiment the dose of a compound of the invention for the treatment of a 70 kg human will be in the range of from about 100 to about 1000 µg. Doses may be adjusted if the compound is administered via a different route. Determination of an appropriate dose for administration by other routes is within the skill of those in the art in light of the foregoing description and the general knowledge in the art.

Delivery of an effective amount of a compound of the invention may entail delivery of a single dosage form or multiple unit doses which may be delivered contemporaneously or separate in time over a designated period, such as 24 hours. Typically, a compound of the invention (alone or in the form of a composition comprising the same) will be administered four, three, two, or most preferably once per day (24 hours).

Compositions

While it is possible for a compound of the invention to be administered alone, it is preferable to present it in the form of a composition, particularly a pharmaceutical composition (formulation). Thus, in another aspect, the invention provides compositions, and particularly pharmaceutical compositions (such as an inhalable pharmaceutical composition) comprising a compound of the invention as an active ingredient and a pharmaceutically acceptable excipient, diluent or carrier. The term "active ingredient" as employed herein refers to any of a compound of Formula I, II, III or IV or a pharmaceutically acceptable salt of any of the foregoing. The pharmaceutically acceptable excipient(s), diluent(s) or carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the aerosol formulation and not deleterious to the recipient thereof. Generally, the pharmaceutically acceptable excipient(s), diluent(s) or carrier(s) employed in the pharmaceutical formulation are "non-toxic" meaning that it/they is/are deemed safe for consumption in the amount delivered in the aerosol formulation and "inert" meaning that it/they does/do not appreciable react with or result in an undesired effect on the therapeutic activity of the active ingredients (fosfomycin and tobramycin). Pharmaceutically acceptable excipients, diluents and carriers are conventional in the art and may be selected using conventional techniques, based upon the desired route of administration. *See,* REMINGTON'S, PHARMACEUTICAL SCIENCES, Lippincott Williams & Wilkins; 21st Ed (May 1, 2005). Preferably, the pharmaceutically acceptable excipient(s), diluent(s) or carrier(s) are Generally Regarded As Safe (GRAS) according to the FDA.

Pharmaceutical compositions according to the invention include those suitable for oral administration; parenteral administration, including subcutaneous, intradermal, intramuscular, intravenous and intraarticular; and administration to the respiratory tract, including the nasal cavities and sinuses, oral and extrathoracic airways, and the lungs, including by use of aerosols which may be delivered by means of various types of dry powder inhalers, pressurized metered dose inhalers, softmist inhalers, nebulizers, or insufflators. The most suitable route of administration may depend upon, several factors including the patient and the condition or disorder being treated.

The formulations may be presented in unit dosage form or in bulk form as for example in the case of formulations to be metered by an inhaler and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier, diluent or excipient and optionally one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with one or more liquid carriers, diluents or excipients or finely divided solid carriers, diluents or excipients, or both, and then, if necessary, shaping the product into the desired formulation.

In one preferred embodiment, the composition is an inhalable pharmaceutical composition which is suitable for inhalation and delivery to the endobronchial space. Typically, such composition is in the form of an aerosol comprising particles for delivery using a nebulizer, pressurized metered dose inhaler (MDI), softmist inhaler, or dry powder inhaler (DPI). The aerosol formulation used in the methods of the present invention may be a liquid (e.g., solution) suitable for administration by a nebulizer, softmist inhaler, or MDI, or a dry powder suitable for administration by an MDI or DPI.

Aerosols used to administer medicaments to the respiratory tract are typically polydisperse, that is they are comprised of particles of many different sizes. The particle size distribution is typically described by the Mass Median Aerodynamic Diameter (MMAD) and the Geometric Standard Deviation (GSD). For optimum drug delivery to the endobronchial space the MMAD is in the range from about 1 to about 10 μm and preferably from about 1 to about 5μm, and the GSD is less than 3, and preferably less than about 2. Aerosols having a MMAD above 10 pm are generally too large when inhaled to reach the lungs. Aerosols with a GSD greater than about 3 are not preferred for lung delivery as they deliver a high percentage of the medicament to the oral cavity. To achieve these particle sizes in powder formulation, the particles of the active ingredient may be size reduced using conventional techniques such as micronisation or spray drying. Non limiting examples of other processes or techniques that can be used to produce respirable particles include spray drying, precipitation, supercritical fluid, and freeze drying. The desired fraction may be separated out by air classification or sieving. In one embodiment, the particles will be crystalline. For liquid formulations, the particle size is determined by the selection of a particular model of nebulizer, softmist inhaler, or MDI.

Aerosol particle size distributions are determined using devices well known in the art. For example a multi-stage Anderson cascade impactor or other suitable method such as those specifically cited within the US Pharmacopoeia Chapter 601 as characterizing devices for aerosols emitted from metered-dose and dry powder inhalers.

Dry powder compositions for topical delivery to the lung by inhalation may be formulated without excipient or carrier and instead including only the active ingredients in a dry powder form having a suitable particle size for inhalation. Dry powder compositions may also contain a mix of the active ingredient and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di- or poly-saccharides (e.g., lactose or starch). Lactose is typically the preferred excipient for dry powder formulations. When a solid excipient such as lactose is employed, generally the particle size of the excipient will be much greater than the active ingredient to aid the dispersion of the formulation in the inhaler.

Non-limiting examples of dry powder inhalers include reservoir multi-dose inhalers, pre-metered multi-dose inhalers, capsule-based inhalers and single-dose disposable inhalers. A reservoir inhaler contains a large number of doses (e.g. 60) in one container. Prior to inhalation, the patient actuates the inhaler which causes the inhaler to meter one dose of medicament from the reservoir and prepare it for inhalation. Examples of reservoir DPIs include but are not limited to the Turbohaler® by AstraZeneca and the ClickHaler® by Vectura. In a pre-metered multi-dose inhaler, each individual dose has been manufactured in a separate container, and actuation of the inhaler prior to inhalation causes a new dose of drug to be released from its container and prepared for inhalation. Examples of multidose DPI inhalers include but are not limited to Diskus® by GSK, Gyrohaler® by Vectura, and Prohaler® by Valois. During inhalation, the inspiratory flow of the patient accelerates the powder out of the device and into the oral cavity. For a capsule inhaler, the formulation is in a capsule and stored outside the inhaler. The patient puts a capsule in the inhaler, actuates the inhaler (punctures the capsule), then inhales. Examples include the Rotohaler™ (GlaxoSmithKline), Spinhaler™ (Novartis), HandiHaler™ (IB), TurboSpin™ (PH&T). With single-dose disposable inhalers, the patient actuates the inhaler to prepare it for inhalation, inhales, then disposes of the inhaler and packaging. Examples include the Twincer™ (U Groningen), OneDose™ (GFE), Manta Inhaler™ (Manta Devices).

Generally, dry powder inhalers utilize turbulent flow characteristics of the powder path to cause the excipient-drug aggregates to disperse, and the particles of active ingredient are deposited in the lungs. However, certain dry powder inhalers utilize a cyclone dispersion chamber to product particles of the desired respirable size. In a cyclone dispersion chamber, the drug enters a coin shaped dispersion chamber tangentially so that the air path and drug move along the outer circular wall. As the drug formulation moves along this circular wall it bounces around and agglomerates are broken apart by impact forces. The air path spirals towards the center of the chamber exiting vertically. Particles that have small enough aerodynamic sizes can follow the air path and exit the chamber. In effect, the dispersion chamber works like a small jet mill.

Depending on the specifics of the formulation, large lactose particles may be added to the formulation to aid in the dispersion through impact with the API particles.

The Twincer™ single-dose disposable inhaler appears to operate using a coin-shaped cyclone dispersion chamber referred to as an "air classifier." See, U.S. Published Patent Application No. 2006/023701 0 to Rijksuniversiteit Groningen. Papers published by the University of Groningen, have stated that a 60 mg dose of pure micronized colistin sulfomethate could be effectively delivered as an inhalable dry powder utilizing this technology.

In preferred embodiments, the aerosol formulation is delivered as a dry powder using a dry powder inhaler wherein the particles emitted from the inhaler have an MMAD in the range of about 1 µm to about 5 µm and a GSD about less than 2.

Examples of suitable dry powder inhalers and dry powder dispersion devices for use in the delivery of compounds and compositions according to the present invention include but are not limited to those disclosed in US7520278; US7322354; US724661 7; US7231 920; US721 9665; US7207330; US6880555; US5,522,385; US6845772; US6637431 ; US6329034; US5,458,1 35; US4,805,81 1; and U.S. Published Patent Application No. 2006/0237010. In one embodiment, the pharmaceutical formulation according to the invention is a dry powder for inhalation which is formulated for delivery by a Diskus®-type device. The Diskus® device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a predetermined amount active ingredient either alone or in admixture with one or more carriers or excipients (e.g., lactose) and/or other therapeutically active agents. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. To prepare the dose for inhalation, the lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the base sheet.

In one embodiment, the pharmaceutical formulation according to the invention is a dry powder for inhalation which is formulated for delivery using a single-dose disposable inhaler, and particularly the Twincer™ inhaler. The Twincer™ inhaler comprises a foil laminate blister with one or more recesses and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers. Each container has therein an inhalable formulation containing a predetermined amount of active ingredient(s) either alone or in admixture with one or more carriers or excipeints (e.g., lactose). The lid sheet will preferably have a leading end portion which is constructed to project from the body of the inhaler. The patient would operate the device and thereby administer the aerosol formulation by 1) removing the outer packaging overwrap, 2) pulling the foil tab to uncover the drug in the blister and 3) inhaling the drug from the blister.

In another embodiment, the pharmaceutical formulation according to the invention is a dry powder for inhalation wherein the dry powder is formulated into microparticles as described in PCT Publication No. WO2009/01 5286 or WO200 7/1 14881 , both to NexBio. Such microparticles are generally formed by adding a counterion to a solution containing a compound of the invention in a solvent, adding an antisolvent to the solution; and gradually cooling the solution to a temperature below about 25°C, to form a composition containing microparticles comprising the compound. The microparticles comprising the compound may then be separated from the solution by any suitable means such as sedimentation, filtration or lyophilization. Suitable counterions, solvents and antisolvents for preparing microparticles of the compounds of the invention are described in WO2009/01 5286.

In another embodiment, a pharmaceutical composition according to the invention is delivered as a dry powder using a metered dose inhaler. Non-limiting examples of metered dose inhalers and devices include those disclosed in US5.261 .538; US5.544.647; US5.622.163; US4.955.371 ; US3.565.070; US3,361 306 and US6.1 16,234 and US71081 59. In a preferred embodiment, a compound of the invention is delivered as a dry powder using a metered dose inhaler wherein the emitted particles have an MMAD that is in the range of about 1 µm to about 5 pm and a GSD that is less than about 2.

Liquid aerosol formulations for delivery to the endobronchial space or lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurized packs, such as metered dose inhalers, with the use of suitable liquefied propellants, softmist inhalers, or nebulizers. Such aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the active ingredient together with a pharmaceutically acceptable carrier or diluent (e.g., water, saline, or ethanol) and optionally one or more therapeutically active agents.

Aerosol compositions for delivery by pressurized metered dose inhalers typically further comprise a pharmaceutically acceptable propellant. Examples of such propellants include fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3,-heptafluoro-n-propane or a mixture thereof. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants e.g., oleic acid or lecithin and cosolvents e.g., ethanol. Pressurized formulations will generally be retained in a canister (e.g., an aluminum canister) closed with a valve (e.g., a metering valve) and fitted into an actuator provided with a mouthpiece.

In another embodiment, a pharmaceutical composition according to the invention is delivered as a liquid using a metered dose inhaler. Non-limiting examples of metered dose inhalers and devices include those disclosed in

US6,253,762, US6,413,497, US7.601 .336, US7.481 .995, US6,743,413, and US7.105.152. In a preferred embodiment, a compound of the invention is delivered as a dry powder using a metered dose inhaler wherein the emitted particles have an MMAD that is in the range of about 1 μm to about 5 μm and a GSD that is less than about 2.

In one embodiment the aerosol formulation is suitable for aerosolization by a jet nebulizer, or ultrasonic nebulizer including static and vibrating porous plate nebulizers. Liquid aerosol formulations for nebulization may be generated by solubilizing or reconstituting a solid particle formulation or may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, and isotonicity adjusting agents. They may be sterilized by in process techniques such as filtration, or terminal processes such as heating in an autoclave or gamma irradiation. They may also be presented in non-sterile form.

Patients can be sensitive to the pH, osmolality, and ionic content of a nebulized solution. Therefore these parameters should be adjusted to be compatible with fosfomycin plus tobramycin and tolerable to patients. The most preferred solution or suspension of fosfomycin plus tobramycin will contain a chloride concentration >30 mM at pH 4.5-8.0 and an osmolality of from about 800-1600mOsm/kg. The pH of the solution can be controlled by either titration with common acids (hydrochloric acid or sulfuric acid, for example) or bases (sodium hydroxide, for example) or via the use of buffers. Commonly used buffers include citrate buffers, acetate buffers, and phosphate buffers. Buffer strengths can range from 2 mM to 50 mM. The preferred pH range is 7-8 because the rate of hydrolysis of fosfomycin to the open-ring glycol impurity product ("fosfomycin Impurity A") increases as fosfomycin is protonated; that is, as the solution becomes more acidic, fosfomycin rapidly degrades to fosfomycin Impurity A, decreasing its potency.

Such formulations may be administered using commercially available nebulizers or other atomizer that can break the formulation into particles or droplets suitable for deposition in the respiratory tract. Non-limiting examples of nebulizers which may be employed for the aerosol delivery of a composition of the invention include pneumatic jet nebulizers, vented or breath enhanced jet nebulizers, or ultrasonic nebulizers including static or vibrating porous plate nebulizers.

A jet nebulizer utilizes a high velocity stream of air blasting up through a column of water to generate droplets. Particles unsuitable for inhalation impact on walls or aerodynamic baffles. A vented or breath enhanced nebulizer works in essentially the same way as a jet nebulizer except that inhaled air passes through the primary droplet generation area to increase the output rate of the nebulizer while the patient inhales.

In an ultrasonic nebulizer, vibration of a piezoelectric crystal creates surface instabilities in the drug reservoir that cause droplets to be formed. In porous plate nebulizers pressure fields generated by sonic energy force liquid through the mesh pores where it breaks into droplets by Rayleigh breakup. The sonic energy may be supplied by a vibrating horn or plate driven by a piezoelectric crystal, or by the mesh itself vibrating. Non-limiting examples of atomizers include any single or twin fluid atomizer or nozzle that produces droplets of an appropriate size. A single fluid atomizer works by forcing a liquid through one or more holes, where the jet of liquid breaks up into droplets. Twin fluid atomizers work by either forcing both a gas and liquid through one or more holes, or by impinging a jet of liquid against another jet of either liquid or gas.

The choice of nebulizer which aerosolizes the aerosol formulation is important in the administration of the active ingredient(s). Different nebulizers have differing efficiencies based their design and operation principle and are sensitive to the physical and chemical properties of the formulation. For example, two formulations with different surface tensions may have different particle size distributions. Additionally, formulation properties such as pH, osmolality, and permeant ion content can affect tolerability of the medication, so preferred embodiments conform to certain ranges of these properties.

In a preferred embodiment, the formulation for nebulization is delivered to the endobronchial space as an aerosol having an MMAD between about 1 µm and about 5 pm and a GSD less than 2 using an appropriate nebulizer. To be optimally effective and to avoid upper respiratory and systemic side effects, the aerosol should not have a MMAD greater than about 5 pm and should not have a GSD greater than about 2. If an aerosol has an MMAD larger than about 5 µm or a GSD greater than about 2 a large percentage of the dose may be deposited in the upper airways decreasing the amount of drug delivered to the site of inflammation and bronchoconstriction in the lower respiratory tract. If the MMAD of the aerosol is smaller than about 1 pm then a large percentage of the particles may remain suspended in the inhaled air and may then be exhaled during expiration.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a sachet, bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binders, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges, comprising the active ingredient in a flavored base such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a base such as gelatin and glycerin or sucrose and acacia.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

In another aspect of the invention, the aerosolizable formulation of a compound of the invention delivers an effective amount of the compound ranging from about 1 to about 5000 μg to the lungs wherein the composition produces plasma concentrations of the β-agonist and/or corticosteroid of less than about 10 nanograms/mL one hour after administration of said composition. In a preferred embodiment of the invention, the plasma concentrations of the β-agonist and/or corticosteroid produced are less than about 5 nanograms/mL one hour after administration of the composition. In a particularly preferred embodiment of the invention, the plasma concentrations of the β-agonist and/or corticosteroid produced are less than about 2 nanograms/mL one hour after administration of the composition.

In another aspect, the invention provides a method of treating pulmonary inflammation and bronchoconstriction comprising treating a subject in need thereof with an effective amount of an inhalable pharmaceutical composition of a compound of the invention wherein the inhalable pharmaceutical composition produces plasma concentrations of the β-agonist and/or corticosteroid comprising the compound of the invention of less than 10 nanograms/mL one hour after administration of said composition. In a preferred embodiment of the method, the plasma concentrations of the β-agonist and/or corticosteroid produced are less than about 5 nanograms/mL one hour after administration of said formulation. In a particularly preferred embodiment of the method, the plasma concentrations of the β-agonist and/or corticosteroid produced are less than about 2 nanograms/mL one hour after administration of said formulation.

In another aspect, the invention provides a method of treating asthma, COPD, bronchitis, bronchiectasis, emphysema or rhinitis in a human subject asthma, bronchitis or COPD comprising treating a the subject with an effective amount of a inhalable pharmaceutical composition of a compound of the invention wherein the inhalable pharmaceutical composition produces plasma concentrations of the β-agonist and/or corticosteroid of less than 10 nanograms/mL one hour after administration of said composition. In a preferred embodiment of the method, the plasma concentrations of the β-agonist and/or corticosteroid produced are less than about 5 nanograms/mL one hour after administration of said formulation. In a particularly preferred embodiment of the method, the plasma concentrations of the β-agonist and/or corticosteroid produced are less than about 2 nanograms/mL one hour after administration of said formulation.

Preferred unit dosage formulations for the compounds of the invention are those containing an effective amount of the active ingredient or an appropriate fraction thereof.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question for example those suitable for oral administration may include flavoring agents.

As noted above, the compounds of the invention may be formulated and/or used in combination with other therapeutically active agents. Examples of other therapeutically active agents which may be formulated or used in combination with the compounds of the invention include but are not limited to anti-inflammatory agents, anticholinergic agents, β-agonists (including selective β_2-agonists), peroxisome proliferator-activated receptor (PPAR) gamma agonists, PPAR delta agonists, epithelial sodium channel blockers (ENaC receptor blockers), kinase inhibitors, antiinfective agents and antihistamines. The present invention thus provides, as another aspect, a composition comprising an effective amount of compound of the invention and another therapeutically active agent selected from anti-inflammatory agents, anticholinergic agents, β-agonists (including selective β_2-agonists), PPAR gamma agonists, PPAR delta agonists, ENaC receptor blockers, kinase inhibitors, antiinfective agents and antihistamines.

Suitable anti-inflammatory agents for use in combination with the compounds of the invention include corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), particularly phosphodiesterase (PDE) inhibitors. Examples of corticosteroids for use in the present invention include oral or inhaled corticosteroids or prodrugs thereof. Specific examples include but are not limited to ciclesonide, desisobutyryl-ciclesonide, budesonide, flunisolide, mometasone and esters thereof (e.g., mometasone furoate), fluticasone propionate, fluticasone furoate, beclomethasone, methyl prednisolone, prednisolone, dexamethasone, 6a,9a-difluoro-1 7a-[(2-furanylcarbonyl)oxy]-1 1β-hydroxy-l 6a-methyl-3-oxo-androsta-1 ,4-diene-1 7E-carbothioic acid S-fluoromethyl ester, 6a,9a-difluoro-1 1β-hydroxy-l 6a-methyl-3-oxo-1 7a-propionyloxy-androsta-1 ,4-diene-1 7β-carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g., the 17-propionate ester or the 17,21-dipropionate ester, fluoromethyl ester, triamcinolone acetonide, rofleponide, or any combination or subset thereof. Preferred corticosteroids for formulation or use in combination with the compounds of the invention are selected from ciclesonide, desisobutyryl-ciclesonide, budesonide, mometasone, fluticasone propionate, and fluticasone furoate, or any combination or subset thereof.

NSAIDs for use in the present invention include but are not limited to sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g., theophylline, PDE4 inhibitors, mixed PDE3/PDE4 inhibitors or mixed PDE4/PDE7 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis (e.g., 5 LO and FLAP inhibitors), nitric oxide synthase (iNOS) inhibitors, protease inhibitors (e.g., tryptase inhibitors, neutrophil elastase inhibitors, and metalloprotease inhibitors) &2-integrin antagonists and adenosine receptor agonists or antagonists (e.g., adenosine 2a agonists), cytokine antagonists (e.g., chemokine antagonists) or inhibitors of cytokine synthesis (e.g., prostaglandin D2 (CRTh2) receptor antagonists).

The PDE4 inhibitor, mixed PDE3/PDE4 inhibitor or mixed PDE4/PDE7 inhibitor may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are selective PDE4 inhibitors (i.e., compounds which do not appreciably inhibit other members of the PDE family). Examples of specific PDE4 inhibitors for formulation and use in combination with the compounds of the present invention include but are not limited to roflumilast, pumafentrine, arofylline, cilomilast, tofimilast, oglemilast, tolafentrine, piclamilast, ibudilast, apremilast, 2-[4-[6,7-diethoxy-2,3-bis(hydroxymethyl)-1-naphthalenyl]-2-pyridinyl]-4-(3-pyridinyl)-1(2H)-phthalazinone (T2585), N-(3,5-dichloro-4-pyridinyl)-1 -[(4-fluorophenyl)methyl]-5-hydroxy-a-oxo-1 H-indole-3-acetamide (AWD-1 2-281 , 4-[(2R)-2-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-phenylethyl]-pyridine (CDP-840), 2-[4-[[[[2-(1 ,3-benzodioxol-5-yloxy)-3-pyridinyl]carbonyl]amino]methyl]-3-fluorophenoxy]-(2R)-propanoic acid (CP-671305), N-(4,6-dimethyl-2-pyrimidinyl)-4-[4,5,6,7-tetrahydro-2-(4-methoxy-3-methylphenyl)-5-(4-methyl-1-piperazinyl)-1 H-indol-1-yl]- benzenesulfonamide, (2E)-2-butenedioate (YM-393059), 9-[(2-fluorophenyl)methyl]-N-methyl-2-(trifluoromethyl)-9H-purin-6-amine (NCS-61 3), N-(2,5-dichloro-3-pyridinyl)-8-methoxy-5-quinolinecarboxamide (D-441 8), N-[(3R)-9-amino-3,4,6,7-tetrahydro-4-oxo-1 -phenylpyrrolo[3,2,1-][1 ,4]benzodiazepin-3-yl]-3H-purin-6-amine (PD-1 68787), 3-[[3-(cyclopentyloxy)-4-methoxyphenyl]methyl]-N-ethyl-8-(1-methylethyl)-3H-purin-6-amine hydrochloride (V-1 1294A), N-(3,5-dichloro-1-oxido-4-pyridinyl)-8-methoxy-2-(trifluoromethyl)-5-quinolinecarboxamide (Sch351 591), 5-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-[(3-methylphenyl)methyl]-(3S,5S)- 2-piperidinone (HT-0712), 5-(2-((1r,4r)-4-amino-1-(3-(cyclopentyloxy)-4-methyoxyphenyl)cyclohexyl)ethynyl)-pyrimidine-2-amine, 6-[3-(dimethylcarbamoyl)phenylsulfonyl]-4-(3-methoxyphenylamino)-8-methylquinoline-3-carboxamide (GSK-256066),cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1 -ol], and 4-[6,7-

diethoxy-2,3-bis(hydroxymethyl)-1-naphthalenyl]-1-(2-methoxyethyl)-2(1 H)-pyridinone (T-440), and any combination or subset thereof.

Leukotriene antagonists and inhibitors of leukotriene synthesis include zafirlukast, montelukast sodium, zileuton, and pranlukast.

Anticholinergic agents for formulation or use in combination with the compounds of the invention include but are not limited to muscarinic receptor antagonists, particularly including pan antagonists and antagonists of the M3 receptors. Exemplary compounds include the alkaloids of the belladonna plants, such as atropine, scopolamine, homatropine, hyoscyamine, and the various forms including salts thereof (e.g., anhydrous atropine atropine sulfate, atropine oxide or HCl, methylatropine nitrate, homatropine hydrobromide, homatropine methyl bromide, hyoscyamine hydrobromide, hyoscyamine sulfate, scopolamine hydrobromide, scopolamine methyl bromide) , or any combination or subset thereof.

Additional anticholinergics for formulation and use in combination with the methantheline, propantheline bromide, anisotropine methyl bromide or Valpin 50, aclidinium bromide, glycopyrrolate (Robinul), isopropamide iodide, mepenzolate bromide, tridihexethyl chloride, hexocyclium methylsulfate, cyclopentolate HCl, tropicamide, trihexyphenidyl CCl, pirenzepine, telenzepine, and methoctramine, or any combination or subset thereof.

Preferred anticholinergics for formulation and use in combination with the compounds of the invention include ipratropium (bromide), oxitropium (bromide) and tiotropium (bromide), or any combination or subset thereof.

Examples of β-agonists for formulation and use in combination with the compounds of the invention include but are not limited to salmeterol, R-salmeterol, and xinafoate salts thereof, albuterol or R-albuterol (free base or sulfate), formoterol (fumarate), fenoterol, indacaterol, terbutaline and salts thereof, and any combination or subset thereof.

Examples of PPAR gamma agonists for formulation and use in combination with the compounds of the invention include but are not limited to thiazolidinediones, rosiglitazone, pioglitazone, and troglitazone.

Examples of ENaC receptor blockers for formulation and use in combination with the compounds of the invention include but are not limited to amiloride and derivatives thereof such as those compounds described in US Patent Nos. 6858615 to Parion Sciences, Inc.

Examples of kinase inhibitors include inhibitors of NFkB, PI3K (phosphatidylinositol 3-kinase), p38-MAP kinase and Rho kinase.

Antiinfective agents for formulation and use in combination with the compounds of the invention include antivirals and antibiotics. Examples of suitable antivirals include Tamiflu® and Relenza®. Examples of suitable antibiotics include but are not limited to aztreonam (arginine or lysine), fosfomycin, and tobramycin, or any combination or subset thereof.

Antihistamines (i.e., H1-receptor antagonists) for formulation and use in combination with the compounds of the invention include but are not limited to:

ethanolamines such as diphenhydramine HCl, carbinoxamine maleate, doxylamine, clemastine fumarate, diphenylhydramine HCl and dimenhydrinate;

ethylenediamines such as pyrilamine maleate (metpyramine), tripelennamine HCl, tripelennamine citrate, and antazoline;

alkylamines such as pheniramine, chloropheniramine, bromopheniramine, dexchlorpheniramine, triprolidine and acrivastine;

pyridines such as methapyrilene,

piperazines such as hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl and cetirizine HCl;

piperidines such as astemisole, levocabastine HCl, loratadine, descarboethoxy loratadine, terfenadine, and fexofenadine HCl;

tri- and tetracyclics such as promethazine, chlorpromethazine trimeprazine and azatadine; and azelastine HCl, or any combination or subset thereof.

In one aspect, the present invention provides a composition comprising a compound of the invention and an anti-inflammatory agent. In one embodiment, the composition comprises a compound of the invention and a corticosteroid. In one particular embodiment, the composition comprises a compound of the invention and a corticosteroid selected from ciclesonide, desisobutyryl-ciclesonide, budesonide mometasone, fluticasone propionate, and fluticasone furoate. In one particular embodiment, the composition comprises a compound of the invention and ciclesonide or desisobutyryl-ciclesonide.

In one aspect, the present invention provides a composition comprising a compound of the invention and a PDE4 inhibitor.

In one aspect, the present invention provides a composition comprising a compound of the invention and a ß2-agonist. In one embodiment, the composition comprises a compound of the invention and salmeterol, R-salmeterol or formoterol. In one particular embodiment, the composition comprises a compound of the invention and salmeterol or R-salmeterol.

In one aspect, the present invention provides a composition comprising a compound of the invention and an anticholinergic agent. In one embodiment, the composition comprises a compound of the invention and tiotropium.

In one aspect, the present invention provides a composition comprising a compound of the invention and anti-histamine.

In the above-described methods of treatment and uses, a compound of the invention may be employed alone, or in combination with one or more other therapeutically active agents. Typically, any therapeutically active agent that has a therapeutic effect in the disease or condition being treated with the compound of the invention may be utilized in combination with the compounds of the invention, provided that the particular therapeutically active agent is compatible with therapy employing a compound of the invention. Typical therapeutically active agents which are suitable for use in combination with the compounds of the invention include the anti-inflammatory agents, anticholinergic agents, β-agonists, antiinfective agents and antihistamines described above.

In another aspect, the invention provides methods for treatment and uses as described above, which comprise administering an effective amount of a compound of the invention and at least one other therapeutically active agent. The compounds of the invention and at least one additional therapeutically active agent may be employed in combination concomitantly or sequentially in any therapeutically appropriate combination. The administration of a compound of the invention with one or more other therapeutically active agents may be by administration concomitantly in 1) a unitary pharmaceutical composition, such as the compositions described above, or 2) separate pharmaceutical compositions each including one or more of the component active ingredients. The components of the combination may be administered separately in a sequential manner wherein the compound of the invention is administered first and the other therapeutically active agent is administered second or vice versa.

When a compound of the invention is used in combination with another therapeutically active agent, the dose of each compound may differ from that when the compound of the invention is used alone. Appropriate doses will be readily determined by one of ordinary skill in the art. The appropriate dose of the compound of the invention, the other therapeutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect, and are within the expertise and discretion of the attendant physician, clinician or veterinarian.

In another aspect, the present invention provides methods for treating any of the conditions enumerated above, comprising administering an effective amount of a compound of the invention and an anti-inflammatory agent. In one embodiment, the method comprises administering an effective amount of a compound of the invention and a corticosteroid. In one particular embodiment, the method comprises administering an effective amount of a compound of the invention and a corticosteroid selected from ciclesonide, desisobutyryl-ciclesonide, budesonide mometasone, fluticasone propionate, and fluticasone furoate. In one particular embodiment, the method comprises administering an effective amount of a compound of the invention and ciclesonide or desisobutyryl-ciclesonide.

In one embodiment the present invention provides a method for treating any of the conditions enumerated above comprising administering an effective amount of a compound of the invention and a PDE4 inhibitor.

In one embodiment the present invention provides a method for treating any of the conditions enumerated above comprising administering an effective amount of a compound of the invention and a β-agonist, particularly a selective β_2-agonist. In one embodiment, the method comprises administering an effective amount of a compound of the invention and salmeterol, R-salmeterol or formoterol. In one particular embodiment, the method comprises administering an effective amount of a compound of the invention and salmeterol or R-salmeterol.

In one embodiment the present invention provides a method for treating any of the conditions enumerated above by administering an effective amount of a compound of the invention and an anticholinergic agent. In one embodiment, the method comprises administering an effective amount of a compound of the invention and tiotropium.

In one embodiment the present invention provides a method for treating any of the conditions enumerated above by administering an effective amount of a compound of the invention and anti-histamine.

In another aspect the present invention provides a combination comprising a compound of the invention and an anti-inflammatory agent for the treatment of any condition enumerated above; and also the use of such combination for the manufacture of a medicament for the treatment of any of the conditions enumerated above. In one embodiment, the combination comprises a compound of the invention and a corticosteroid selected from ciclesonide, desisobutyryl-ciclesonide, budesonide mometasone, fluticasone propionate, and fluticasone furoate. In one particular embodiment, the combination comprises a compound of the invention and ciclesonide or desisobutyryl-ciclesonide.

In another aspect the present invention provides a combination comprising a compound of the invention and a PDE4 inhibitor for the treatment of any condition enumerated above; and also the use of such combination for the manufacture of a medicament for the treatment of any of the conditions enumerated above.

In another aspect the present invention provides a combination comprising a compound of the invention and a β-agonist for the treatment of any condition enumerated above; and also the use of such combination for the manufacture of a medicament for the treatment of any of the conditions enumerated above. In one embodiment the combination comprises a compound of the invention and salmeterol, R-salmeterol or formoterol. In one particular embodiment, the combination comprises a compound of the invention and salmeterol or R-salmeterol.

In another aspect the present invention provides a combination comprising a compound of the invention and an anticholinergic agent for the treatment of any condition enumerated above; and also the use of such combination for the manufacture of a medicament for the treatment of any of the conditions enumerated above. In one embodiment the combination comprises a compound of the invention and tiotropium.

In another aspect the present invention provides a combination comprising a compound of the invention and an antihistamine for the treatment of any condition enumerated above; and also the use of such combination for the manufacture of a medicament for the treatment of any of the conditions enumerated above.

The present invention also provides processes for preparing the compounds of the invention and to the synthetic intermediates useful in such processes, as described in detail below.

Having generally described this invention, a further understanding can be obtained by reference to certain specific examples which are provided herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

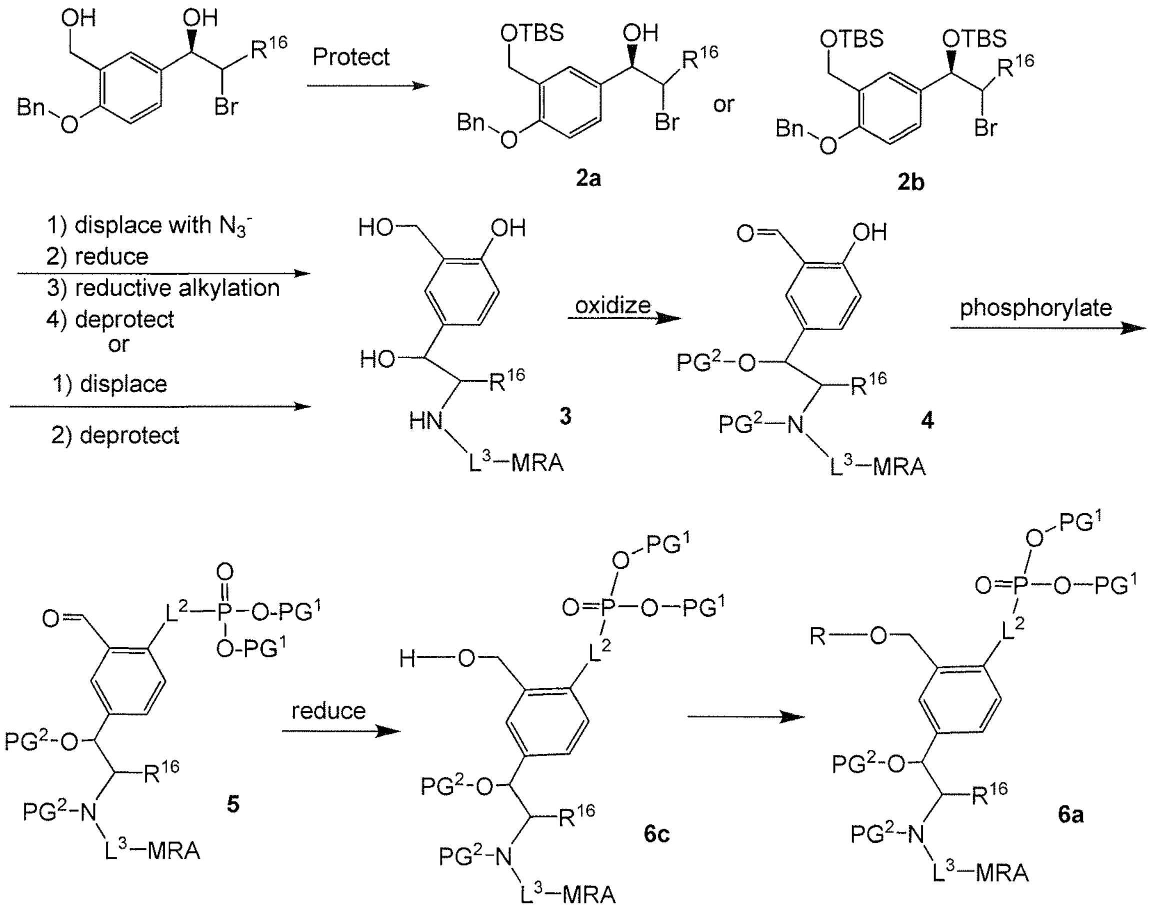
Certain abbreviations and acronyms are used in describing the experimental details. Although most of these would be understood by one skilled in the art, the following table contains a list of many of these abbreviations and acronyms.

Abbreviation	Meaning
Bn	Benzyl
Boc	Tert-butoxycarbonyl
Boc_2O	di-tert-butyldicarbonate
CDI	carbonyldiimidazole
ACN	acetonitrile
DBU	1,5-diazabicyclo[5.4.0]undecene
DCM	dichloromethane
DIEA	N,N-diisopropylethylamine
DCC	dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
DMF	dimethylformamide
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethyl ether
ESI	electrospray ionization
HATU	2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl

	uronium hexafluorophosphate
HPLC	High performance liquid chromatography
iPrOH	Isopropyl alcohol
Me	methyl
MeOH	methanol
m/z or m/e	mass to charge ratio
MH$^+$	mass plus 1
MH$^-$	mass minus 1
MS or ms	mass spectrum
Ms	methanesulfonate
Ph	phenyl
PMP	1,2,2,6,6-pentamethylpiperidine
Py	Pyridyl / pyridine
rt or r.t.	room temperature
SCX	Strong cation exchange
TBAF	tetrabutylammonium fluoride
TBAI	Tetra-butylammonium iodide
t-Bu	Tert-butyl
TEA	triethylamine
TBS	t-butyldimethylsilyl
TBSCI	t-butyldimethylsilyl chloride
TBSO	t-butyldimethylsilyloxy
TFA	trifluoroacetic acid
Tfcr	trifluoromethanesulfonate
Tf_20	trifluoromethanesulfonyl anhydride
THF	tetrahydrofuran
TLC or tic	thin layer chromatography
d	parts per million down field from tetramethylsilane

Compounds of Formula I may be prepared according to the general procedure illustrated in Scheme 1.

Scheme 1



wherein:

each PG^1 is a phosphate protecting group such as methyl, ethyl, benzyl or t-butyl;

R is a leaving group with the oxygen such as mesylate or triflate;

each PG^2 is H or Boc; and

all other variables are as defined herein.

The bromohydrin starting material is commercially available or may be prepared using conventional techniques. A primary benzylic alcohol could be selectively protected **(2a)** with TBSCl at room temperature and bis protection **(2b)** could be achieved at higher temperature. The intermediate of formula **(3)** can be obtained by multiple processes. According to one process, the compound of formula **(2a)** or **(2b)** is reacted with sodium azide (NaN_3) in a suitable aprotic solvent such as DMF to give an azide which may then be reduced to the corresponding amine (not shown) with no racemization of the chiral center. A reductive amination of the corresponding amine and a compound of formula CHO-MRA, wherein MRA is as defined above, followed by deprotection yields the compound of formula **(3)** wherein L^3 is $-CH_2-$. Compounds of formula CHO-MRA are commercially available or may be produced using conventional processes.

An alternate route includes coupling the compound of formula **(2a)** or **(2b)** with the amine of formula H_2N-L^3-MRA at elevated temperature in the presence of a base such as DIEA to effect the bromide displacement. Subsequent deprotection of the resulting intermediate can yields the compound of formula **(3).** The amine compounds of formula H_2N-L^3-MRA may be prepared using conventional techniques.

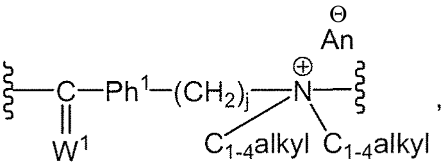
The compound of formula **(3)** may be oxidized using conventional oxidation techniques and oxidizing agents to prepare compounds of formula **(4).** Suitable oxidation techniques include, for example, manganese(IV) oxide in chloroform. As will be apparent to those skilled in the art, it is desirable to install amine and/or alcohol protecting groups prior to oxidation. The choice of protecting groups on the compound of formula **(4)** will be based at least in part on the steric bulk of the particular β-agonist side chain (R^{15}) selected. Suitable protecting groups include Boc. Methods are well known in the art for installing and removing such protecting groups and such conventional techniques may be employed in the instant reaction as well.

The compound of formula **(4)** may be phosphorylated using conventional techniques and phosphorylating agents. Examples of suitable phosphorylation techniques include but are not limited to reacting with di-t-butyl-phosphobromidate synthesized *in situ* in a one-pot procedure and alkylating at 50°C with di-tert-butyl chloromethyl phosphate (Krise *et al., J Med Chem* (1999) 42:3094-3100). The aldehyde moiety of the thus produced compound of formula **(5)** may be reduced using conventional techniques with reagents such as sodium borohydride at 0°C. If desired, additional secondary alcohol protection can be introduced by reaction with excess of di-t-butyl-dicarbonate. The foregoing reduction may then be employed to prepare the primary alcohol analog of formula **(6c, R=H).**

The installation of the leaving group (R) on the compound of formula **(6c)** may be accomplished using conventional techniques. By way of example, the installation of the methanesulfonate leaving group may be carried out at room temperature, using methanesulfonyl chloride (MsCl) in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP) to give **6a** (R=Ms). In case of a triflate leaving group the reaction may be carried out at -78°C in order to minimize the formation of byproducts to give **6a** (R=triflate).

The foregoing process may be utilized to prepare the corresponding R-isomer of a compound of Formula I by substituting the R-enantiomer of the N-Boc-protected compound of formula **(5)** starting material for the racemate. Similarly the corresponding S-isomer of a compound of Formula I may be made by using the S-enantiomer of the N-Boc-protected compound of formula **(5).** This approach may be utilized to prepare enantiomerically enriched mixtures of any of the compounds of Formula I which contain a chiral center, and pharmaceutically acceptable salts thereof.

More specifically, compounds of Formula (I) wherein L^1 is selected from



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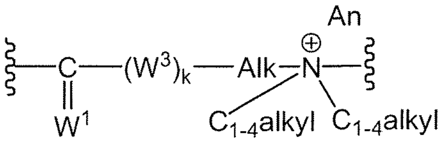

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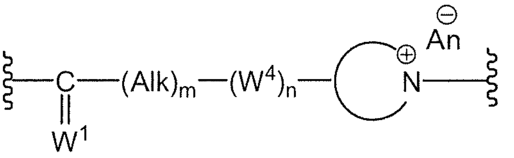

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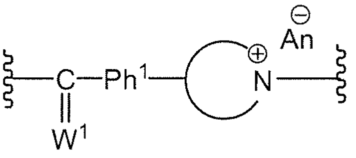

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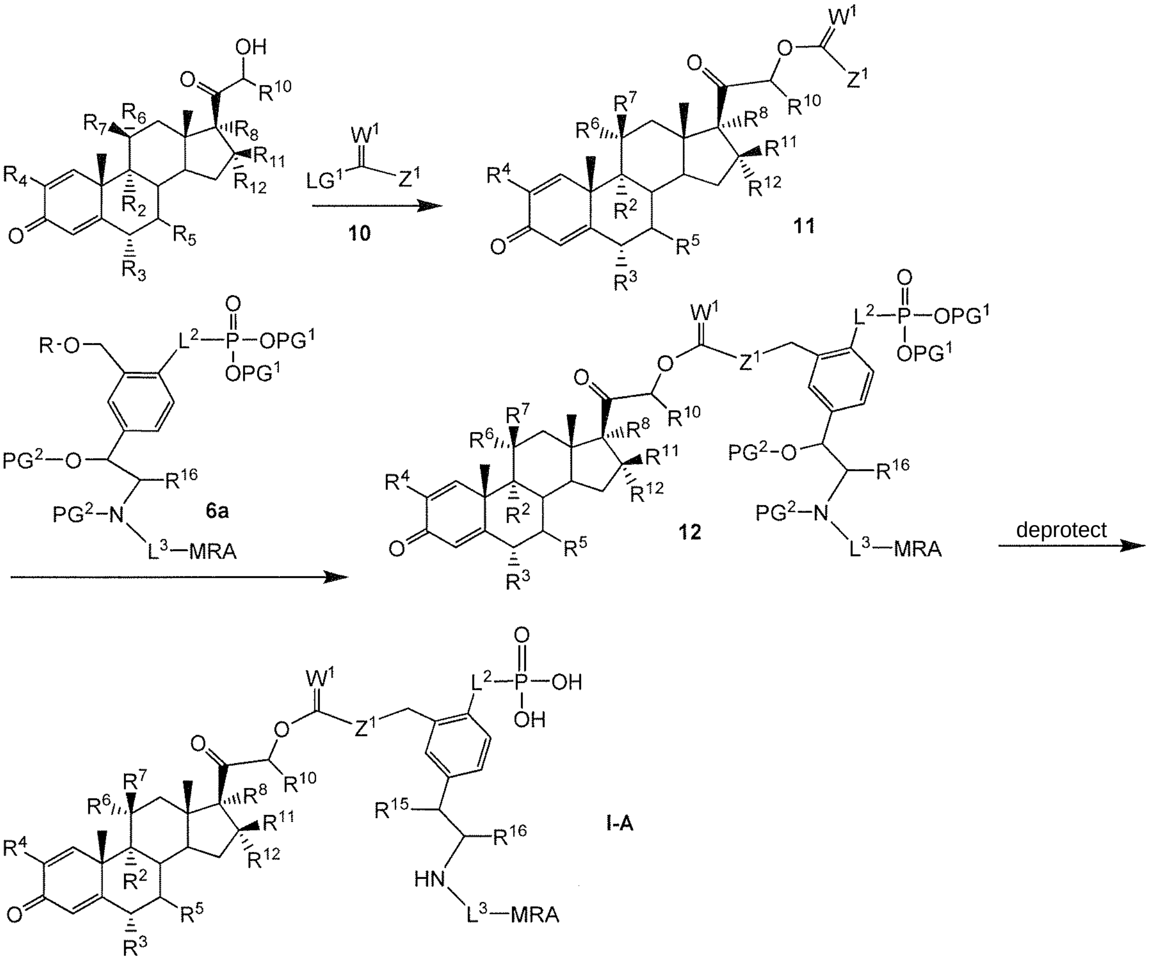
may be prepared according to **Scheme** 2 as follows

Scheme 2



wherein:

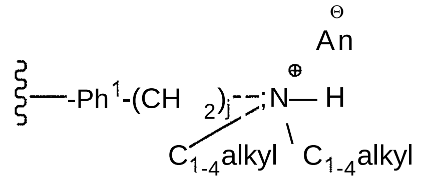
LG^1 is a suitable leaving group such as chloro or bromo or an activated ester such as 7-azabenzotriazol-1-yl;

each PG^1 is a phosphate protecting group such as methyl, ethyl, benzyl or t-butyl;

Each R is a leaving group with the oxygen such as mesylate or triflate;

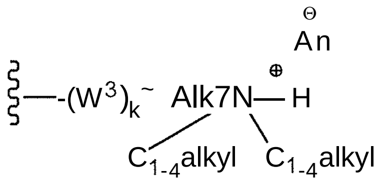
each PG^2 is H or Boc;

Z^1 is



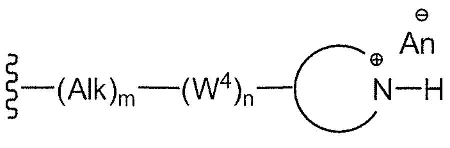
$$-Ph^1-(CH_2)_j-\overset{\overset{\ominus}{An}}{\overset{\oplus}{N}}(C_{1-4}alkyl)(C_{1-4}alkyl)-H$$

,

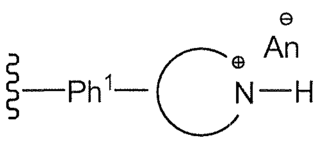


$$-(W^3)_k-Alk7\overset{\overset{\ominus}{An}}{\overset{\oplus}{N}}(C_{1-4}alkyl)(C_{1-4}alkyl)-H$$

,



, and



; and

all other variables are as defined herein.

Generally, the process comprises the steps of

a) reacting a Steroid with a compound of formula (10) to prepare the compound of formula (11).

b) coupling a compound of formula (11) with a compound of Formula (6) to prepare a compound of formula (12) or a pharmaceutically acceptable salt thereof; and

c) deprotecting the compound of formula (12) to prepare a compound of Formula I-A or a pharmaceutically acceptable salt thereof.

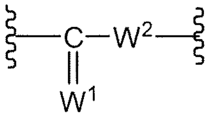
More particularly, the 21-hydroxyl group of the Steroid may be derivatized with a variety of linkers through formation of an ester, carbamate or carbonate to yield the compound of formula (11). As an example, N,N-dialkyl-a-aminoester was prepared by reacting the steroid with chloroacetyl chloride in DMF, followed by the nucleophilic substitution with a corresponding dialkylamine. Alternatively, HATU in the presence of DIEA may be used as an activating reagent for 21-esterification. Carbamate linkers may be synthesized by forming the 21-chloroformate by reaction of phosgene with steroid, followed by the treatment with the appropriate amines. As another example, the 21-hydroxyl moiety of a steroid can be activated with p-nitrophenylchloroformate, followed by displacement with an alcohol yielding 21-carbonates. The steroids and compounds of formula 10 are either commercially available or may be prepared using conventional techniques.

Coupling a compound of formula 11 with a compound of formula 6 may be accomplished by activating the benzyl alcohol of the protected, phosphorylated β-agonist of formula 6, optionally in the presence of a catalyst such as sodium iodide. The reaction may be carried out at an appropriate temperature based upon the leaving group, e.g., room temperature for mesylate or reduced temperature for the triflate. Suitable solvents include acetonitrile and methylene chloride.

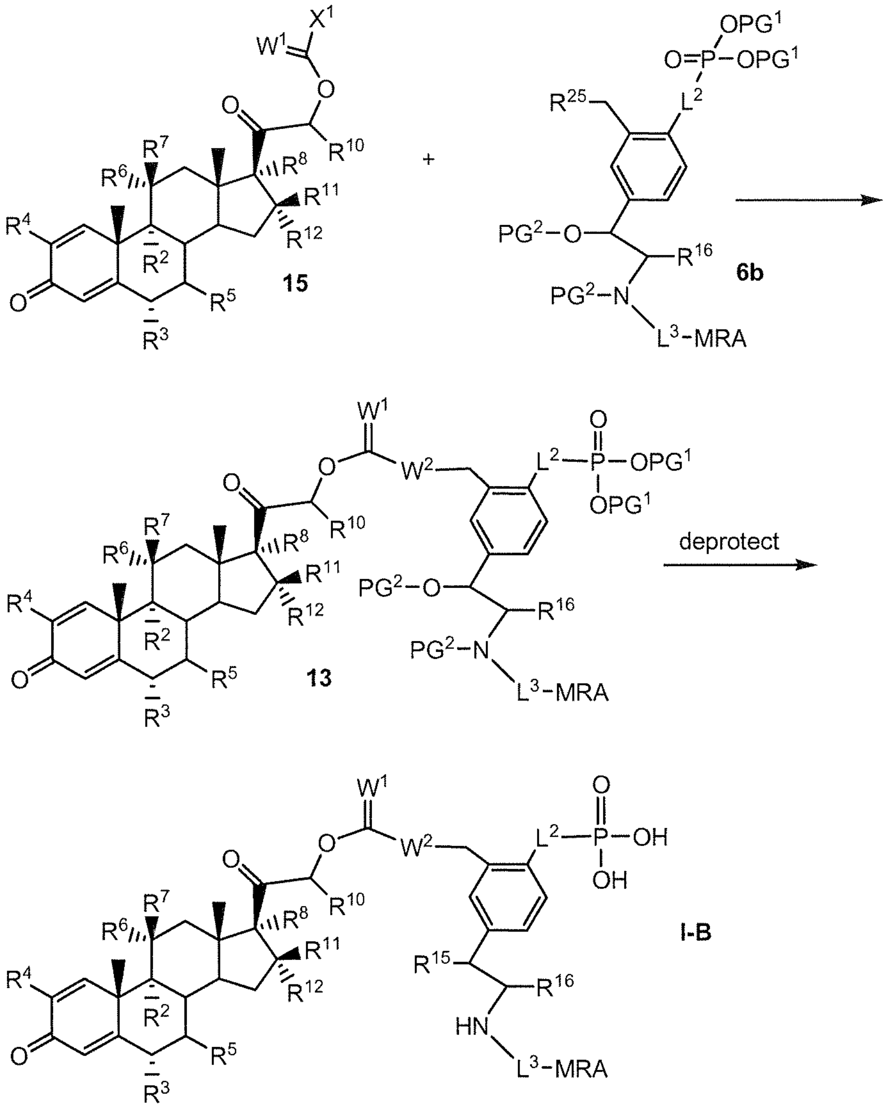
Alternatively, intermediate (6c) may be treated with $BF_3 \cdot OEt_2$ at 0°C for 10 min then added to a steroid amine and PMP. Typically, the reaction is carried out at reduced temperature, (e.g., -78°C) and $Tf_2$0 is added to give a quaternary ammonium linker at L^1.

The resulting compound of formula **12** may be deprotected using conventional processes, including mild acidolysis, either by brief treatment with HCI in dioxane or by low-temperature treatment with TFA in dichloromethane at about 0°C. The optimal method for removing the protecting groups may be based upon the definition of L^2. For example, in those embodiments wherein L^2 is -0-, deprotection with HCI is preferred whereas in those embodiments wherein L^2 is OCH_2O, deprotection via trifluoroacetic acid may be preferred.

As will be apparent to those skilled in the art, the choice of protecting groups on the compound of formula **12** will be based at least in part on the steric bulk of the particular MRA group selected.

Compounds of Formula I wherein L^1 is  $-C(=W^1)-W^2-$ may be prepared according to the process illustrated in **Scheme 3**.

Scheme 3



wherein:

X^1 is halo, particularly Cl;

R^{25} is OH or NH_2;

R^{15} is OH;

each PG^1 is a phosphonic acid protecting group such as methyl, ethyl, benzyl or t-butyl;

each PG^2 is H or Boc; and

all other variables are as defined herein.

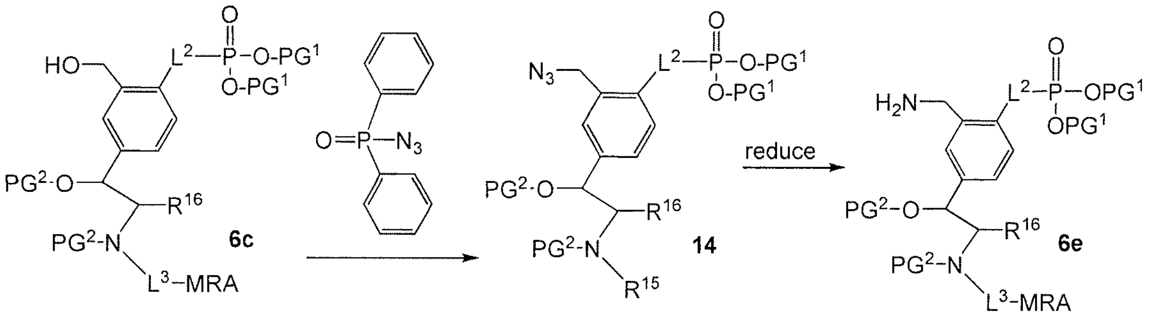
Generally, the process comprises the steps of

a) coupling a compound of formula (15) with a compound of formula (6b) to prepare a compound of formula (13) or a pharmaceutically acceptable salt thereof; and

b) deprotecting the compound of formula **(13)** to prepare a compound of Formula I-B, or a pharmaceutically acceptable salt thereof.

More particularly, a compound of formula **(15)** may be reacted with the compound of formula **(6b)** in the presence of a base such as 1,2,2,6,6-pentamethylpiperidine, N,N-diisopropylethylamine, triethylamine or other amine base in the presence of DMAP if needed. The reaction may be carried out at an appropriate temperature based the definition of R^{25}. Suitable solvents include acetonitrile and methylene chloride. Deprotection of a compound of formula **(13)** may be carried out using conventional techniques including those described above.

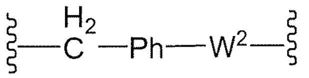
The compound of formula **(15)** may be prepared by reacting the corresponding steroid with excess phosgene at room temperature to give the corresponding chloroform ate. Suitable steroids are commercially available or may be prepared by conventional techniques. The compounds of formula **(6b)** wherein R^{25} is OH may be prepared by the processes described above, wherein the additional protection group installation step is omitted. Compounds of formula (**6b**) wherein R^{25} is NH_2 may be prepared by the process illustrated below.



wherein all other variables are as defined above.

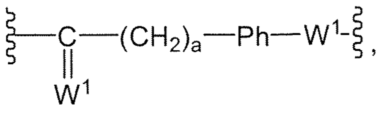
A compound of formula **(6c)** is reacted with diphenyl azidophosphate to give the azide compound of formula **(14)**, which may be reduced by reaction with a conventional reducing agent, such as triphenyl phosphine, using standard techniques, to yield the compound of formula **(6e)**.

Compounds of Formula I wherein L^1 is



$$-\overset{H_2}{C}-Ph-W^2-$$

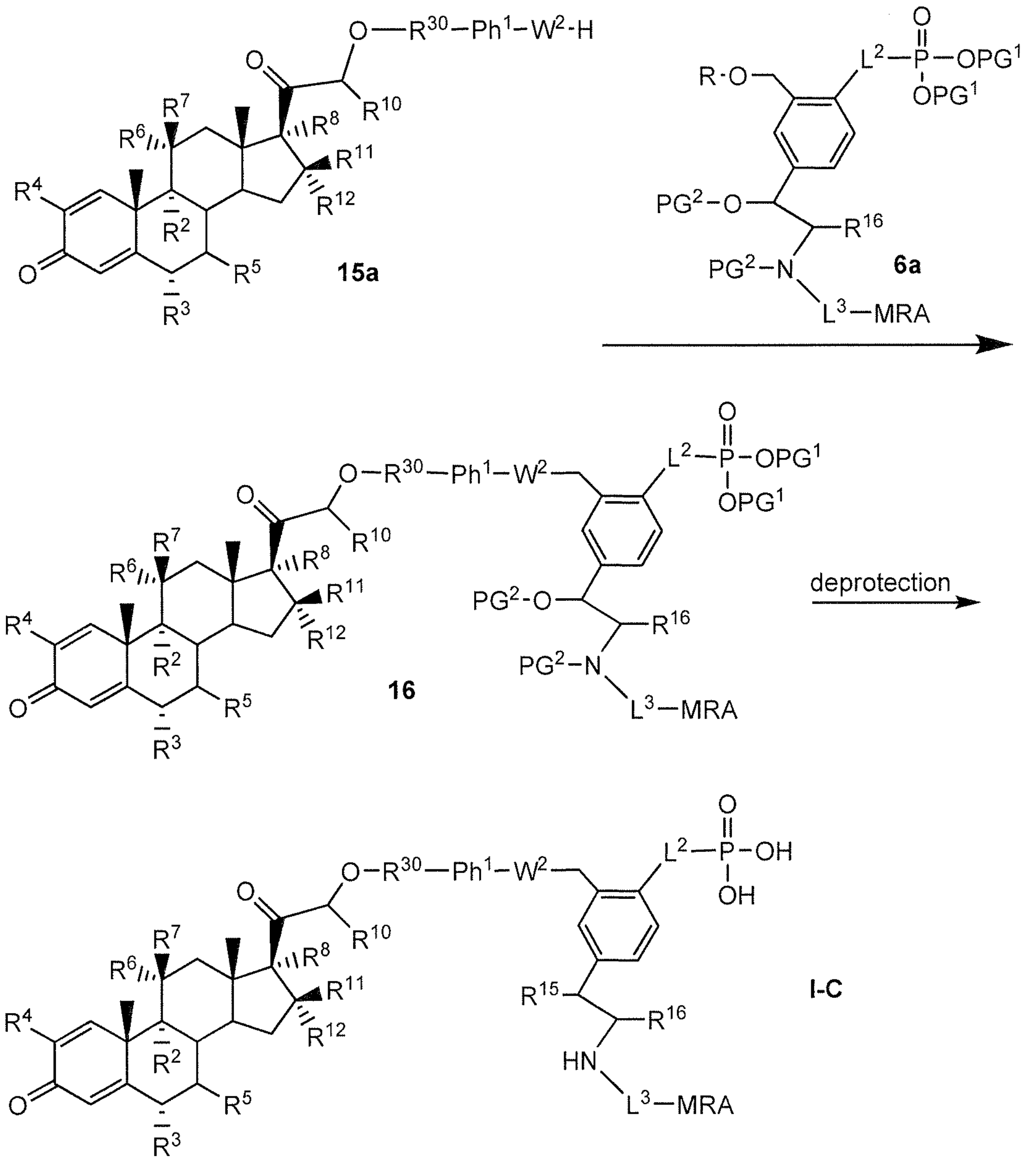
or



$$-\underset{W^1}{\overset{\|}{C}}-(CH_2)_a-Ph-W^1-,$$

(i.e., compounds of Formula I-C) may be prepared according to the process illustrated in **Scheme 4.**

Scheme 4



wherein:

R^{30} is -(CH_2)- and W^2 is O, S or N(R^1); or

R^{30} is -C(=0)-(CH_2)$_a$- and W^2 is 0 or S, wherein a is 0, 1, 2, 3, 4, 5 or 6;

each PG^1 is a phosphonic acid protecting group such as methyl, ethyl, benzyl or t-butyl;

R^{15} is OH;

R is a leaving group with the oxygen such as mesylate or triflate;

each PG^2 is H or Boc; and

all other variables are as defined herein.

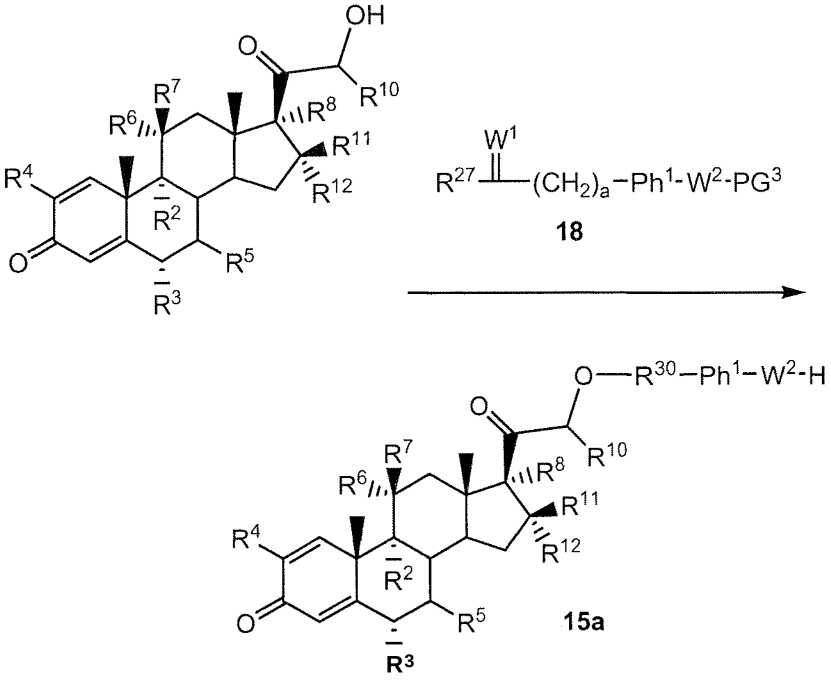
Generally, the process comprises the steps of

a) coupling a compound of formula **(15)** with a compound of formula **(6a)** to prepare a compound of formula **(16)** or a pharmaceutically acceptable salt thereof; and

b) deprotecting the compound of formula **(16)** to prepare a compound of Formula I-C, or a pharmaceutically acceptable salt thereof.

More particularly, a compound of formula **(15)** may be reacted with the compound of formula **(6a)** in an analogous manner to that described above for the coupling of a steroid to a compound of formula **(6c).** Deprotection of a compound of formula **(16)** may be carried out using conventional techniques including those described above.

Compounds of formula **(15)** may be prepared from the corresponding steroid as follows:


18

15a

wherein:

R^{27} is halo, particularly Cl, or OH;

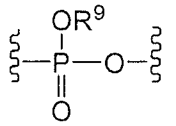
PG^3 is a silyl, acetate, or benzyl protecting group optionally substituted by methoxy or nitro;

R^{30} is $-C(=O)-(CH_2)_a-$ and W^2 is O or S, wherein a is 1-6, or

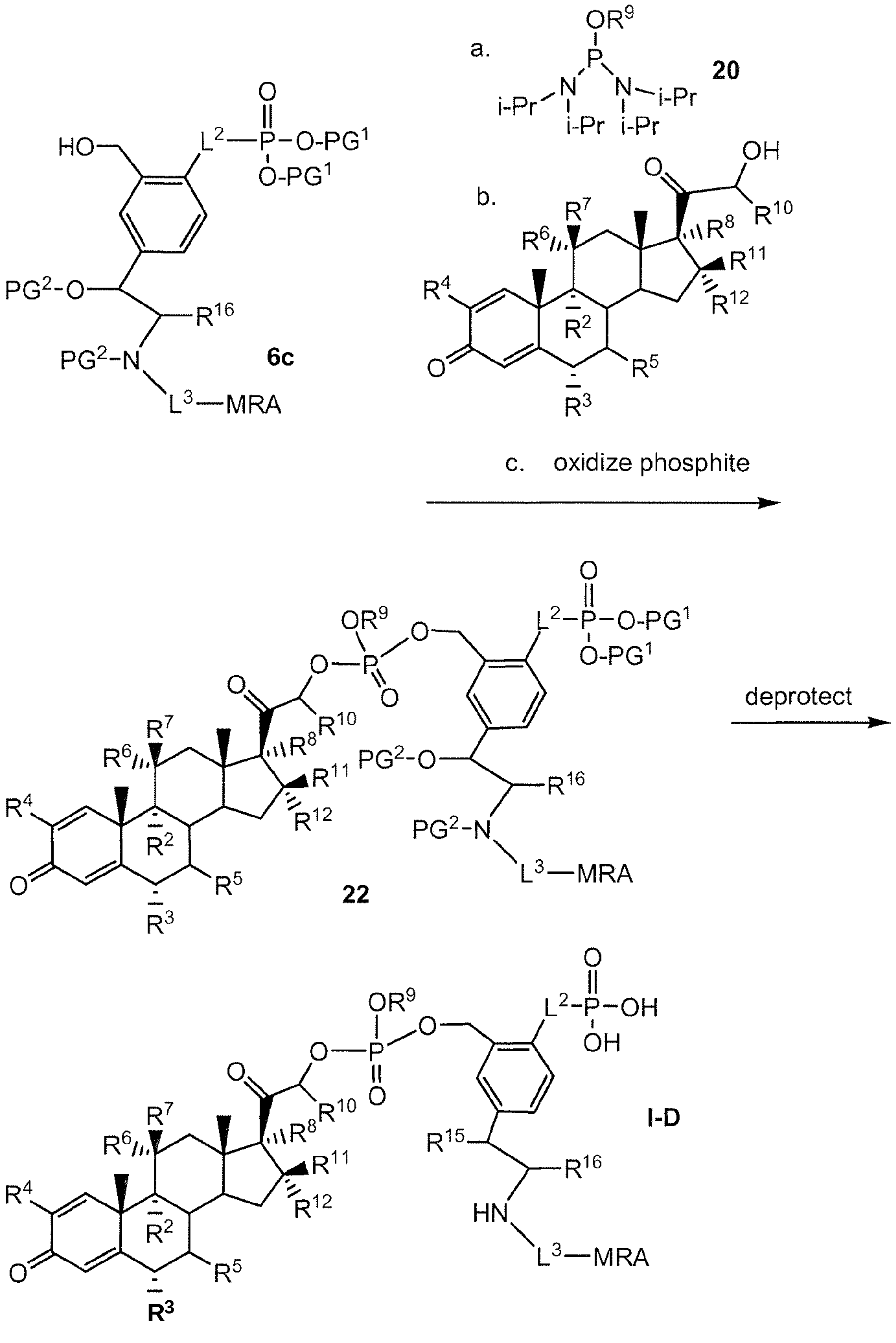
R^{30} is $-(CH_2)-$ and W^2 is O, S or $N(R^1)$; and

all other variables are as defined above.

The compound of formula (15) may be prepared by reacting the corresponding steroid with a compound of formula (18) with or without an activating agent such as HATU, and a general amine base such as triethylamine, DIEA, or the like, in acetonitrile or dimethylformamide at appropriate temperature. A compound of formula (18) is commercially available or may be prepared using commercially available reagents and conventional techniques.

Compounds of Formula I wherein L^1 is  , i.e., compounds of Formula I-D, may be prepared according to the process illustrated in Scheme 5.

Scheme 5



wherein:

each PG^1 is a phosphonic acid protecting group such as methyl, ethyl, benzyl or t-butyl;

each PG^2 is H or Boc;

R^{15} is OH; and

all other variables are as defined herein.

Advantageously, the reaction may be carried out as a one-pot reaction. Generally, the process comprises the steps of

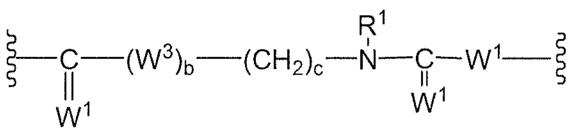
a) reacting a compound of formula **(6c)** with a compound of formula **(20)** and a steroid, in the presence of an activator, followed by phosphite oxidation to prepare a compound of formula **(22)** or a pharmaceutically acceptable salt thereof; and

b) deprotecting the compound of formula **(22)** to prepare a compound of Formula I-D, or a pharmaceutically acceptable salt thereof.

More specifically, the process comprises reacting a compound of formula **(6c)** with a compound of formula **(20)** in a suitable solvent such as tetrahydrofuran at an appropriate temperature, followed by addition of an activator that includes tetrazole or 5-(ethylthio)tetrazole. Advantageously the reaction may be continued in the same vessel without isolation or purification of intermediates. The steroid is added and reacted, preferably in the presence of the activator, followed by phosphite oxidation. Phosphite oxidation may be accomplished with conventional means including reaction with terf-butyl hydrogen peroxide, iodine, 3-chloroperoxybenzoic acid or oxone. The compound of formula **(22),** thus produced may be deprotected using conventional techniques including those described above (see *also,* Meier et al., *J.Med Chem* 2008 50(6):1 335-1346).

The compounds of formula **(6c)** may be prepared as described above. The compounds of formula **(20)** are commercially available or may be prepared using commercially available reagents and conventional techniques.

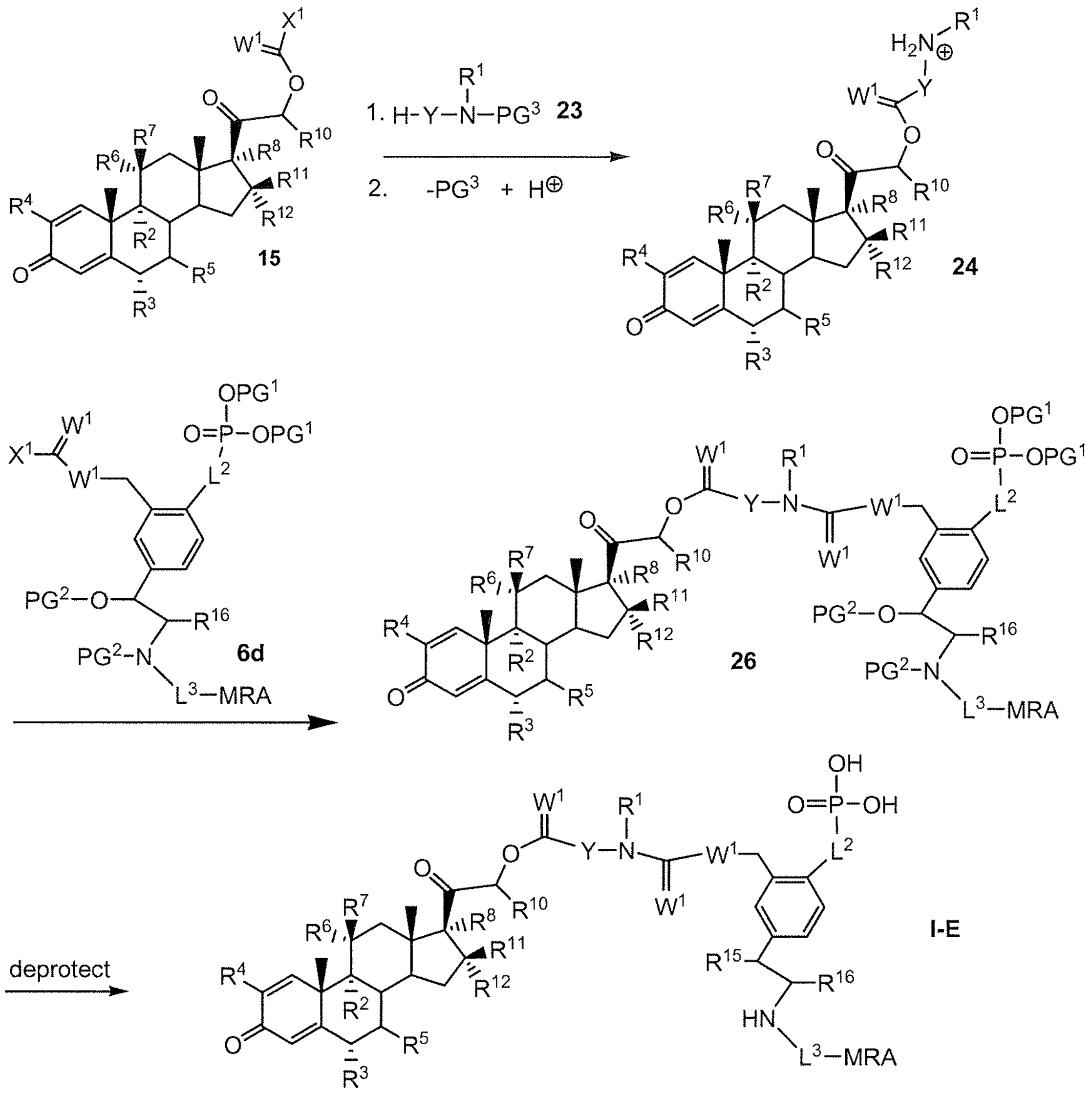
Compounds of Formula I wherein L^1 is



$$\text{—}\underset{\underset{W^1}{\|}}{C}\text{—}(W^3)_b\text{—}(CH_2)_c\text{—}\overset{\overset{R^1}{|}}{N}\text{—}\underset{\underset{W^1}{\|}}{C}\text{—}W^1\text{—}$$

, i.e., compounds of Formula I-E may be prepared according to the process illustrated in **Scheme 6.**

Scheme 6



wherein:

X^1 is halo, particularly Cl;

Y is $-(W^3)_b-(CH_2)_c-$;

each PG^1 is a phosphonic acid protecting group such as methyl, ethyl, benzyl or t-butyl;

each PG^2 is H or Boc;

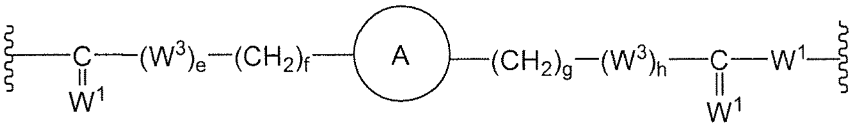
PG^3 is benzyl or Boc;

R^{15} is OH; and

all other variables are as defined herein.

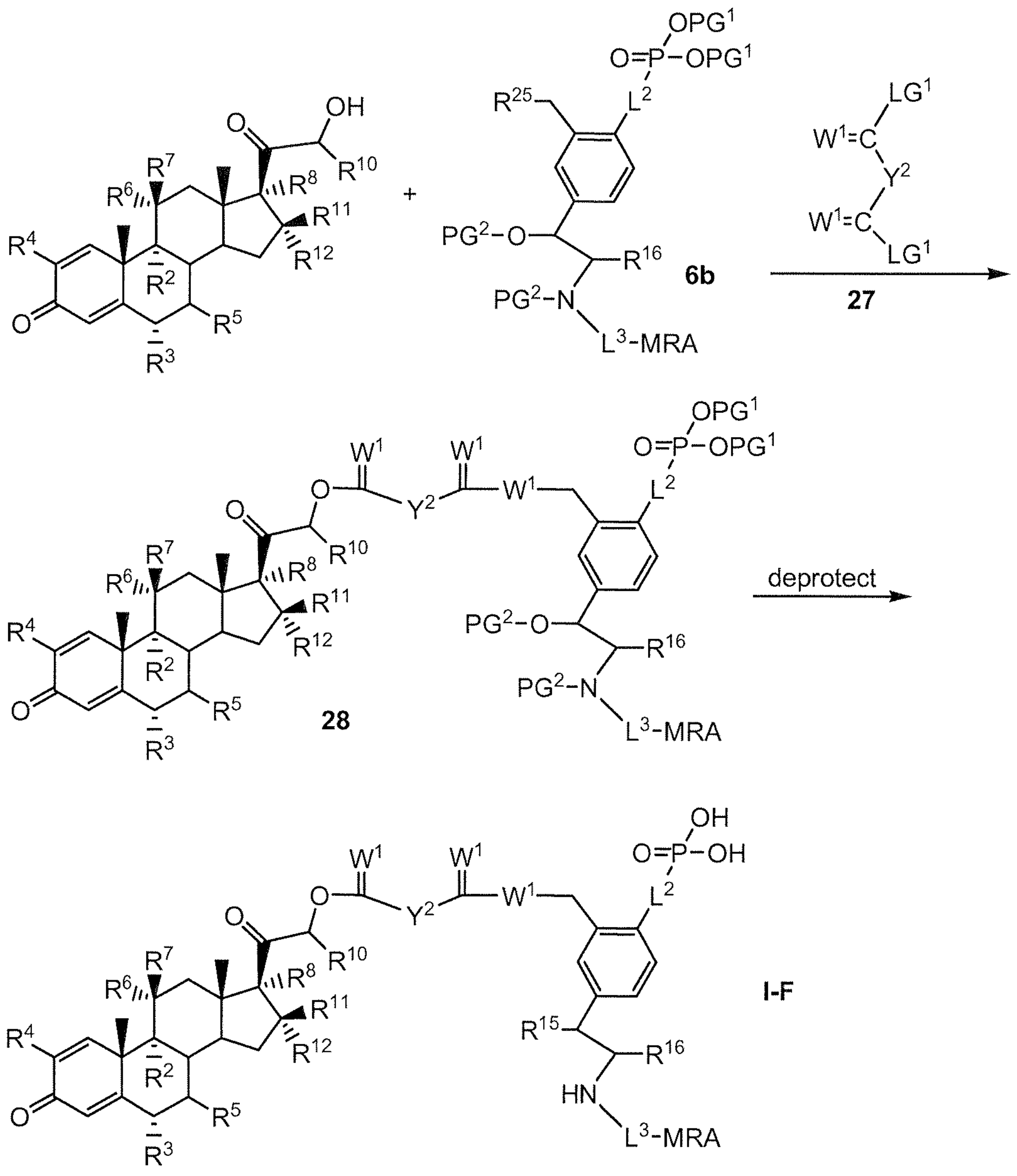
A compound of formula (24) may be obtained by reacting a compound of formula (15) with a compound of formula (23) with triethylamine at appropriate temperature in CH_2Cl_2 follow by deprotection using conventional methods including hydrogenation in acid such as acetic acid or acid hydrolysis with HCl or TFA. A compound of formula **(6d)** may be prepared by the same process as compound of formula (15) by substituting the steroid with the compound of formula **(6c).** A compound of formula **(24)** is coupled with a compound of formula **(6d)** in presence of base such as triethylamine at appropriate temperature to prepare a compound of formula **(26)** in a manner analogous to the process described in H.W. Scheeren and et al. *J. Org. Chem.* 2001, 8815. The resulting compound of formula **(26)** may be deprotected using acid as previously described.

Compounds of Formula I wherein L^1 is



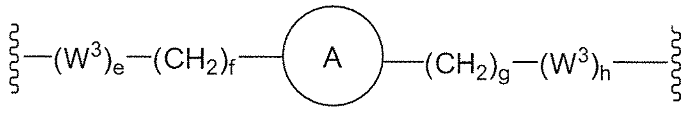
, i.e., compounds of Formula I-F may be prepared according to the process illustrated in **Scheme 7.**

Scheme 7



wherein

LG^1 is a leaving group such as halo, preferably chloro or an activated carboxylic acid using HATU;

Y^2 is 
$-(W^3)_e-(CH_2)_f-\text{(A)}-(CH_2)_g-(W^3)_h-$;

each PG^1 is the same or different and is an alcohol protecting group such as methyl, ethyl, benzyl or t-butyl;

each PG^2 is H or Boc; and

all other variables are as defined herein.

Generally, the process comprises the steps of

a) coupling a steroid with a compound of formula (6b) in the presence of a compound of formula (27), to prepare a compound of formula (28) or a pharmaceutically acceptable salt thereof; and

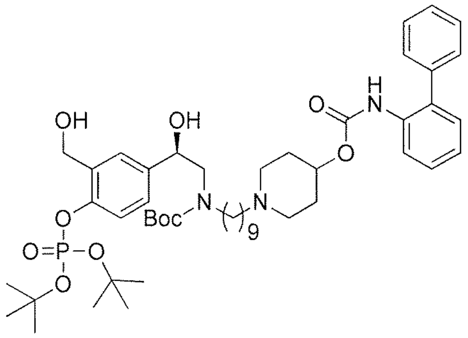
b) deprotecting the compound of formula (28) to prepare a compound of Formula I-F, or a pharmaceutically acceptable salt thereof.

More particularly, a steroid may be reacted with a compound of formula (6b) in the presence of a compound of formula (27), in a manner analogous to the process described above. Suitable solvents include acetonitrile and methylene chloride. Deprotection of a compound of formula (28) may be carried out using conventional techniques including those described above.

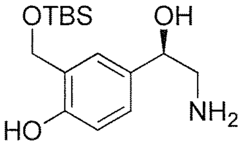
Examples

The foregoing may be better understood from the following examples, which are presented for the purposes of illustration and are not intended to limit the scope of the inventive concepts. The invention is defined solely by the claims which follow. In the following examples, compounds are named using standard IUPAC naming principles where possible. The naming convention employed for the novel compounds are exemplified by Examples below.

Intermediate 1: (R)-tert-butyl I9-[4-IT(1 ,1'-biphenyl)-2-ylcarbamoylloxy1piperidin-1-vnnonylir2-f4-[(di-tert-butoxyphosphoryl)oxy1-3-(hvdroxymethyl)phenyll-2-hydroxyethyllcarbamate

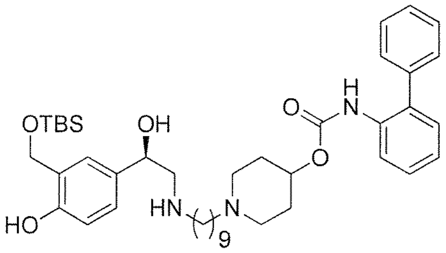


A. (R)-4-(2-amino-1-hydroxyethyl)-2-[[(tert-butyldimethylsilyl)oxy]methyl]-phenol



TBSCl (1.8 g, 12.2 mmol) and imidazole (1.13 g, 16.62 mmol) were added to a stirring solution of (R)-1-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-bromoethanol (2 g, 5.54 mmol) in CH_2Cl_2 (50 mL) at room temperature (rt). The resulting suspension was stirred for 1h then quenched with H_20 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_20 (100 mL), brine (100 mL), dried over Na_2S0_4, and concentrated to give a colorless oil (3.45 g). Chromatography (3:1 hexanes/EtOAc) afforded pure ether (2.3 g, 92 %) as a colorless oil. The ether was dissolved in DMF (50 mL) and NaN_3 (662 mg, 10.2 mmol) was added. The resulting mixture was heat to 80 °C and stirred for 4h. After cooling to rt. the reaction mixture was pour into H_20 (75 mL) and the aqueous was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_20 (2 x 100 mL), brine (100 mL), dried over Na_2S0_4, and concentrated to give a light yellow oil (1.95 g). With no further purification the material was dissolved in MeOH (50 mL) and 20 % w/w $Pd(OH)_2/C$ (662 mg, 0.942) was added. The reaction vessel was attached to a balloon with H_2 (g) and stirred over night. The resulting suspension was filtered through celite and concentrated to give a yellow semi solid (1.51 g). The residue was recrystallized from EtOAc/hexanes to give the title compound (980 mg, 65 % from mono-TBS ether) as an off white solid. ES/MS calculated for $C_{15}H_{27}NNa0_3Si$ 320.2, found *m/z* = 320.2 (M+Na).

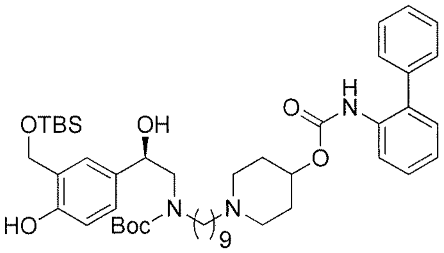
B. (R)-1-[9-[[2-[3-[[(tert-butyldimethylsilyl)oxy]methyl]-4-hydroxyphenyl]-2-hydroxyethyl]amino]nonyl]piperidin-4-yl [1,1'-biphenyl]-2-ylcarbamate



Acetic acid (0.761 mL, 13.3 mmol) was added to a stirring solution of 1-(2-oxononyl)piperidin-4-yl biphenyl-2-ylcarbamate (US2005/113417, 5.79 g, 13.3

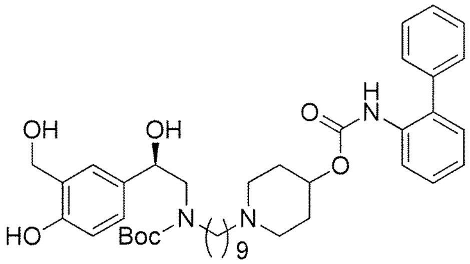
mmol) in CH_2Cl_2 (100 mL). The resulting mixture was cooled to 0 °C and (R)-4-(2-amino-1-hydroxyethyl)-2-[[(tert-butyldimethylsilyl)oxy]methyl]-phenol (7.18 g, 15.9 mmol) was added. After stirring for 30 min $NaBH(OAc)_3$ (8.5 g, 39.9 mmol) was added in portions. The reaction mixture was warmed to rt then stirred for additional 2h and quenched with satd. $NaHC0_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with H_20 (100 mL), brine (100 mL), dried over Na_2S0_4, and concentrated to give crude product (15 g) as yellow solid foam. Chromatography (9:1, CH_2Cl_2/MeOH, 0.1 % Et_3N) afforded (R)-1-[9-[[2-[3-[[(tert-butyldimethylsilyl)oxy]methyl]-4-hydroxyphenyl]-2-hydroxyethyl]amino]nonyl]piperidin-4-yl [1,1'-biphenyl]-2-ylcarbamate (8 g, 70 %). ES/MS calculated for $C_42H_64N3O_5Si$ 718.5, found m/z = 718.5 (M+H).

C. (R)-tert-butyl [9-[4-[[(1,1'-biphenyl)-2-ylcarbamoyl]oxy]piperidin-1-yl]nonyl][2-[3-[[(tert-butyldimethylsilyl)oxy]methyl]-4-hydroxyphenyl]-2-hydroxyethyl]carbamate



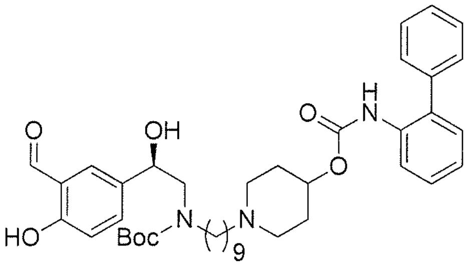
Solid K_2C0_3 (2.8 g, 20.6 mmol) and $(Boc)_20$ (3.59 g, 16.4 mmol) were added to a stirring solution of (R)-1-[9-[[2-[3-[[(tert-butyldimethylsilyl)oxy]methyl]-4-hydroxyphenyl]-2-hydroxyethyl]amino]nonyl]piperidin-4-yl [1,1'-biphenyl]-2-ylcarbamate (9.87 g, 13.7 mmol) in dioxane/H_20 (2:1, 130 mL) at rt. The resulting solution was stirred over night then diluted with EtOAc (150 mL). The organic layer was washed with H_20 (100 mL), brine (100 mL), dried over Na_2S0_4, and concentrated to give a yellow foamy solid (15.3 g). Chromatography (9:1, CH_2Cl_2/MeOH, 0.1 % Et_3N) afforded the title compound (7.24 g, 64 %) as a white solid foam. ES/MS calculated for $C_{47}H_{72}N_3O_7Si$ 818.5, found *m/z* = 818.6 (M+H).

D. (R)-tert-butyl [9-[4-[[(1 ,1'-biphenyl)-2-ylcarbamoyl]oxy]piperidin-1-yl]nonyl][2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyi]ethyl]carbamate



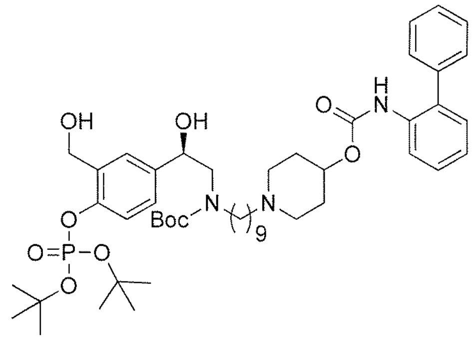
A 1.0 M (THF) solution of TBAF (8.8 mL, 8.8 mmol) was added to a stirring solution of (R)-tert-butyl [9-[4-[[(1 ,1'-biphenyl)-2-ylcarbamoyl]oxy]piperidin-1-yl]nonyl][2-[3-[[(tert-butyldimethylsilyl)oxy]methyl]-4-hydroxyphenyl]-2-hydroxyethyljcarbamate (7.2 g, 8.8 mmol) in THF (80 mL) at rt. The reaction mixture was stirred for 4h then quenched with satd. NaHC0 $_3$ (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_20 (100 mL), brine (100 mL), dried over Na_2S0_4, and concentrated to give a yellow oil (6.97 g). Chromatography (9:1 , CH_2Cl_2/MeOH, 0.1 % Et_3N) afforded the title compound (6.1 7 g, 99 %) as a white solid foam. ES/MS calculated for $C_{41}H_58N_30_7$ 704.4, found *m/z* = 704.5 (M+H).

E. (R)-tert-butyl [9-[4-[[(1 ,1'-biphenyl)-2-ylcarbamoyl]oxy]piperidin-1 -yl]nonyl][2-(3-formyl-4-hydroxyphenyl)-2-hydroxyethyl]carbamate



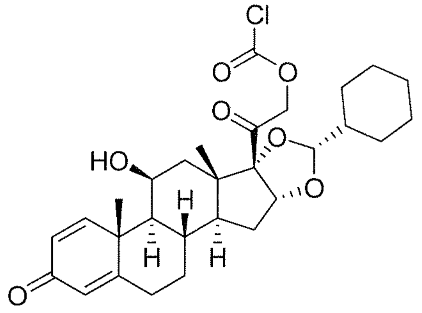
Mn0 $_2$ (7.5 g, 86.7 mmol) was added to a stirring solution of (R)-tert-butyl [9-[4-[[(1 ,1'-biphenyl)-2-ylcarbamoyl]oxy]piperidin-1-yl]nonyl][2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]carbamate (6.1 g, 8.67 mmol) in $CHCl_3$ (80 mL) at rt. The resulting suspension was stirred over night then filtered through celite. The filtrate was concentrated and purified by chromatography (9:1 , CH_2Cl_2/MeOH, 0.1 % Et_3N) to give the title compound (3.71 g, 61 %) as a yellow solid foam. ES/MS calculated for $C_{41}H_{56}N_30_7$ 702.4, found *m/z* = 702.5 (M+H).

F. (R)-tert-butyl [9-[4-[[(1 ,1'-biphenyl)-2-ylcarbamoyl]oxy]piperidin-1-yl]nonyl][2-[4-[(di-tert-butoxyphosphoryl)oxy]-3-(hydroxymethyl)phenyl]-2-hydroxyethyl]carbamate



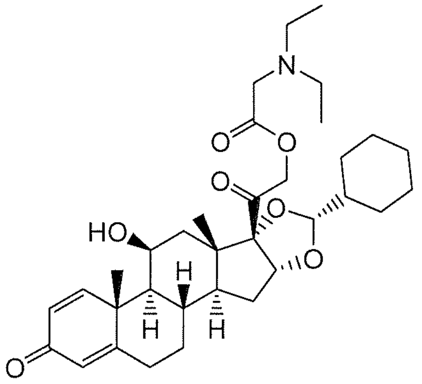
A solution of di-f-butylphosphite (683 mg, 3.52 mmol, in 1 mL CH_2Cl_2) was added drop wise to a stirring solution of benzyltetraethylammonium chloride (62 mg, 0.271 mmol), $BrCCl_3$ (0.401 mL, 4.07 mmol), and 20% (w/v) NaOH (5.4 mL, 27.1 mmol) in CH_2Cl_2 (5.4 mL) at 0 °C. The reaction mixture was warmed to rt for 2h then re-cooled to 0 °C. To this mixture a solution of (R)-tert-butyl [9-[4-[[(1 ,1'-biphenyl)-2-ylcarbamoyl]oxy]piperidin-1-yl]nonyl][2-(3-formyl-4-hydroxyphenyl)-2-hydroxyethyl]carbamate (1.9 g, 2.71 mmol) and DMAP (33 mg, 0.271 mmol) in CH_2Cl_2 (2 mL) was added. The resulting suspension was stirred for an additional 3h at rt and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 10 % (w/v) citric acid (50 mL), satd. $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2S0_4, and concentrated to give a yellow oil (2.64 g). The material was dissolved in THF (20 mL) and $NaBH_4$ (205 mg, 5.42 mmol) in H_20 (2 mL) was added at 0 °C. The resulting mixture was stirred for 30 min then quenched with H_20 (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with satd. $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated to give a light yellow oil (2.51 g). Chromatography (9:1 , CH_2Cl_2/MeOH, 0.1 % Et_3N) afforded the title compound (1.1 g,) as a white solid foam. ES/MS calculated for $C_{49}H_{75}N_3O_{10}P$ 896.5, found *m/z* = 896.6 (M+H).

Intermediate 2: [[11β,16α1-[15,16-((R)-cyclohexylmethylene)bis(oxy)1-11-hydroxypregna-1,4-diene-3,20-dion-21-vn chloroformate



Phosgene (20% in toluene, 56 mL, 106 mmol) was added to a stirred solution of des-isobutyryl-ciclesonide (5 g, 10.6 mmol) in THF (100 mL) at rt. The resulting mixture was stirred for 2 h then concentrated to give a yellow solid (6.77 g). Recrystallization (EtOAc/hexanes) afforded the title compound (3.7 g, 65 %) as an off white solid.

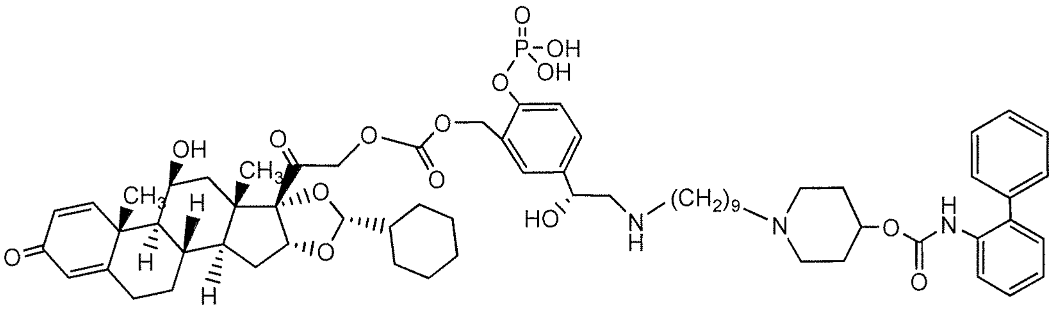
Intermediate 3: 4-Diethylaminoacetic acid [[11β,168]-í[((R)-cvcloηeχvl-methylene)bis(oxy)1-11-hydroxypregna-1,4-diene-3,20-dion-21-vl]] ester



Chloroacetyl chloride (1.7 mL, 21.2 mmol) was added to a stirred solution of desisobutyryl ciclesonide (1 g, 2.1 mmol) in DMF (10 mL). The reaction mixture was stirred for 30 min at rt and then poured into H_20 (100 mL). The resulting suspension was filtered and the filter cake was washed with H_20 (50 mL), then dried to give a yellow solid (1.22g). The material was redissolved in acetone (50mL) followed by the addition of NaI (334 mg, 2.2 mmol) and diethylamine (2.3 mL, 22 mmol). The resulting mixture was refluxed for 30 min, cooled, then poured into H_20 (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2S0_4, and concentrated to give a yellow oil (1 g). Crystallization from

EtOAc and hexanes gave the title compound (0.72 g, 58 % after 2 steps) as off-white crystals. ^{1}H NMR (400 MHz, CDCl3) d 6.30 (dd, 1H, *J* = 1.9, 10.1 Hz), 6.05 (s, 1H), 4.96 (d, 1H, *J* = 17.6 Hz), 4.84 (d, 1H, *J* = 5.0 Hz), 4.74 (d, 1H, *J* = 17.6 Hz), 4.52 (brm, 1H), 4.35 (d, 1H, *J* = 4.6 Hz), 3.46 (d, 2H, J = 2.1 Hz), 2.69 (q, 4H, *J* = 7.1 Hz), 2.57 (m, 1H), 2.35 (m, 1H), 2.25-2.02(m, 3H), 1.88 (dd, 1H, *J* = 2.58, 14.03 Hz), 1.8-1 .51 (m, 10H), 1.47 (s, 3H), 1.37-0.99 (m, 14H). 0.97 (s, 3H); ES/MS calculated for $C_{34}H_{5}oN0_{7}$ 584.4, found *m/z* = 584.4 (MH^+)

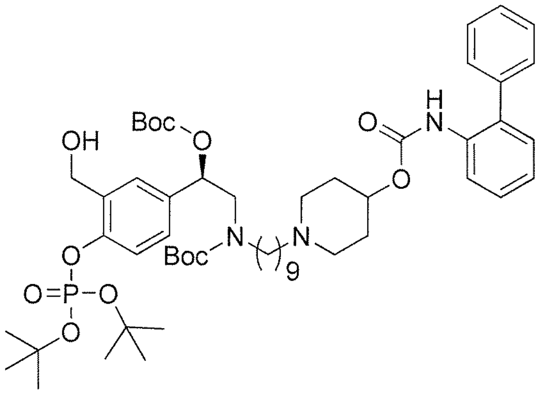
Example 1: r(R)-1-r9-r2-r3-πт[11β .16α'l-π 5,16-((R)-cyclohexylmethylene)bis(oxy)l-1 1-hydroxypregna-1 ,4-diene-3,20-dion-21 -vnoxycarbonyloxy1methyll-4-(phosphonooxy)phenyll-2-hvdroxyethylaminolnonynpiperidin-4- ν π (biphenyl-2-yl Carbamate



Intermediate 2 (892 mg, 1.67 mmol), Et_3N (0.233 mL, 1.67 mmol), and DMAP (204 mg, 1.67 mmol) were added to a stirring solution of intermediate 1 (500 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) at rt. The reaction mixture were stirred for 4d then quenched with 10 % (w/v) citric acid (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with satd. $NaHC0_3$ (40 mL), H_20 (40 mL), brine (40 mL), dried over Na_2S0_4, and concentrated to give a yellow oil (1.82 g). Chromatography (1:3 hexanes/EtOAc, 0.1 % Et_3N) afforded carbonate (190 mg). The carbonate was dissolved in CH_2Cl_2 (1 mL) then neat TFA (1 mL) was added at rt. The reaction mixture was stirred for 6h then concentrated to give a residue. The residue was purified using an SCX column, then passed through Cl⁻ exchange Dowex resin followed by lyophilization to give the title compound (67 mg) as a white solid. ^{31}P NMR (400 MHz, DMSO-c/6) d-5.497; ES/MS calculated for $C_65H87N30_{15}P$ 1180.6, found *m/z* = 1180.6 (M+H).

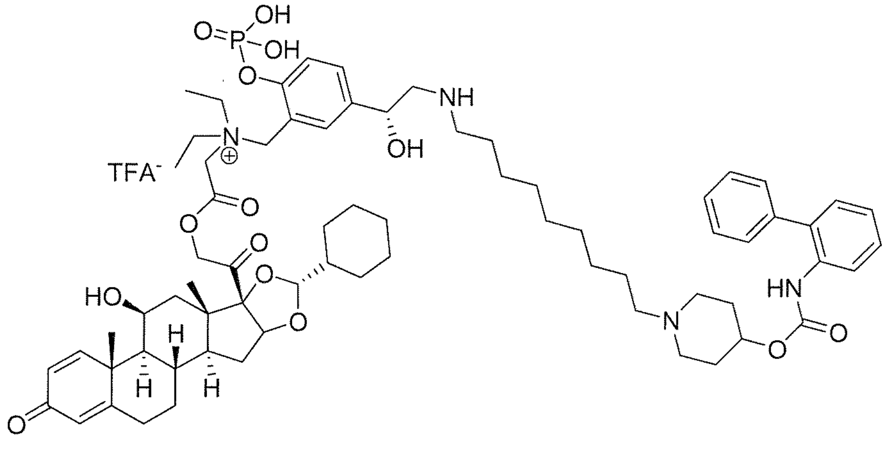
Example 2: (R)-f5-f2-f9-i4-(Biphenyl-2-ylcarbamoyloxy)piperidin-1 -vnnonylaminol-1-hvdroxyethyll-2-phosphonooxybenzyll-(diethyl)-ff1 1β,16α1-i[15,1 6-((R)-cvclohexylmethylene)bis(oxy)l-1 1-hydroxypregna-l ,4-diene-3,20-dion-21-yllcarbonylmethyllammonium Trifluoroacetic Acid Salt

A. (R)-tert-butyl [9-[4-[[(1 ,1'-biphenyl)-2-ylcarbamoyl]oxy]piperidin-1-yl]nonyl][2-[(tert-butoxycarbonyl]oxy]-2-[4-[(di-tert-butoxyphosphoryl)oxy]-3-(hydroxymethyl)phenyl]ethyl]carbamate



The title compound was synthesized in a manner analogous to that described for compound intermediate 1, using 2 equiv. of $(Boc)_20$, 0.1 equiv. of DMAP, and 3 equiv. of pyridine in acetonitrile after the phosphorylation. $NaBH_4$ reduction afforded the title compound. ES/MS calcd. for $C_{59}H_{91}N_3O_{14}P$ 1096.6, found *m/z* = 1096.6 (M+H).

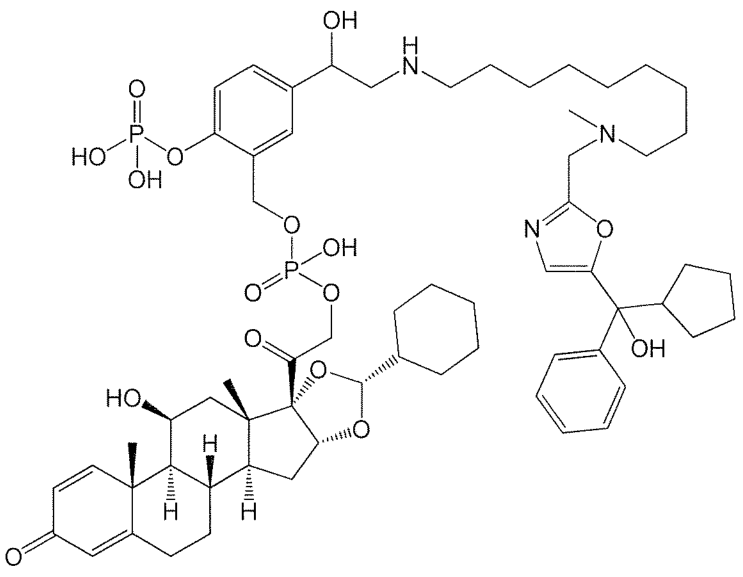
B.



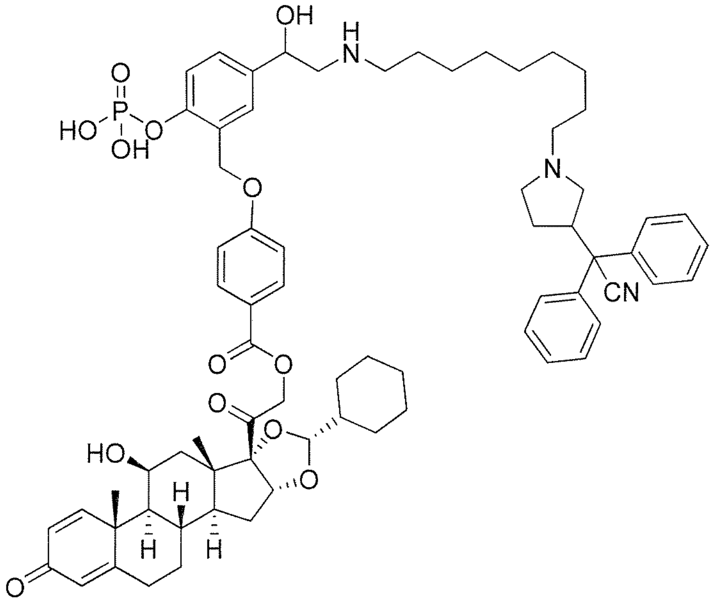
Neat $BF_3 \cdot OEt_2$ (0.029 mL, 1.13 mmol) was added to a stirred solution of Intermediate 1 (200 mg, 0.18 mmol) in CH_2Cl_2 at 0 °C and stirred for 10 min. To this solution PMP (0.082 mL, 0.456 mmol) and intermediate 3 (89 mg, 0.1 52 mmol) were added then cooled to -78 °C. A solution of Tf_20 (0.038 mL, 0.228 mmol) in CH_2Cl_2 (0.23 mL) was added drop wise and the internal temperature was kept below -74 °C. The resulting mixture was warmed to rt slowly and stirred for 3.5 h then concentrated. The residue was dissolved in EtOAc (50 mL) and the organic layer was washed with 10 % (w/v) citric acid (50 mL), satd. $NaHC0_3$ (50 mL), brine (50 mL), dried over Na_2S0_4, and concentrated to give a yellow oil (297 mg). With no further purification, the oil was dissolved in CH_2Cl_2 (2 mL) and TFA (2 mL) was added at rt. The reaction mixture was stirred for 2h then concentrated. Purification using SCX column followed by recrystallization (CH_2Cl_2/Et_20) afforded the title compound (50 mg) as an off white solid. ^{31}P NMR (400 MHz, DMSO-d6) d -5.212; ES/MS calculated for $C_{70}H_{98}N_40_{14}P^+$ 1249.7, found *m/z* = 1249.7 (M^+).

The following examples may be prepared using methods analogous to those described above in Examples 1 and 2 and the earlier description of synthetic methods.

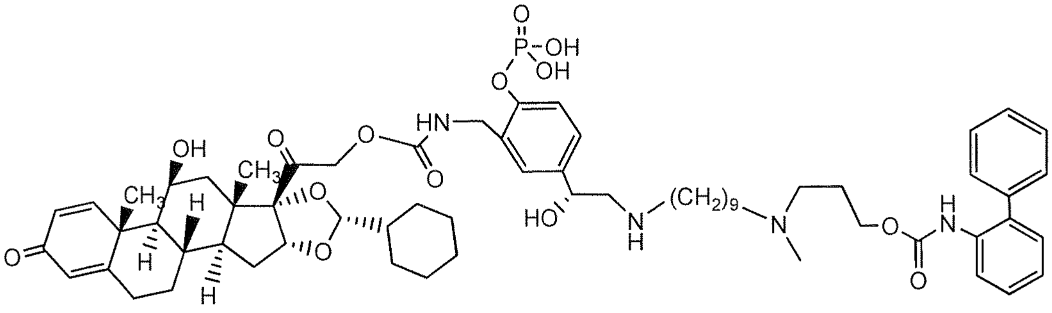
Example 3: Phosphonic acid f5-[1-hydroxy-2-f[9-[[r5-[cvclopentyl(hvdroxy)(phenyl)methvnoxazol-2-vnmethvn(methyl)amino1nonvnaminolethyl1-2-(2-phosphonooxy)benzvn ester ff11β,16al-[1 5,1 6-((R)-cyclohexylmethylene)bis(oxy)1-1 1-hvdroxypregna-1 ,4-diene-3,20-dion-21-yll ester



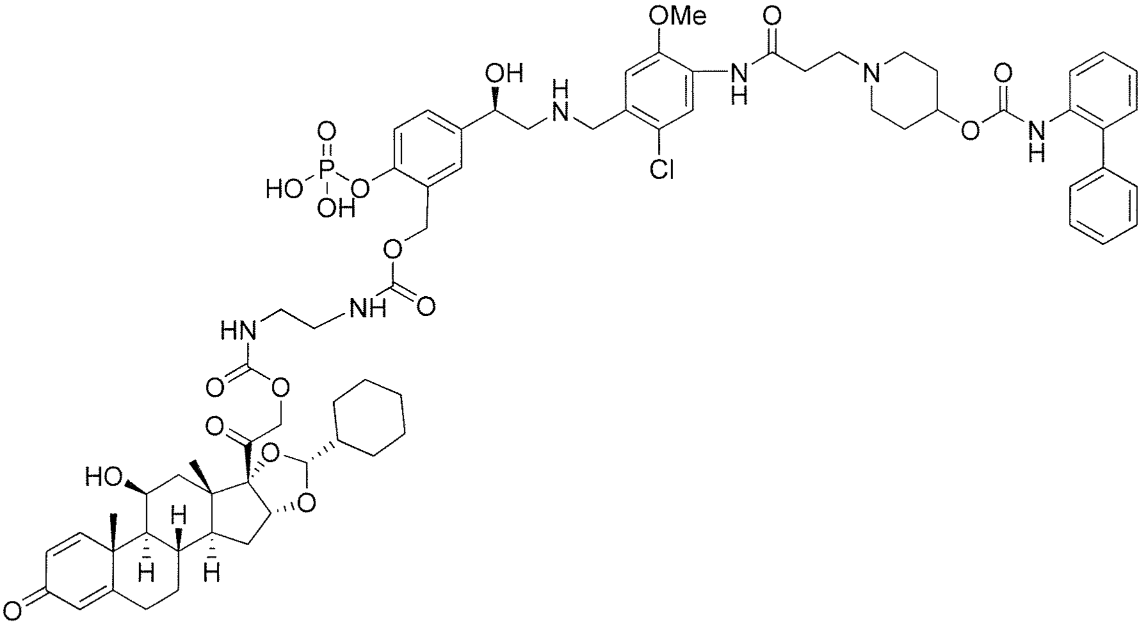
Example 4: ⌈5-⌈1-Hvdroxy-2-r9-r3-(cvanodiphenylmethyl)pyrrolidin-1 - yllnonylaminolethvn-2- phosphonooxybenzyloxylbenzoic acid ⌈⌈11β ,16α 1-[1 6,17-((R)-cvclohexylmethylene)bis(oxy)1-1 1-hydroxypregna-1 ,4-diene-3,20-dion-21-vH ester



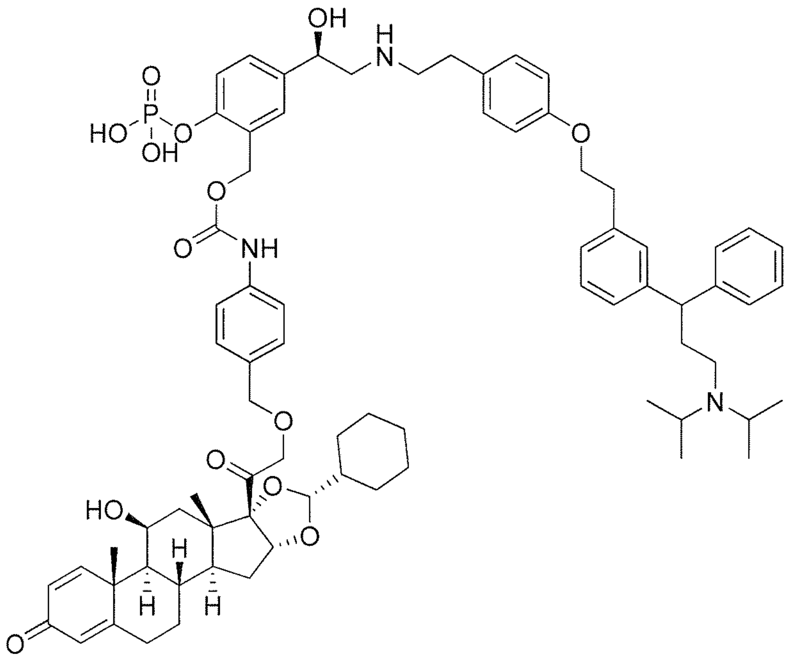
Example 5; г3-гí9-г2-г3-гггг11ß,16a1**-ri5**,1 6-((R)-cvclohexylmethylene)bis(oxy)1-11-hydroxypregna-1 ,4-diene-3,20-dion-21 -ynoxycarbonylaminolmethyll-4-(phosphonooxy)phenyl1-2-hvdroxyethylamino1nonyn(methyl)amino1propyn (biphenyl-2-yl)carbamate



Example 6: г1 - г3 - гг5 - Cﬂ югогг 2 - г4 - ггггг1 1ß,16a]-[15,16-((R)-cyclohexylmetliylene)bis(oxy)1-1 1-hydroxypregna-1 ,4-diene-3,20-diori-21 -ylloxoxarbonylaminol-l ,4-dioxobutynaminocarbonyloxylmethyll-4-(phosphonooxy)phenvn-2-hvdroxyethylamino1methvn-2-methoxyphenvnamino1-3-oxopropyllpiperidine-4-yll (biphenyl-2-yl)carbamate



Example 7: г4-гг11β .16a]-[16,17-((R)-cyclohexylmethylene)bis(oxy)1-1 1-hydroxypregna-1 ,4-diene-3,20-dion-21-oxylmethylphenvncarbamic acid [5-г(1R)-2-r4 -r3-r3-(diisopropylamino)-1 -phenylpropyllpheriylethoxy1phenylethylaminol-1-hydroxyethyn-2-(phosphonooxy)benzyll ester



Example 8: Method for Evaluating Stability of Steroid C-21 Esters, Carbonates and Carbamates in Rat Lung Homogenate

Preparation of rat lung homogenate

Lungs from Fischer 344 rats are obtainable fresh by overnight delivery at 4°C from BioReclamation Inc. (Hicksville, NY). Lungs are weighed and homogenized in a 1:3 w/v ratio with sterile phosphate buffered saline (PBS, 10mM, pH 7.4) in glass vials on ice. After centrifugation at 3,000 x g for 10 min at 4°C the supernatant is decanted into sterile conical tubes and placed on ice. The total protein content of the supernatant is determined by the bicinchoninic acid (BCA) method (Pierce Biotechnology, Rockford, IL), using bovine serum albumin (BSA) as the standard. Lung homogenates are prepared to a final concentration of 1 mg total protein/mL in 10mM PBS, pH 7.4.

In vitro metabolism of steroid 21-esters, carbonates, carbamates in rat lung homogenate

Compounds are incubated with active or heat-inactivated rat lung homogenate in 10mM PBS (pH 7.4). Heat-inactivation is achieved by incubation at 80°C for 30 min, after which the homogenate is allowed to cool to rt, stored overnight at 4°C. The homogenate is used for the assay and standard curve preparations. Before use, each homogenate preparation is equilibrated for 15 min in a 37°C water bath. The metabolism reactions are initiated by the addition of stock solutions of 21-derivatized steroids ciclesonide and desisobutyryl ciclesonide in 1 mM dimethyl sulfoxide (DMSO) to a final concentration of 900 nM. DMSO (2.7 µL) is added to 3 mL of temperature-equilibrated homogenate serves as a control. Aliquots (100 µL) of homogenate + compound are added to 400 pL quenching solution consisting of 100% HPLC-grade acetonitrile + 500 ng/mL glyburide for the zero time point (n = 3 for each time point). The glyburide serves as an internal LC/MS/MS standard. The remainder of each drug + homogenate solution is aliquoted into a 96-well tissue culture plates. After an additional 30min and 120 min incubation at 37°C, 100 µL aliquots are added to 400 µL quenching solution. Denatured proteins in the quenching solution are separated by centrifugation at 3000 x g for 2 min at 4°C, and 160 µL of the supernatants are transferred to new 96-well plate for analysis by LC/MS/MS. Collection plates are covered with plastic film and kept on ice. For storage, covered plates are kept stored at -80°C until further use.

Liquid chromatography and mass spectrometry analysis (LC/MS/MS)

An aliquot (50 pL) of each sample is diluted with 50 µL of water containing internal standard at 4 °C. The diluted samples are then centrifuged for 20 min at 3000 rpm at 4 °C. An aliquot of 20 pL of the solution is injected into the TSQ Ultra Quantum LC/MS/MS system. The compounds are separated by HPLC using a HyPurity C18 HPLC column (30 X 2.1 mm, 5 µ) from ThermoHypersil. A Multiplex LX-2 HPLC system (Cohesive Technologies, Franklin, MA) with two identical Agilent 1100 series binary pumps (P/N G1312A) are used for elution and separation. Samples are maintained at 4°C in an HTS Pal autosampler (LEAP Technologies, Carrboro, NC) in order to reduce any potential spontaneous hydrolysis of the compounds before injection onto the HPLC. The analytes are eluted using the following mobile phases: Mobile phase A contains 1% acetonitrile in 10 mM ammonium formate aqueous solution with 1% formic acid. Mobile phase B contains 80% acetonitrile in 10 mM ammonium formate with 1% formic acid. The HPLC elution program used to elute the analytes is as follows:

Time (sec)	Step Comments	Flow Rate (mL/min)	Mobile Phase A (%)	Mobile Phase B (%)
90	Sample Loading	0\50	100	0
150	Ramp	0.50	50	50
180	Elution	0.50	0	100
120	Re-equilibrium	0.50	100	0

The samples are further analyzed by tandem mass spectrometry using a TSQ Quantum Ultra triple quadrupole mass spectrometer (Thermo Finnigan, San Jose, CA) using a selective reaction monitoring (SRM) scan type. The mass spectrometry parameters used are as follows:

Ion Source	Source CID (V)	Spray voltage (V)	Sheath gas pressure (Arb)	Aux gas pressure (Arb)	Capillary temp. (°C)
ESI +	10	4000	40	15	350

Data analysis

Nine-point standard curves for each test compound are prepared and analyzed in heat-inactivated lung homogenate. The concentration range is from 1 nM to 10 μM. The calibration curves of the steroid linkers, ciclesonide (CIC) and desisobutyryl ciclesonide (des-CIC) are evaluated by linear regression analysis. The data represent the mean percent remaining compound in both types of homogenate at 2 hours, 37°C and the value for mean concentration remaining of the parent compound and des-CIC at 2 hours, 37°C.

Example 9: Pharmacokinetic Analysis of Drug Levels of Salmeterol, Desisobutyryl Ciclesonide ("des-ciclesonide") and Compounds of the Invention Conducted in Lung, Bronchoalveolar Lavage Fluid and Plasma After IT Administration in the Rat

Dosing

Compounds of the invention are formulated for intratracheal (IT) dosing in 10%EtOH, 90% Sterile Water, and are dosed in male Sprague-Dawley rats at 3 mg/kg or 1 mg/kg. Each dosing group consists of 3 male, naïve purebred Sprague-Dawley rats. At dosing, the animals are weighed. The animals are fasted overnight prior to dose administration and up to 2 hr after dosing. The compounds are administered IT using a Penn Century Microsprayer (Model 1A-1B).

Sample Collection and Analysis

A. Plasma

Blood samples are collected at 0.5, 2, and 4 hours post-dose. Each blood sample (0.5-0.6 ml_ per sample) is collected via the orbital sinus (following anesthesia for BAL procedure) into tubes containing EDTA anti-coagulant in containers surrounded by dry ice at 0.5, 2 and 4 hr (mean, n=6). Blood samples are stored at -20 ± 5 °C until shipped for analysis.

B. BALF

The animals are anesthetized with an intramuscular (IM) injection of a ketamine/xylazine/acepromazine (80/10/2 mg/kg) cocktail at a dose volume of 1.1 mL/kg. A cannula (modified Bard® infant feeding tube) is inserted into the trachea. Warmed sterile saline is injected into the lungs. The lungs are gently massaged by palpation of the chest for approximately 45 seconds. The fluid (BALF) is recovered and placed on ice. The procedure is repeated two more times, and all three BALF samples are pooled. The fluid is centrifuged under refrigerated conditions at 350 g for 10 min. The supernatant and cell pellet are collected and stored at approximately -70°C until shipped for analysis.

C. Lung tissue Collection

Immediately following each BAL procedure, the lungs from each animal are removed, blotted dry, weighed, and stored frozen at -70°C until shipped for analysis.

D. Assay Methods

An LC/MS/MS method is used to measure the concentration of compound in plasma.

Bioanalytical Method

1. Lung homogenate

A 3x w/v of 1xPBS buffer (90:10-PBS:ACN) is added to each lung tissue. The sample is homogenized with Polytron (PT1200) and a 50uL supernatant sample is injected to an LC/MSMS.

2. Sample Processing

An aliquot of 50 μI_ of each plasma sample is treated with 100 μL of acetonitrile (ACN) containing internal standard. After the protein precipitation, an aliquot of 100 μI_ of the supernatant is transferred to a clean 96-well plate and mixed with 100 μI_ of water. An aliquot of 30 μI_ of the above solution is injected to the TSQ Ultra Quantum LC/MS/MS system.

3. HPLC Condition

A HyPurity C18 HPLC column (30 X 2.1 mm, 5 μ) from ThermoHypersil (Part #: 22105-032130) is used. Mobile phase A contains 1% acetonitrile in 10 mM ammonium formate aqueous solution with 1% formic acid. Mobile phase B contains 80% acetonitrile in 10 mM ammonium formate with 1% formic acid. An Agilent 1100 series binary pump (P/N G1312A Bin Pump) is used for elution and separation. HTS Pal autosampler from LEAP Technologies, Carrboro, NC is used.

HPLC elution program:

Time (sec)	Step Comments	Flow Rate (mL/min)	Mobile Phase A (%)	Mobile Phase B (%)
90	Sample Loading	0.50	100	0
150	Ramp	0.50	50	50
180	Elution	0.50	0	100
120	Re-equilibrium	0.50	100	0

4. Mass Spectrometry

TSQ Quantum Ultra triple quadrupole mass spectrometer from Thermo Finnigan, San Jose, CA is used in selective reaction monitoring (SRM) operation mode, Tune file: ESI_tune1 12807J3L.

Mass spectrometry parameters:

Ion source	Source CID (V)	Spray voltage (V)	Sheath gas pressure (Arb)	Aux gas pressure (Arb)	Capillary temperature (°C)
ESI +	10	4000	40	15	350

Results

The results will demonstrate whether the compounds of the invention are metabolized to salmeterol and desisobutyryl ciclesonide in the lung following IT administration. Based upon the structure of the compounds of the invention, it is believed that the results will demonstrate that the compounds of the invention are metabolized to salmeterol and desisobutyryl ciclesonide.

Example 10: Drug Metabolism Studies Using Airway Epithelial Cells Cultured at an Air-Liquid Interface

Cryopreserved passage 1 cells are cultured in bronchial epithelial growth medium (Fulcher, M.L., et al., *Well-differentiated human airway epithelial cell cultures.* Methods Mol Med, 2005. 107: p.183-206) on 100 mm Type I collagen-coated plastic dishes. At 70% confluence, passage 2 cells are transferred to type IV collagen-coated Millicell membranes (Millipore, Bedford, MA) in medium that supports growth at an air-liquid-interface (ALI) (Fulcher *et al.,* 2005). Cells are maintained at an ALI and allowed to differentiate fully for approximately 28 days. Approximately 24 hrs prior to the start of the experiment, the apical surfaces of the cells are washed with sterile phosphate buffered saline (PBS, 10mM, pH 7.4) and the basolateral media is replaced with fresh ALI media. Approximately 1 hour prior to the start of the experiment, the apical surfaces of the cells are washed once again with PBS and the basolateral media replaced with fresh ALI media. At time = 0 hr, the test article is diluted from a 10 mM stock solution in DMSO to a 40 μM solution in ALI media/PBS/10% EtOH/water (v/v). 50 μl of the resulting 40 μM solution is immediately added to the apical surface of the cells. 200 μL of the dosing solution is also added to 800 μL of 100% ACN and frozen immediately on dry ice. The remaining dosing solution is placed in the incubator with the cells. The dosing solution and cells are allowed to incubate for 10, 120 and 240 min at which points the apical surfaces of cells from 4 millicell cell culture inserts (n = 4) are washed with 3 x 100 μL of PBS or 10% EtOH/water (v/v) per millicell. The three washes from each millicell cell culture insert are pooled. The entire basolateral medium from each millicell cell culture insert is also collected as are the airway epithelial cells which are excised from each millicell cell culture insert and added to 300 μl of 90% ACN/0.1 % formic acid/9.9% water and immediately frozen on dry ice. The cells are thawed and lysed for 2 mins with a sonicator (Misonix, Farmingdale, NY) set at 30 Amp. The cell suspension is then centrifuged at 18,000 g for 2 min and 50 μL of the supernatant is added to 200 μL of acetonitrile containing 100 ng mL^{-1} glyburide. 50 μL of the pooled apical washes and basolateral medium is also added to 200 μL of ACN containing 100 ng ml^{-1} glyburide. These samples are then frozen on dry ice and kept at -80 °C for their analysis by LC/MS/MS. At the same 10, 120 and 240 min time points, 200 μL of the dosing solution is added to 800 μL of ACN and immediately frozen on dry ice. These dosing solution samples are also kept at -80 °C for analysis by LC/MS/MS. Untreated control cells dosed at the apical surface with 50 μL of test article vehicle (ALI media/PBS/10% EtOH/water (v/v) are also included to provide apical, basolateral and cellular matrices for LC/MS/MS analytical standards.

The above samples are thawed prior to centrifugation for 10 minutes at 3000 rpm at 4 °C. An aliquot of 150 pL of the above solution is mixed with 150 μL of water. 10 pL of the acetonitrile/water mix are injected into the Applied Biosystems/ Sciex API 5000 LC/MS/MS system. The compounds are separated by HPLC using a Zorbax Extend C18 HPLC column (50 X 2.1 mm, 3.5 μ) from Agilent Technologies. An Aria Transcend duplexed HPLC system (Thermo Fisher, Franklin, MA) with two identical Agilent 1100 series binary pumps (P/N G1312B) are used for elution and separation. Samples are maintained at 4°C in an HTS Pal autosampler (LEAP Technologies, Carrboro, NC) in order to reduce any potential spontaneous hydrolysis of the compounds before injection onto the HPLC. The analytes are eluted using the following mobile phases: Mobile phase A contains 1% acetonitrile in 10 mM ammonium formate aqueous solution with 1% formic acid. Mobile phase B contains 80% acetonitrile in 10 mM ammonium formate with 1% formic acid. The HPLC elution program used to elute the analytes is as follows:

Time (sec)	Step Comments	Flow Rate (mL/min)	Mobile Phase A (%)	Mobile Phase B (%)
30	Sample Loading	0.50	90	10
150	Ramp	0.50	50	50
180	Elution	0.50	0	100
90	Re-equilib.	0.50	90	10

The samples are further analyzed by tandem mass spectrometry using an ABI/Sciex API 5000 triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA) using a selective reaction monitoring (SRM) scan type. The mass spectrometry parameters are as follows:

Ion source	CAD gas pressure (arb)	Spray voltage (V)	Curtain gas pressure (Arb)	GS1 gas pressure (Arb)	GS21 gas pressure (Arb)	Capillary temp. (°C)
ESI +	6	5000	25	40	60	350

Eleven-point standard curves for each test compound are prepared and analyzed in heat-inactivated lung homogenate, the concentration ranged from 1 nM to 10 µM. The calibration curves of the steroid linkers, ciclesonide (CIC) and desisobutyryl ciclesonide (des-CIC) are prepared by quadratic regression analysis.

The results indicate the amount of each of 1) the parent compound of the invention, 2) salmeterol and 3) desisobutyryl ciclesonide in the apical and cellular compartments and whether the amount in each compartment increases or decreases over time. It is expected that the amount of the compound of the invention will decrease over time in both the apical and cellular compartments while the amount of salmeterol and desisobutyryl ciclesonide will increase in the cellular compartment.

Example 11: In vivo Efficacy of Compound of the Invention in the Mouse Ovalbumin Model of Lung Inflammation

Mice (Balb/c) are immunized by intraperitoneal injection of ovalbumin (10 µg OVA suspended in 2 mg aluminum hydroxide) on day 0 and 7. One group is sensitized and treated with vehicle (NSV). One group is immunized with sterile water only and treated with vehicle to serve as a nonsensitized (negative) control (Vehicle). Ciclesonide (positive control treatment; 1X per day (day 14 and 15; 3 mg/kg), Compound of the invention at 1, 3, and 6 mg/kg) or vehicle is delivered by intratracheal (IT) instillation 1X/day (day 14 and 15), 1 hour prior to OVA inhalation challenge. On days 14 and 15, the animals are exposed to OVA by inhalation (3 h; 5 mg/m^3). Forty eight hours following the last OVA challenge (day 17) mice are sacrificed. Bronchoalveolar lavage (BAL) is taken from each animal to collect cells and fluid. Cell numbers and differentials were calculated from BAL.

Example 12: LPS-Induced Airway Inflammation in Rats

Compound of the invention is evaluated in an LPS-induced airway inflammation model in rats. Male Fischer 344 rats (n = 8/group) are treated with either vehicle or test article by intratracheal instillation in 400 µL volume 1 hour prior to LPS challenge. Animals are then exposed to LPS by nose-only inhalation exposure for 10 minutes at 5 mg/m^3, resulting in an estimated 5 µg lung deposition. Animals are sacrificed 4 hours after LPS exposure. Lungs are lavaged for bronchoalveolar lavage cell differentials and cytokine analysis by Luminex multiplex immunoassay. It is believed that compounds of the invention and ciclesonide will inhibit LPS-induced airway inflammation measured as neutrophil influx and TNFa production at doses tested ($p<-0.05$ versus vehicle control).

Example 13: Tobacco Smoke Model of Airway Inflammation in Mice

Compounds of the invention may be evaluated in a tobacco-smoke-induced airway inflammation model in female C3H mice. Vehicle and test compounds are delivered by intratracheal instillation in 10% ethanol: water to animals anesthetized with 3-5% isoflurane (n=8 animals per test article group). All compounds will be delivered on a daily (5 days per week) schedule for 3 weeks during the smoke exposures. Mice are exposed to cigarette smoke for 6 hours per day, 5 days per week for 3 weeks, in H1000 or H2000 chambers. Type 2R4F research cigarettes (Kentucky Tobacco Research and Development Center) are used in the study. Total particulate material (TPM) exposure is kept at 100 TPM/m^3 for the first week to allow animals to reduce adverse effects during adaptation to smoke exposure. TPM exposure is maintained between 100 and 250 mg TPM/m^3 during the remainder of the study. After 3 weeks, animals are euthanized and bronchoalveolar lavage fluid is obtained for cell differentials and cytokine analysis by Luminex multiplex immunoassay. Inhibition of neutrophil influx is not expected in other treatment groups, including ciclesonide, salmeterol xinafoate, and ciclesonide + salmeterol xinafoate combination. In a 20-plex Luminex assay for cytokines and growth factors, it is expected that the compounds of the invention will exhibit inhibition of tobacco-smoke-induced IL-1α and MIP-1α production ($p<0.05$ versus vehicle control at 1.0 and 0.6 mg/kg doses).

Example 14: Ragweed-Induced Bronchoconstriction in Dogs

The compound of the invention may be assesed for bronchodilator activity in a ragweed-induced bronchoconstriction model in beagle dogs. Dogs are mechanically ventilated during each experiment. Airflow and tidal volume are measured using a differential pressure transducer located in front of the endotracheal tube. An esophageal balloon catheter placed in the esophagus is used to determine transpulmonary pressure. Pulmonary resistance and dynamic lung compliance are calculated from the simultaneous measurement of transpulmonary pressure and respiratory flow. The canine exposure system is designed to expose an anesthetized animal via an intubation tube. Dogs are administered vehicle or test article by inhalation 30 minutes before ragweed antigen exposure (n=4). Dogs are challenged with ragweed antigen (ragweed short, *Ambrosia artemisifolia,* Greer, Lenoir, NC) by inhalation (5 breaths). Immediately following ragweed challenge, changes in pulmonary resistance and compliance are measured for up to 30 min.

At doses of 20 mg/kg of the compound of the invention, an inhibition of ragweed-induced increases in pulmonary resistance ($p<0.05$ versus vehicle control) is expected. An inhibition of increased pulmonary resistance change following antigen challenge ($p<0.05$ versus vehicle control) may also be observed at 10 mg/kg of salmeterol xinafoate (10 mg/kg).

Example 15: *Ascaris suum*-induced Pulmonary Responses in Sheep

The compound of the invention is assessed for inhibition of early and late phase bronchoconstriction and development of airway hyperreactivity in sheep sensitized to *Ascaris suum* antigen as previously described (Abraham, W.M., A. Ahmed, I Serebrlakov, I.T. Lauredo, J. Bassuk, J.A. Adams, and M.A. Sackner. Am. J. Respir. Crit. Care. Med. 2006; 174:743-752). Early and late phase responses are measured as a function of increased pulmonary resistance during the 8 hour period following antigen. Airway hyperreactivity is evaluated as a function of PC400, the number of carbachol breath units required to induce a four-fold increase in bronchoconstriction measured 24 hours after antigen challenge. One breath unit is defined as one breath of a 1% w/v carbachol solution. Test compound is administered either by a pre-dosing or duration of action protocol. In the pre-dosing regimen, animals are dosed once daily for four days, with the last dose administered 1 hr before antigen. In the duration of action regimen, animals are dosed once daily for four days, with the last dose administered 24 hours before antigen. Test compound, *Ascaris* antigen, and carbachol are administered by nebulized aerosol to intubated sheep.

Using the predosing regimen, inhibition of late phase bronchoconstriction and development of airway hyperreactivity is expected with both compounds of the invention and ciclesonide.

In the duration of action regimen a reduction of early phase bronchoconstriction and complete inhibition of late phase bronchoconstriction and development of airway hyperreactivity is expected with compounds of the invention. An inhibition of late phase bronchoconstriction and development of airway hyperreactivity is also expected with a combination of ciclesonide + salmeterol. In contrast, reduced efficacy is expected with ciclesonide and salmeterol alone.

Example 16: Carbachol-induced bronchoconstriction in sheep

The compounds of the invention may be assessed for inhibition of carbachol-induced bronchoconstriction as previously described (Abraham, W.M., A. Ahmed, I Serebrlakov, A.N. Carmillo, J. Ferrant, A.R. de Fougerolles, E.A. Garber, P. J. Gowals, V.E. Kotellansky, F. Taylor, R. R. Lobb. Am. J. Respir. Crit. Care. Med. 2004; 169:97-104). Bronchoconstriction is evaluated as a function of increased pulmonary resistance following carbachol challenge. Measurements of R_L are repeated immediately after inhalation of buffer and after each administration of 10 breaths of increasing concentrations of carbachol solution (0.25%, 0.5%, 1.0%, and 2.0% w/v). Test compound is administered either by a pre-dosing or duration of action protocol. In the pre-dosing regimen, animals are dosed once daily for four days, with the last dose administered 1 hr before carbachol challenge. In the duration of action regimen, animals are dosed once daily for four days, with the last dose administered 24 hours before carbachol challenge. Test article and carbachol are administered by nebulized aerosol to intubated sheep.

Using the predosing regimen, inhibition of carbachol-induced bronchoconstriction may be observed with the compounds of the Invention and salmeterol xinafoate. Inhibition ($p<0.05$) of carbachol-induced bronchoconstriction may also be observed with the compounds of the invention in the duration of action regimen.

Example 17: Pharmaceutical Formulations:

A. DPI Formulation for Multidose Blister Strip or Capsule Based Inhaler

Target Unit Dose:

500 meg micronized compound of Formula I ("API")
15 mg lactose monohydrate for inhalation.

Micronize the API using a mill (e.g. jet mill) to a mass median aerodynamic diameter (MMAD) from about 1 to about 10 μM, and preferably a MMAD from about 1 to about 5 μM.

The lactose may be milled or sieved. Suitable commercial sources of lactose include DMV-Fonterra Excipients (Lactohale®) and Frieslandfoods Domo (Respotise®).

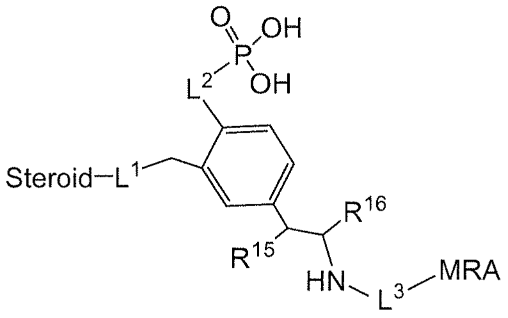
500 mg of API is blended with 15 g of lactose using an appropriate mixer (e.g. Turbula® Powder Blender). Additional fine lactose particles of less than 10 μιτι may be added. The blended product is filled into capsules or blister strips.

B. pMDI Liquid Suspension or Liquid Solution Formulation
Target Unit Dose:
250 meg of micronized API
150 μI of propellant (e.g., HFA 134a or 227)

Each canister is to contain 120 dose equivalents of API and propellant + 10% overage. Each canister is filled with 33 mg of API and sealed with a metering valve. The canister is then pressurized with 19.8 mL of propellant.

Claims:

1. A compound of Formula I:



I

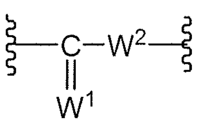
or a pharmaceutically acceptable salt thereof,

wherein:

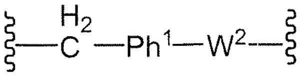
Steroid is a corticosteroid moiety bound to L^1 through O;

L^1 is a selected from

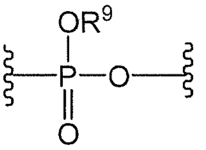
a bond,



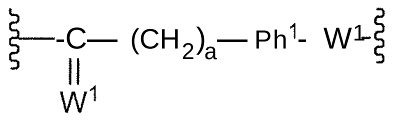
$-C(=W^1)-W^2-$,



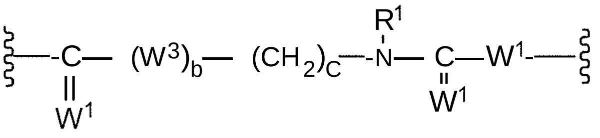
$-CH_2-Ph^1-W^2-$,



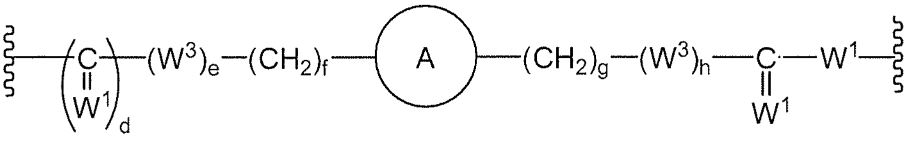
$-P(=O)(OR^9)-O-$,



$-C(=W^1)-(CH_2)_a-Ph^1-W^1-$,



$-C(=W^1)-(W^3)_b-(CH_2)_c-N(R^1)-C(=W^1)-W^1-$,



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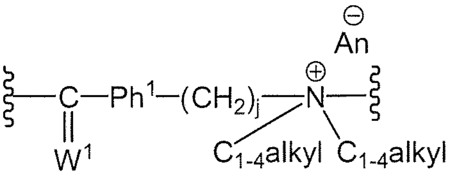
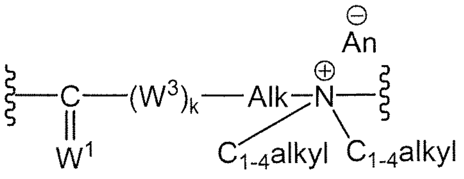
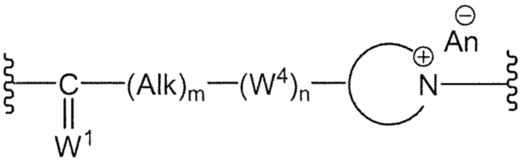


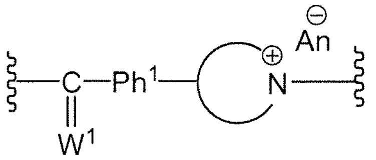
$-C(=W^1)-Ph^1-(CH_2)_j-N^{\oplus}(C_{1-4}alkyl)(C_{1-4}alkyl)-\quad An^{\ominus}$,



$-C(=W^1)-(W^3)_k-Alk-N^{\oplus}(C_{1-4}alkyl)(C_{1-4}alkyl)-\quad An^{\ominus}$,



, and



;

wherein:

each W^1 is the same or different and is O or S;

W^2 is O, S or $N(R^1)$;

Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, **C_{1-4}**alkyl, **OH, C_{1-4}**alkoxyl, **NH_2, N(H)C$_{1-4}$**alkyl, and **N(C$_{1-4}$**alkyl)$_2$;

R^9 is **H, C_{1-4}**alkyl, or phenyl;

a is 0, 1, 2, 3, 4, 5 or 6;

each R^1 is the same or different and is independently **H** or **C_{1-4}**alkyl;

b is 0 and c is 1, 2, 3, 4, 5 or 6, or b is 1 and c is 2, 3, 4, 5 or 6;

each **W^3** is the same or different and is independently **-O-** or **- N**(R^1)-;

d and e are both 0 and f is 1 or

d is 1, e is 0 or 1 and f is 0, 1, 2, 3, 4, 5 or 6;

Ring A is phenyl, pyridyl or pyrimidyl each optionally substituted on any available carbon with a substituent selected from halo, **C_{1-4}**alkyl, **OH, C_{1-4}**alkoxyl, **NH_2, N(H)C$_{1-4}$**alkyl, and **N(C$_{1-4}$**alkyl)$_2$;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0 or 1;

j is 0, 1, 2, 3, 4, 5 or 6;

k is 0 or 1;

each Alk is the same or different and is selected from

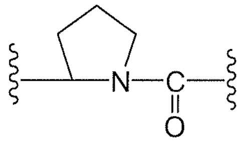
C_{1-6}alkylene or **C_{1-6}**alkenylene each optionally substituted on nonadjacent carbons by 1, 2 or 3 substituents, selected from halo, **OH, C_{1-4}**alkoxyl, **NH_2, N(H)C$_{1-4}$**alkyl, or **N(Ci-**$_4$alkyl)$_2$;

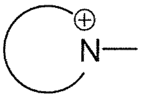
$C_{3..6}$cycloalkylene **-C_{1-4}**alkylene; and

-CH(AA)- wherein AA is a proteinogenic amino acid side chain;

m is 0 or 1;

n is 0 or 1 and **W^4** is **-N(H)-C(O)-;**

or $(Alk)_m$ and **$(W^4)_n$** join to form:  ;



is a quaternary N-heteroaryl having 5 or 6 ring atoms wherein one ring atom is a quaternary N and optionally one additional ring atom is N; or a quaternary N-heterocycle having 5 or 6 ring atoms wherein one ring atom is a quaternary N-methyl and optionally one additional ring atom is N, wherein said N-heteroaryl and said N-heterocycle are optionally substituted on any available ring atom with C_{1-4}alkyl;

each $A\eta^{\ominus}$ is a pharmaceutically acceptable counterion;

L^2 is a -O- or -0-CH$_2$-0-;

R^{15} is H, F, OH or methyl;

R^{16} is H, methyl or ethyl;

L^3 is selected from:

C_{4-12}alkylene, C_{4-12}alkenylene, or C_{4-12}alkynylene, each optionally substituted once or twice by a C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl or a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S;

d-ealkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene wherein one carbon of said alkylene, alkenylene or alkynylene is *optionally* replaced by a C_{3-6}cycloalkylene, C_{3-6}cycloalkenylene, phenylene, or a 5-6 membered heterocyclene having 1 or 2 heteroatoms selected from N, O or S;

Alk^1-Q^1-Alk^2;

Alk^1-RG^1- Q^1-Alk^2

Alk^1-RG^1-Q^1-Alk^2-Q^1-Alk^3; and

Alk^1- Q^1-RG^1-Q^1-Alk^2;

wherein:

Alk^1 is C_{1-6}alkylene;

each Q^1 is the same or different and is -O-, -S-, -N(H)-, -N(C_{1-4}alkyl)-, -C(O)N(H)-, -C(O)N(C_{1-4}alkyl)-,-N(H)C(O)-, or -N(C_{1-4}alkyl)C(O)-;

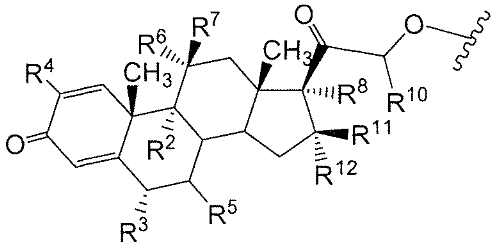
Alk^2 and Alk^3 are each the same or different and are C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene;

RG^1 is phenylene or pyridylene each optionally substituted by 1, 2, 3 or 4 substituents selected from halo, C_{1-6}alkyl, C_{1-4}haloalkyl, OH, C_{1-4}alkylOH, O-C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl, N(C_{1-6}alkyl)$_2$, and CN;

and

MRA is a moiety having muscarinic receptor antagonist activity.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein Steroid is a corticosteroid moiety of formula:



wherein:

each R^2, R^3, R^4, and R^5 are the same or different and are independently H, C_{1-4}alkyl or halo;

R^6 and R^7 are the same or different and are independently H or OH; or R^6 and R^7 taken together with the carbon to which they are attached form a >C=O group;

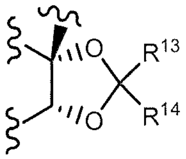
R^8 is H, OH, O(CO)C_{1-4}alkyl, or O(CO)OCi $_{-4}$alkyl;

each R^{10} and R^{11} is the same or different and is independently H or C_{1-4}alkyl;

R^{12} is H, OH, or C_{1-4}alkyl; or

R^{11} and R^{12} taken together with the carbon to which they are attached form a >=CH_2 group; or

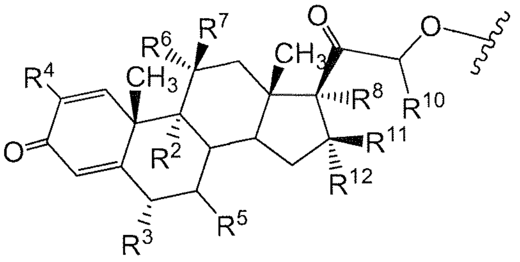
R^{12} and R^8 taken together with the carbons to which they are attached form a 1,3-dioxolane ring represented by formula B:



formula B;

wherein one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, $C_{1.10}$alkyl, C_{2-}ioalkenyl, C_{2-}ioalkynyl, optionally substituted $C_{3.10}$cycloalkyl, optionally substituted C_{3-}iocycloalkenyl, or optionally substituted 5-6 membered heterocycle wherein 1 or 2 ring atoms are selected from N, O and S, and wherein said cycloalkyi, cycloalkenyl, and said heterocycle are each optionally substituted 1, 2 or 3 times with a substituent selected from halo, C_{1-4}alkyl, and O-C_{1-4}alkyl.

3. The compound according to any of claims 1-2 or a pharmaceutically acceptable salt thereof, wherein Steroid is a corticosteroid moiety of formula:



wherein:

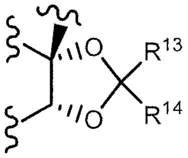
R^2, R^3, R^4, and R^5 are the same or different and are each independently H, methyl, F or Cl;

R^6 is H;

R^7 is OH;

R^{10} and R^{11} are H;

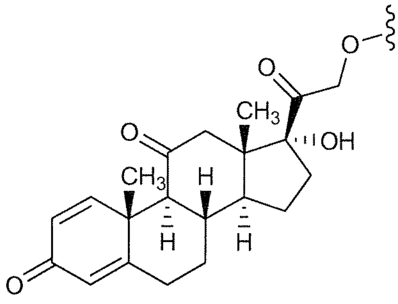
R^{12} and R^8 taken together with the carbons to which they are attached form a 1,3-dioxolane ring represented by formula B:



formula B;

one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, C_1-C_{10}alkyl, or C_3-C_{10}cycloalkyl.

4. The compound according to any of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein Steroid is a corticosteroid moiety of formula: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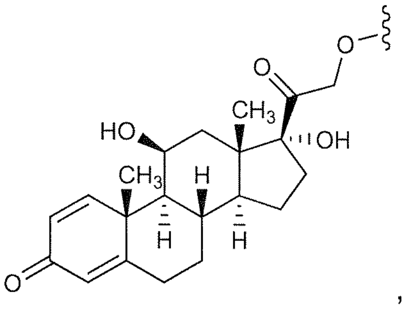
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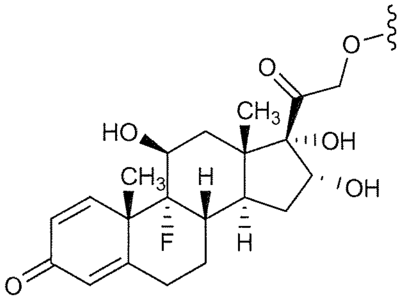
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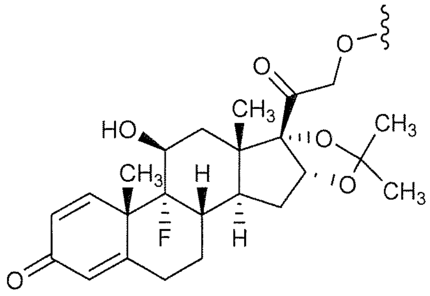
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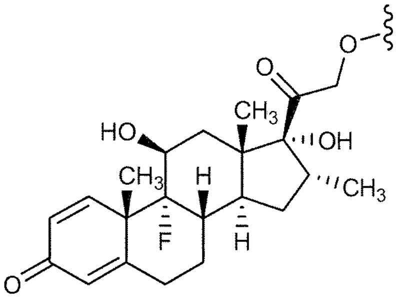
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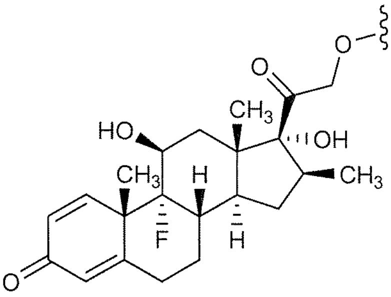
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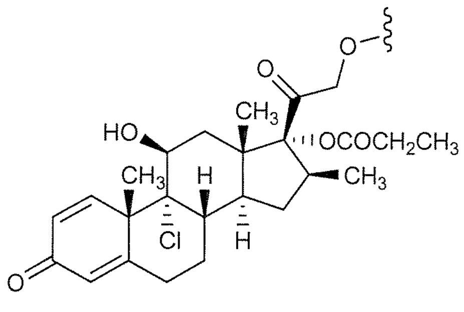
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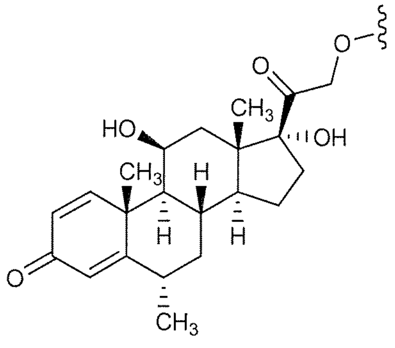
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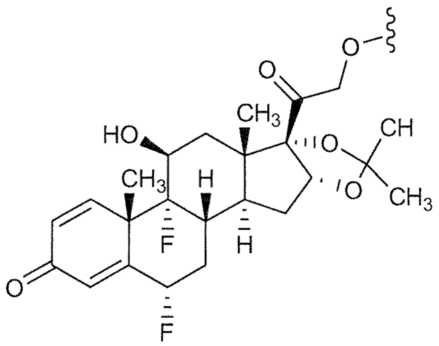
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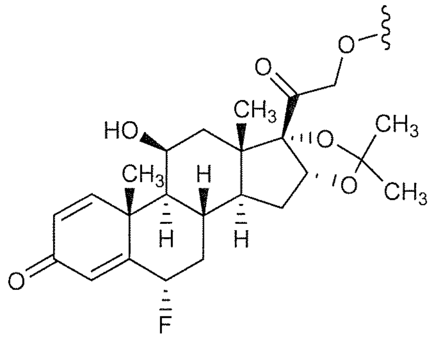
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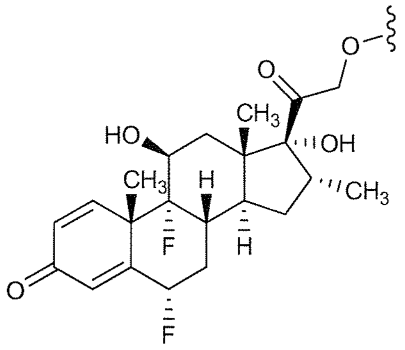

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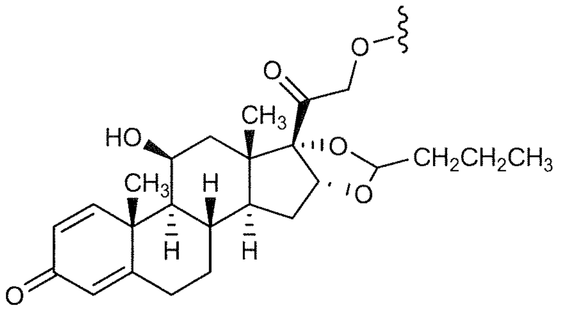

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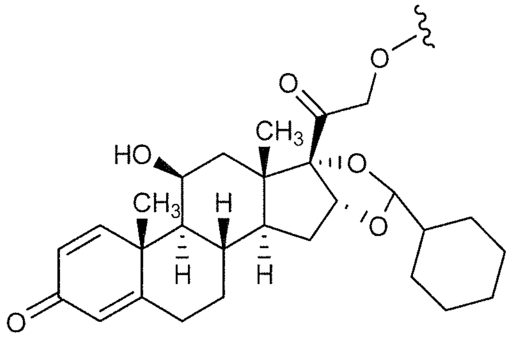

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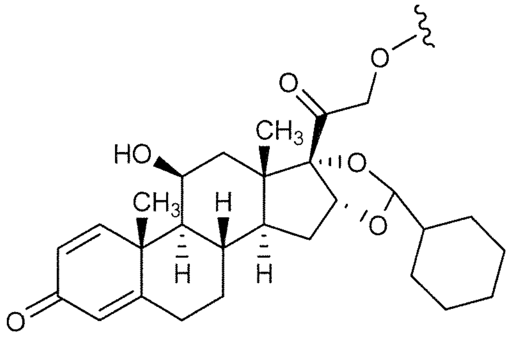
5. The compound according to any of Claims 1-4 or a pharmaceutically acceptable salt thereof, wherein Steroid is a corticosteroid moiety of formula:



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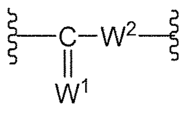
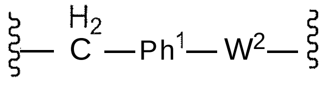
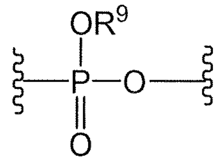
6. The compound according to any of claims 1-5 or a pharmaceutically acceptable salt thereof, wherein L^1 is selected from

a) 
$-\underset{\underset{W^1}{\|}}{C}-W^2-$
, wherein W^1 is O, and W^2 is O, N(H), or N(CH_3);

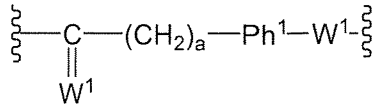
b) 
$-\overset{H_2}{C}-Ph^1-W^2-$
, wherein Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo or methyl or twice with the same or different

substituents selected from halo and methyl, and W^2 is O, N(H), or $N(CH_3)$;

c) 

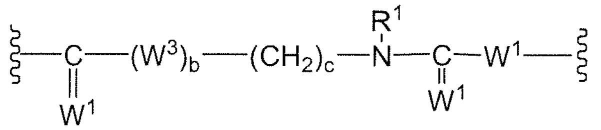
$-P(=O)(OR^9)-O-$

, wherein R^9 is H;

d) 

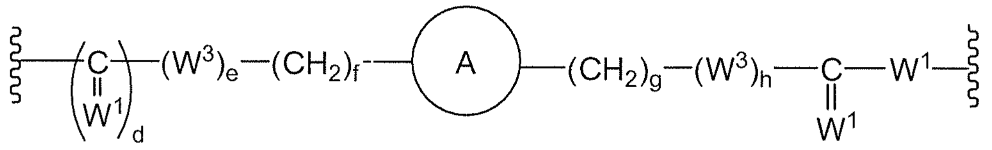
$-C(=W^1)-(CH_2)_a-Ph^1-W^1-$

, wherein each W^1 is O, a is 1 or 2, and Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo or methyl or twice with the same or different substituents selected from halo and methyl;

e) 

$-C(=W^1)-(W^3)_b-(CH_2)_c-N(R^1)-C(=W^1)-W^1-$

, wherein each W^1 is 0 , b is 0 and c is 1, 2 or 3, or b is 1, W^3 is N(H) and c is 2 or 3, and R^1 is H or CH_3;

f) 

$-(C(=W^1))_d-(W^3)_e-(CH_2)_f-(A)-(CH_2)_g-(W^3)_h-C(=W^1)-W^1-$

,

wherein

d and e are both 0 and f is 1, or

d is 1, e is 1, $(W^3)_e$ is O, and f is 0, 1, 2 or 3, or

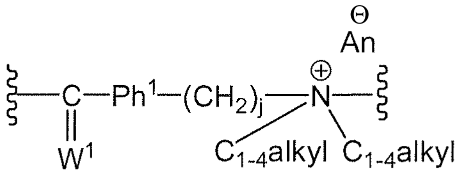
d is 1, e is 0 and f is 0, 1, 2 or 3,

Ring A is phenyl or pyridyl each optionally substituted once or twice with the same or different substituent selected from halo and methyl,

g is 0, 1 or 2,

h is 0 or h is 1 and $(W^3)_h$ is O, and

each W^1 is O;

g) 

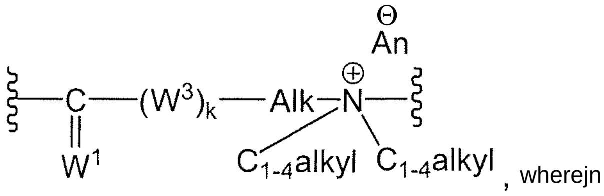
$-C(=W^1)-Ph^1-(CH_2)_j-N^{\oplus}(C_{1\text{-}4}alkyl)(C_{1\text{-}4}alkyl)-\ An^{\ominus}$

, wherein

W^1 is O,

Ph^1 is unsubstituted phenyl or phenyl substituted once with a halo or methyl or twice with the same or different substituents selected from halo and methyl, and

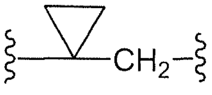
j is 1, 2 or 3;

h) 

, wherejn

W^1 is O,

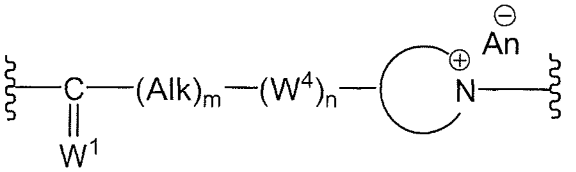
k is 0, and

Alk is $C_{1\text{-}4}$alkylene, -CH(NH_2)-(CH_2)$_4$-, -CH(AA)-, or  ; or

W^1 is O,

k is 1 and W^3 is O or N(CH_3), and

Alk is $C_{1\text{-}4}$alkylene;

i) 

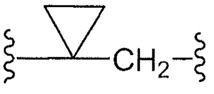
, wherein

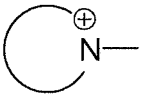
W^1 is O,

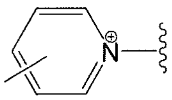
m and n are both 0,

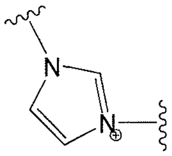
or m is 1 and n is 0,

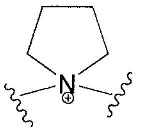
or m and n are both 1 and W^4 is N(H)C(0),

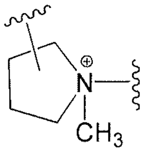
Alk is $C_{1\text{-}4}$alkylene, -CH(NH_2)-(CH_2)$_4$-, -CH(AA)-, or  , and

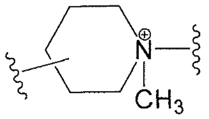
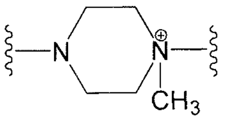
 is selected from



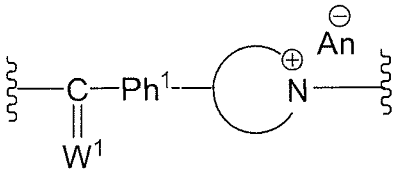






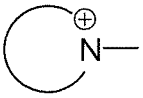
 and 

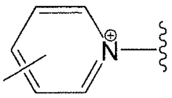
and

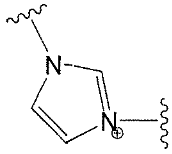
k)  , wherein

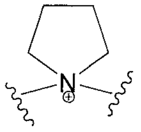
W^1 is O,

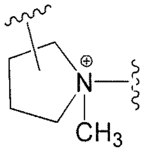
Ph^1 is unsubstituied phenyl or phenyl substituted once with a halo or methyl or twice with the same or different substituents selected from halo and methyl, and

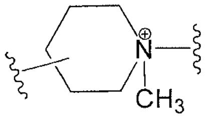
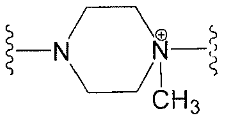
 is selected from

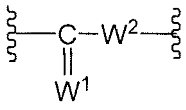


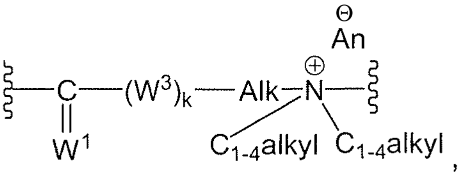






 and 

7. The compound according to any of claims 1-6 or a pharmaceutically acceptable salt thereof, wherein L^1 is  $-\underset{W^1}{\underset{\Vert}{C}}-W^2-$, wherein W^1 is O, and W^2 is O, N(H), or N(CH_3).

8. The compound according to any of claims 1-6 or a pharmaceutically acceptable salt thereof, wherein L^1 is , W^1 is O, k is 0, and Alk is C_{1-4}alkylene.

9. The compound according to any of claims 1-8 or a pharmaceutically acceptable salt thereof, wherein L^2 is -0-.

10. The compound according to claims 1-9 or a pharmaceutically acceptable salt thereof, wherein R^{15} is OH and R^{16} is H.

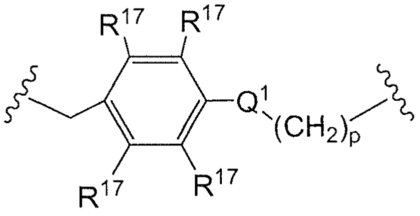
11. The compound according to any of claims 1-10 or a pharmaceutically acceptable salt thereof, wherein L^3 is C_{4-12}alkylene, C_{4-12}alkenylene, or C_{4-12}alkynylene, each optionally substituted once or twice by a C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl or a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S.

12. The compound according to any of claims 1-11 or a pharmaceutically acceptable salt thereof, wherein L^3 is unsubstituted C_{4-12}alkylene.

13. The compound according to any of claims 1-12 or a pharmaceutically acceptable salt thereof, wherein L^3 is linear, unsubstituted Cgalkylene.

14. The compound according to any of claims 1-10 or a pharmaceutically acceptable salt thereof, wherein L^3 is Alk^1-RG^1- Q^1-Alk^2.

15. The compound according to any of claims 1-10 or 14 or a pharmaceutically acceptable salt thereof, wherein L^3 is



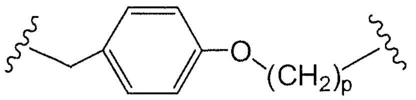
wherein:

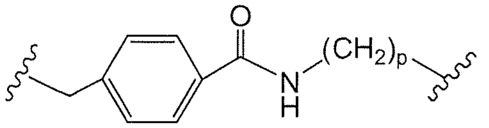
each R^{17} is the same or different and is independently selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, OH, C_{1-4}alkylOH, O-C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl, N(C_{1-6}alkyl)$_2$, and CN;

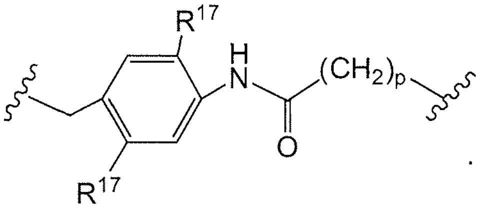
Q^1 is -O-, -C(O)N(H)- or -N(H)C(O)-; and

p is 1, 2, 3, 4, 5 or 6.

16. The compound according to any of claims 1-10 or 14-15 or a pharmaceutically acceptable salt thereof, wherein L^3 is

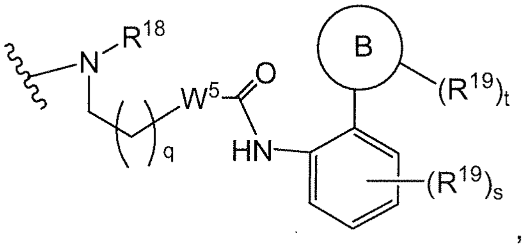
a)  ,

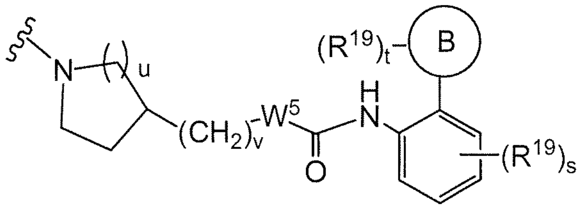
b)  , or

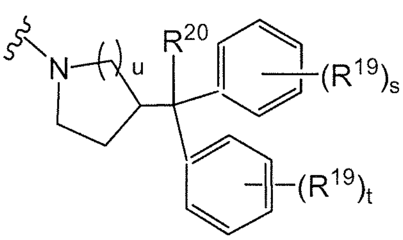
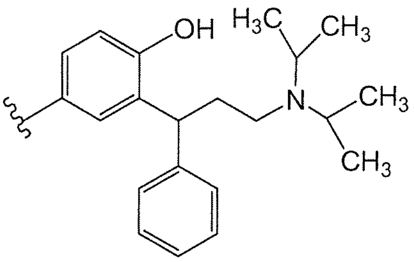
c)  .

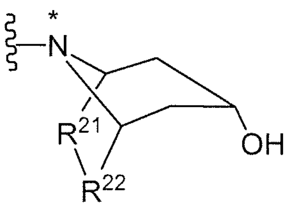
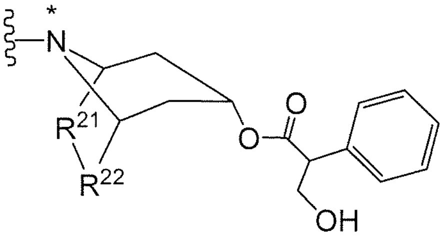
17. The compound according to any of claims 1-16 or a pharmaceutically acceptable salt thereof, wherein MRA is a moiety having muscarinic receptor antagonist activity which is bound to L^3 through a N of MRA.

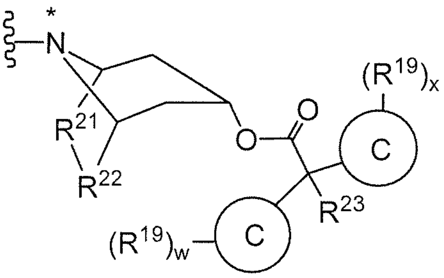
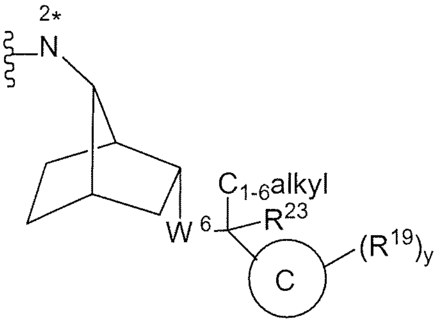
18. The compound according to any of claims 1-16 or a pharmaceutically acceptable salt thereof, wherein MRA is selected from:

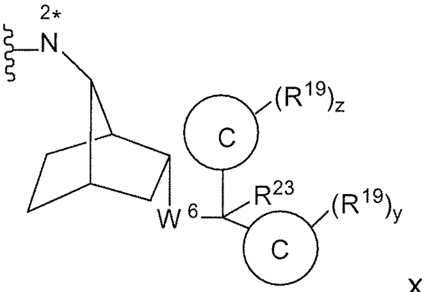
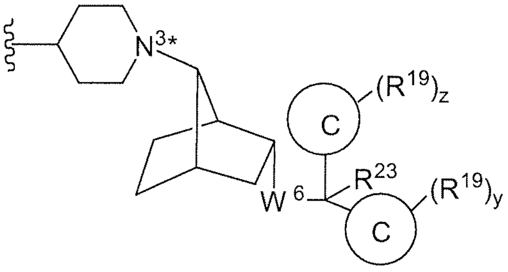
i)  ,

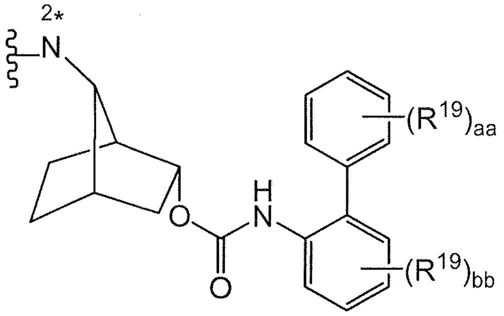
ii)  ,

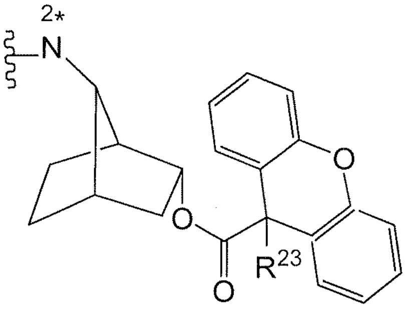
iii)  , iv)  ,

v)  , vi)  ,

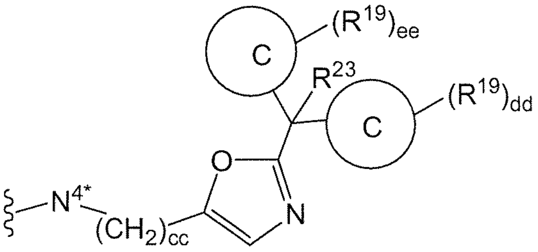
vii)  , viii)  ,

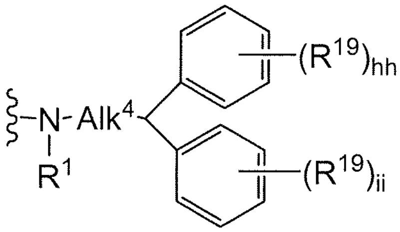
ix)  x)  ,

xi) 

, xii) 

,

xiii) 

, xiv) 

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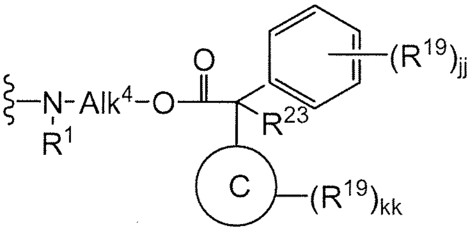
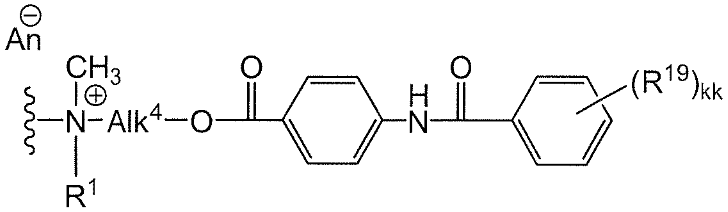
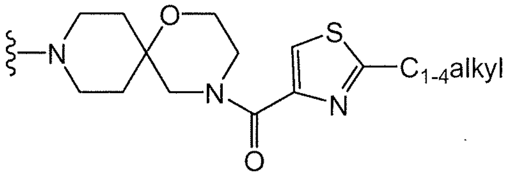
xv) 

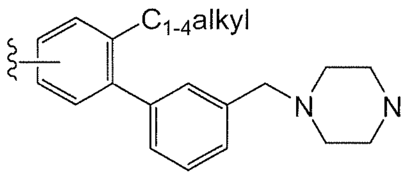
,

xvi) 

,

xvii) 

, and

xviii) 

;

wherein:

R^{18} is **H**, **Ci**$_{-6}$alkyl, **C**$_{3\text{-}6}$alkenyl, **C**$_{3\text{-}6}$alkynyi, or **C**$_{3\text{-}6}$cycloalkyl;

q is 1, 2, 3, 4, 5, 6, or 7;

W^5 is O, **NH,** or **N(C**$_{1\text{-}6}$alkyl);

each s, t, w, x, y, z, aa, bb, dd, ee, hh, ii, jj, and kk, is the same or different and is independently 0, 1, 2, or 3;

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, OH, O-C_{1-6}alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-Ci $_{-6}$alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl and N(C_{1-6}alkyl)$_2$ and CN;

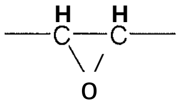
each Ring B is phenyl or 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S;

u is 1 or 2;

v is 0, 1, 2 or 3;

R^{20} is CN, CO_2H, CO_2C_{1-6}alkyl, $CONH_2$, CON(H)C_{1-6}alkyl, CON(C_{1-6}alkyl)$_2$, OH;

N* is N, $(N^{\oplus}H)A\eta^{\theta}$, $(N^{\circledR}\text{-}CH_3)An^{\ominus}$, or $(N^{\oplus}\text{-}CH(CH_3)_2)An^{\ominus}$;

R^{21} and R^{22} together are -CH_2-CH_2-, -CH=CH- or  ;

each Ring C is the same or different and is selected from phenyl, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl having 1 or 2 heteroatoms selected from N, O and S;

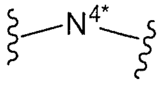
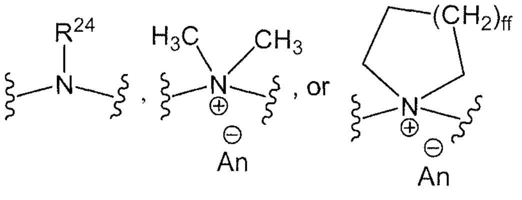
R^{23} is H or OH;

N^{2*} is $N(R^{24})$ or $(N^{\circledR}(CH_3)_2)An^{\ominus}$;

R^{24} is H or C_{1-6}alkyl;

W^6 is -O-C(=O)-, -O-CH_2-, or -N(H)C(=O)- ;

N^{3*} is N or N0(CH_3)$An^{\ominus}$;

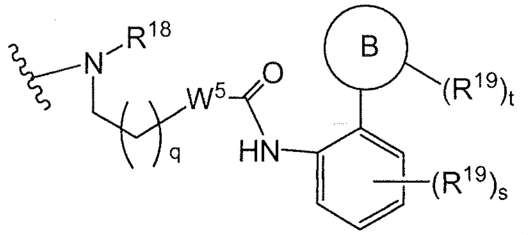
 is  , wherein R^{24} is H or C-i-$_6$alkyl, and ff is 1 or 2;

cc is 1, 2 or 3;

Alk^4 is C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene; and

$An^{\circledR}$ is a pharmaceutically acceptable counterion.

19. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

i)  , wherein

R^{18} is H or C_{1-6}alkyl;

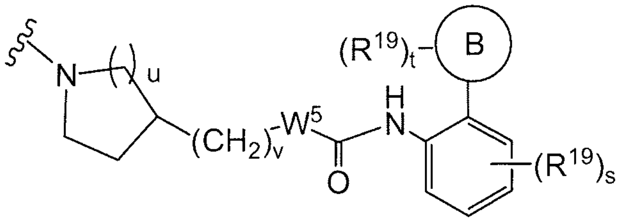
q is 1, 2 or 3;

W^5 is O;

s and t are both 0; and

Ring B is phenyl, thiophenyl, pyridyl or thiazolyl.

20. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

ii)  , wherein

u is 2;

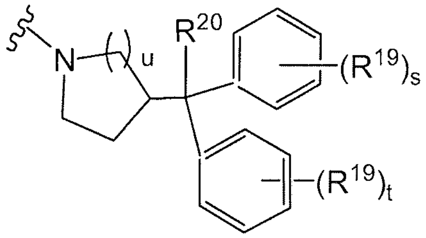
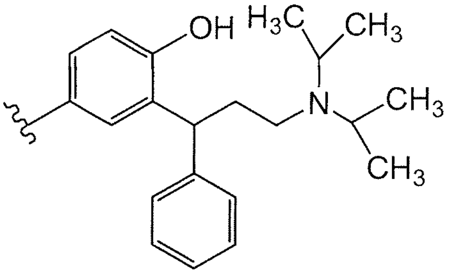
v is 0;

W^5 is O;

s and t are both 0; and

Ring B is phenyl, thiophenyl, pyridyl or thiazolyl.

21. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

iii)  , or iv) 

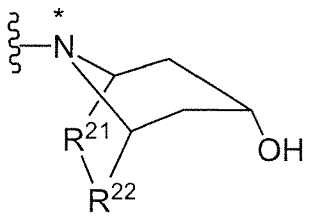
wherein

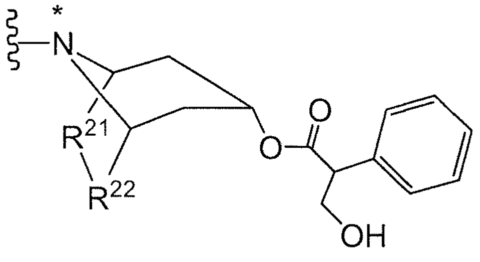
u is 2;

R^{20} is $CONH_2$;

s and t are both 0.

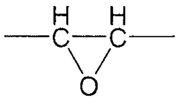
22. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is selected from

v) 

, and vi) 

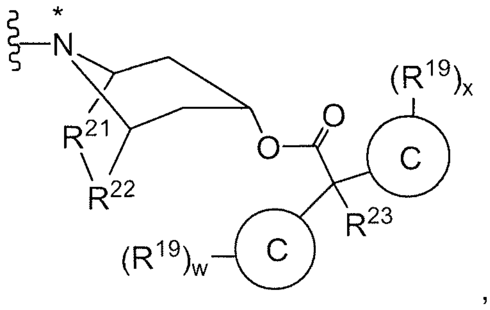
, wherein

N* is N, ($N^{\oplus}H$)$An^{\ominus}$, ($N^{\oplus}$-CH_3)$An^{\ominus}$, or ($N^{\oplus}$-$CH(CH_3)_2$)$An^{\ominus}$; and

R^{21} and R^{22} together are $-CH_2-CH_2-$, $-CH=CH-$ or 

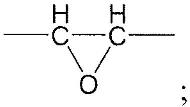
.

23. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

vii) 

, wherein

N* is N, ($N^{\oplus}H$)$An^{\ominus}$, ($N^{\oplus}$-CH_3)$An^{\ominus}$, or ($N^{\oplus}$-$CH(CH_3)_2$)$An^{\ominus}$;

R^{21} and R^{22} together are $-CH_2-CH_2-$, $-CH=CH-$ or 

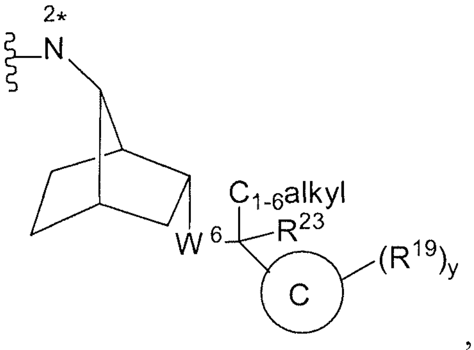
;

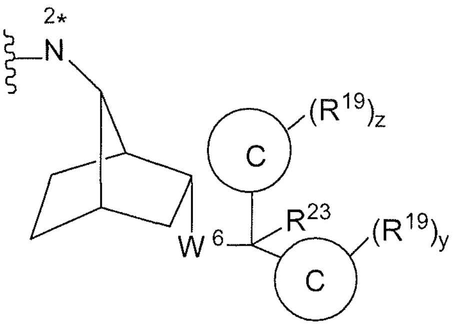
each Ring C is the same or different and is selected from phenyl, cyclohexyl, thiophenyl, thiazolyl, and pyridyl;

w and x are both 0; and

R^{23} is OH.

24. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is selected from

viii) 

, and ix) 

,

wherein

N^{2*} is $N(R^{24})$ or $(N^{®}(CH_3)_2)An^{\ominus}$; R^{24} is H or CH_3;

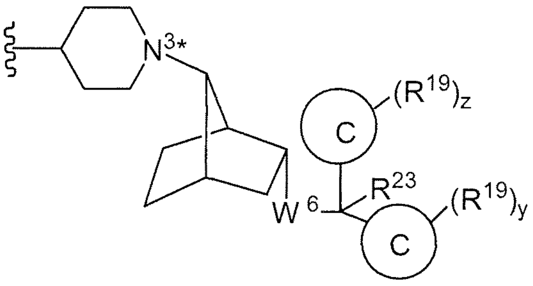
W^6 is -0-C(=0)-;

R^{23} is OH;

each Ring C is the same or different and is selected from phenyl, cyclohexyl, thiophenyl, thiazolyl, and pyridyl; and

y and z are both 0.

25. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

x) 

, wherein

N^{3*} is N or $N9(CH_3)An^{\ominus}$;

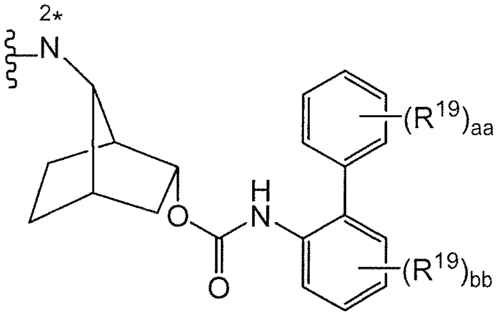
W^6 is -O-C(=O)-;

R^{23} is OH;

each Ring C is the same or different and is selected from phenyl, cyclohexyl, thiophenyl, thiazolyl, and pyridyl; and

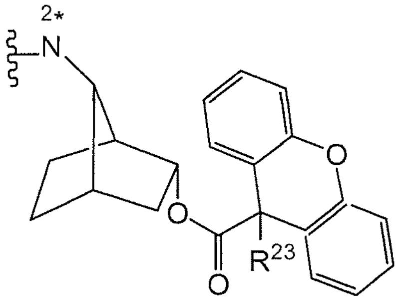
y and z are both 0.

26. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

X!) 

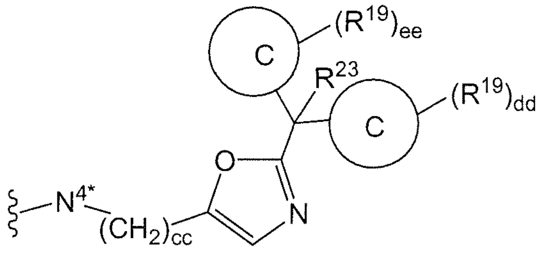
, wherein N^{2*} is $N(R^{24})$ or $(N^{®}(CH_3)_2)An^{\ominus}$; R^{24} is H or CH_3; and aa and bb are both 0.

27. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

xii) 

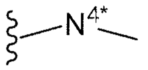
, wherein N^{2*} is $N(R^{24})$ or $N^{W}(CH_3)_2$; R^{24} is H or CH_3; and R^{23} is H or OH.

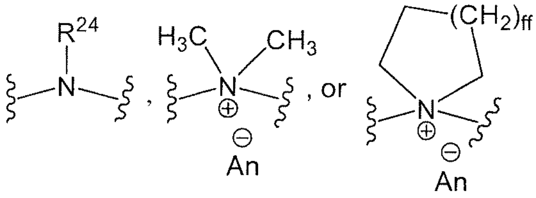
28. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

xiii) 

,

wherein



is 

, wherein ff is 1 or 2;

R^{24} is H or CH_3;

$An^{®}$ is a pharmaceutically acceptable counterion;

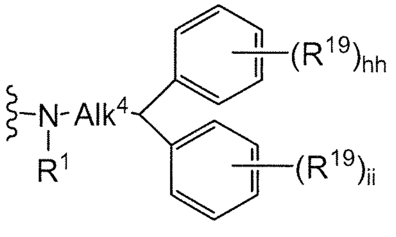
cc is 1;

R^{23} is H or OH;

each Ring C is the same or different and is selected from phenyl, cyclopentyl, cyclohexyl, thiophenyl, thiazolyl, and pyridyl; and

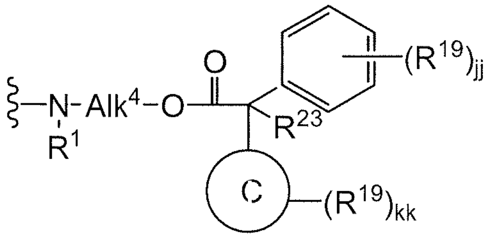
y and z are both 0.

29. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

xiv) 

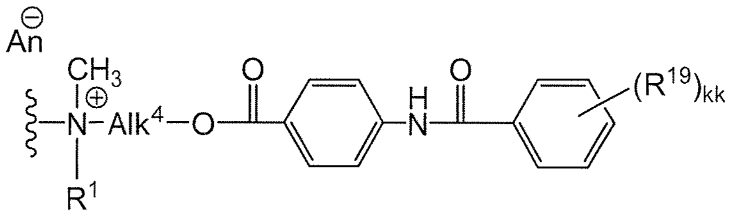
, wherein R^1 is H or CH_3; Alk^4 is C_{1-4}alkylene or C_{2-4}alkenylene; and hh and ii are both 0.

30. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

xv) 

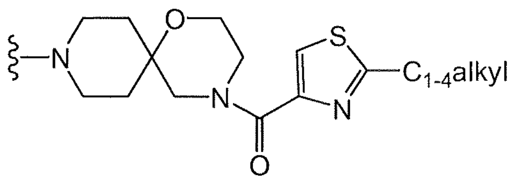
, wherein R^1 is H or CH_3; Alk^4 is C_{1-4}alkylene or C_{2-4}alkenylene; jj and kk are both 0; and Ring C is C_{3-}6cycloalkyl.

31. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

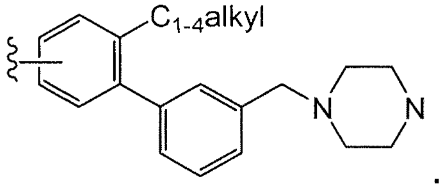
xvi) 

, wherein wherein R^1 is H or CH_3; Alk^4 is C_{1-4}alkylene or C_{2-4}alkenylene; and kk is 0.

32. The compound according to any of claims 1-18 or a pharmaceutically acceptable salt thereof, wherein MRA is

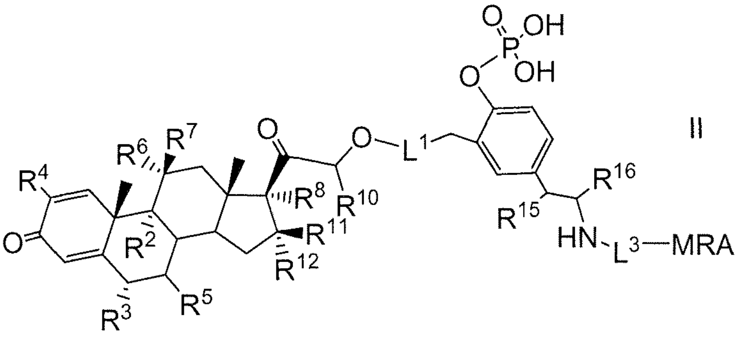


xvii) or xviii)



.

33. The compound according to any of Claims 1-32 or a pharmaceutically acceptable salt thereof, which is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

each R^2, R^3, R^4, and R^5 are the same or different and are independently **H**, **C**$_{1-4}$alkyl or halo;

R^6 and R^7 are the same or different and are independently **H** or **OH;** or R^6 and R^7 taken together with the carbon to which they are attached form a **>C=O** group;

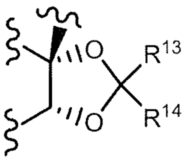
R^8 is **H, OH, O(CO)C$_{1-4}$alkyl**, or **O(CO)OC** $_{1-4}$alkyl;

each R^{10} and R^{11} is the same or different and is independently **H** or **C**$_{1-4}$alkyl;

R^{12} is **H, OH,** or C_{1-4}alkyl; or

R^{11} and R^{12} taken together with the carbon to which they are attached form a **>=CH$_2$** group; or

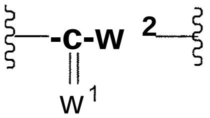
R^{12} and R^8 taken together with the carbons to which they are attached form a 1,3-dioxolane ring represented by formula B:

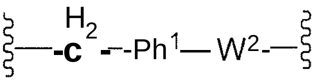

formula B;

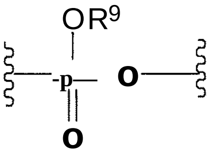
wherein one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, $C_{1\text{-}10}$alkyl, $C_{2\text{-}}$i o alkenyl, $C_{2\text{-}1}$o alkynyl, optionally substituted Cs.-iocycloalkyl, optionally substituted $C_{3\text{-}10}$cycloalkenyl, or optionally substituted 5-6 ring atom heterocycle wherein 1 or 2 ring atoms are selected from N, O and S, and wherein said cycloalkyl, cycloalkenyl, and said heterocycle are each optionally substituted 1, 2 or 3 times with a substituent selected from halo, $C_{1\text{-}4}$alkyl, and 0-Ci $_{-4}$alkyl;

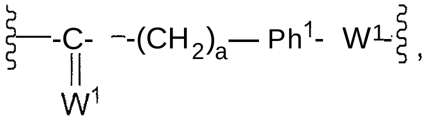
L^1 is a selected from

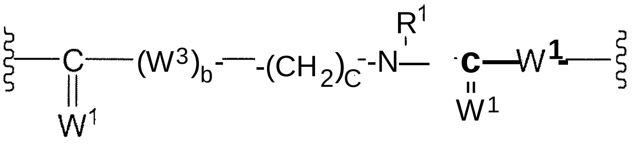
a bond,

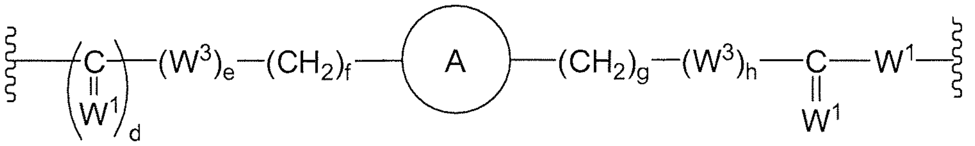

$-C(=W^1)-W^2-$,

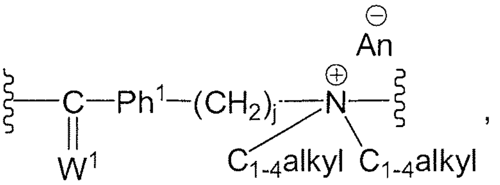

$-CH_2-Ph^1-W^2-$,

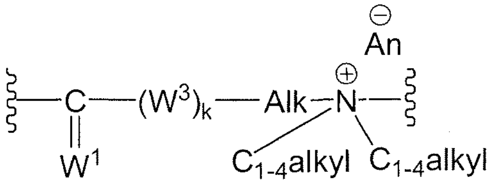

$-P(OR^9)(=O)-O-$,

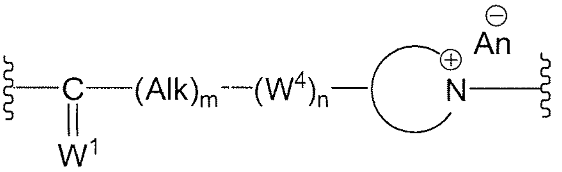

$-C(=W^1)-(CH_2)_a-Ph^1-W^1-$,

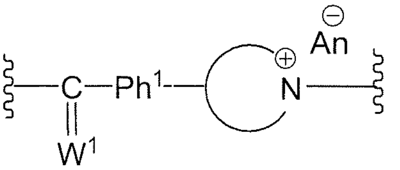

$-C(=W^1)-(W^3)_b-(CH_2)_c-N(R^1)-C(=W^1)-W^1-$,


$-(C(=W^1))_d-(W^3)_e-(CH_2)_f-A-(CH_2)_g-(W^3)_h-C(=W^1)-W^1-$,


$-C(=W^1)-Ph^1-(CH_2)_j-N^{\oplus}(C_{1\text{-}4}alkyl)(C_{1\text{-}4}alkyl)-\ An^{\ominus}$,


$-C(=W^1)-(W^3)_k-Alk-N^{\oplus}(C_{1\text{-}4}alkyl)(C_{1\text{-}4}alkyl)-\ An^{\ominus}$,


$-C(=W^1)-(Alk)_m-(W^4)_n-N^{\oplus}-\ An^{\ominus}$, and


$-C(=W^1)-Ph^1-N^{\oplus}-\ An^{\ominus}$;

wherein:

each W^1 is the same or different and is O or S;

W^2 is O, S or $N(R^1)$;

Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, N(H)C_{1-4}alkyl, and N(C_{1-4}alkyl)$_2$;

R^9 is H, C_{1-4}alkyl, or phenyl;

a is 0, 1, 2, 3, 4, 5 or 6;

each R^1 is the same or different and is independently H or C_{1-4}alkyl;

b is 0 and c is 1, 2, 3, 4, 5 or 6, or b is 1 and c is 2, 3, 4, 5 or 6;

each W^3 is the same or different and is independently -O- or -N(R ^{1})-;

d and e are both 0 and f is 1 or

d is 1, e is 0 or 1 and f is 0, 1, 2, 3, 4, 5 or 6;

Ring A is phenyl, pyridyl or pyrimidyl each optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, N(H)C_{1-4}alkyl, and N(C_{1-4}alkyl)$_2$;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0 or 1;

j is 0, 1, 2, 3, 4, 5 or 6;

k is 0 or 1;

each Alk is the same or different and is selected from

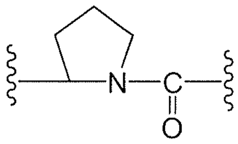
a C_1-$_6$alkylene or Ci$_{-6}$alkenylene each optionally substituted on nonadjacent carbons by 1, 2 or 3 substituents, selected from halo, OH, C_{1-4}alkoxyl, NH_2, N(H)C_{1-4}alkyl, or N(C·|.$_4$alkyl)$_2$;

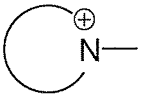
C_{3-6}cycloalkylene-Ci $_{-4}$alkylene; and

-CH(AA)- wherein AA is a proteinogenic amino acid side chain;

m is 0 or 1;

n is 0 or 1 and W^4 is -N(H)-C(O)-;

or (Alk)$_m$ and (W^4)$_n$ join to form:  ;



is a quaternary N-heteroaryl having 5 or 6 ring atoms wherein one ring atom is a quaternary N and optionally one additional ring atom is N; or a quaternary N-heterocycle having 5 or 6 ring atoms wherein one ring atom is a quaternary N-methyl and optionally one additional ring atom is N, wherein said N-heteroaryl and said N-heterocycle are optionally substituted on any available ring atom with C_{1-4}alkyl;

each An® is a pharmaceutically acceptable counterion;

L^2 is a -O- or -0-CH $_2$-0-;

R^{15} is H, F, OH or methyl;

R^{16} is H, methyl or ethyl;

L^3 is selected from:

$C_{4\cdot12}$alkylene, C_{4-12}alkenylene, or C_{4-12}alkynylene, each optionally substituted once or twice by a C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl or a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S;

C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene wherein one carbon of said alkylene, alkenylene or alkynylene is *optionally* replaced by a c 3-6cycloalkylene, C_3.6cycloalkenylene, phenylene, or a 5-6 membered heterocyclene having 1 or 2 heteroatoms selected from N, O or S;

Alk^1-Q^1-Alk^2;

Alk^1-RG^1- Q^1-Alk^2

Alk^1-RG^1-Q^1-Alk^2-Q^1-Alk^3; and

Alk^1- Q^1-RG^1-Q^1-Alk^2;

wherein:

Alk^1 is C_{1-6}alkylene;

each Q^1 is the same or different and is -O-, -S-, -N(H)-, -N(Ci $_{-4}$alkyl)-, -C(0)N(H>, -C(O)N(C $_{1-4}$a!kyl)-,-N(H)C(O)-, or -N(C $_{1-4}$alkyl)C(O)-;

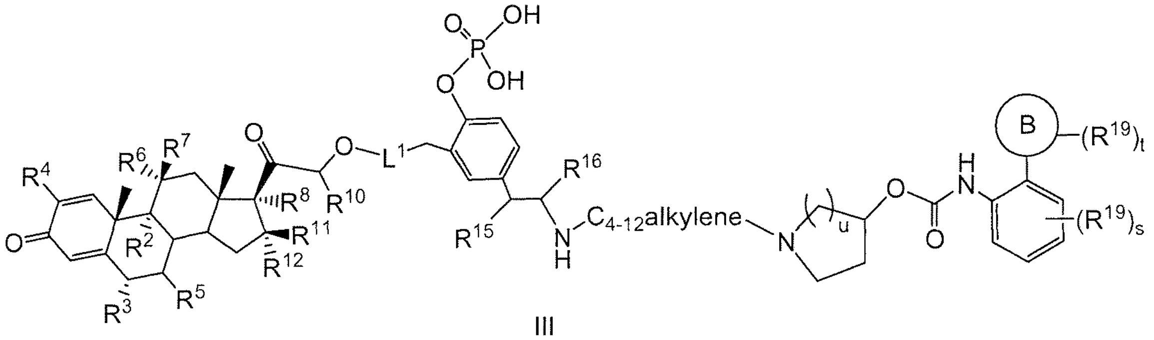
Alk^2 and Alk^3 are each the same or different and are C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene;

RG^1 is phenylene or pyridylene each optionally substituted by 1, 2, 3 or 4 substituents selected from halo, C_{1-6}alkyl, $C_{1\text{\textunderscore}4}$haloalkyl, OH, C_{1-4}alkylOH, O-C_{1-6}alkyl, S-Ci $_{-6}$alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)C_{1-6}alkyl, N(C_{1-6}alkyl)$_2$, and CN;

and

MRA is a moiety having muscarinic receptor antagonist activity.

34. The compound according to any of Claims 1-32 or a pharmaceutically acceptable salt thereof, which is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

each R^2, R^3, R^4, and R^5 are the same or different and are independently H, C_{1-4}alkyl or halo;

R^6 and R^7 are the same or different and are independently H or OH; or R^6 and R^7 taken together with the carbon to which they are attached form a >C=0 group;

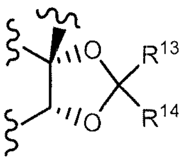
R^8 is H, OH, O(CO)Ci $_{-4}$alkyl, or O(CO)OC $_{1-4}$alkyl;

each R^{10} and R^{11} is the same or different and is independently H or C_{1-4}alkyl;

R^{12} is H, OH, or C_{1-4}alkyl; or

R^{11} and R^{12} taken together with the carbon to which they are attached form a >=CH $_2$ group; or

R^{12} and R^8 taken together with the carbons to which they are attached form a 1,3-dioxolane ring represented by formula B:

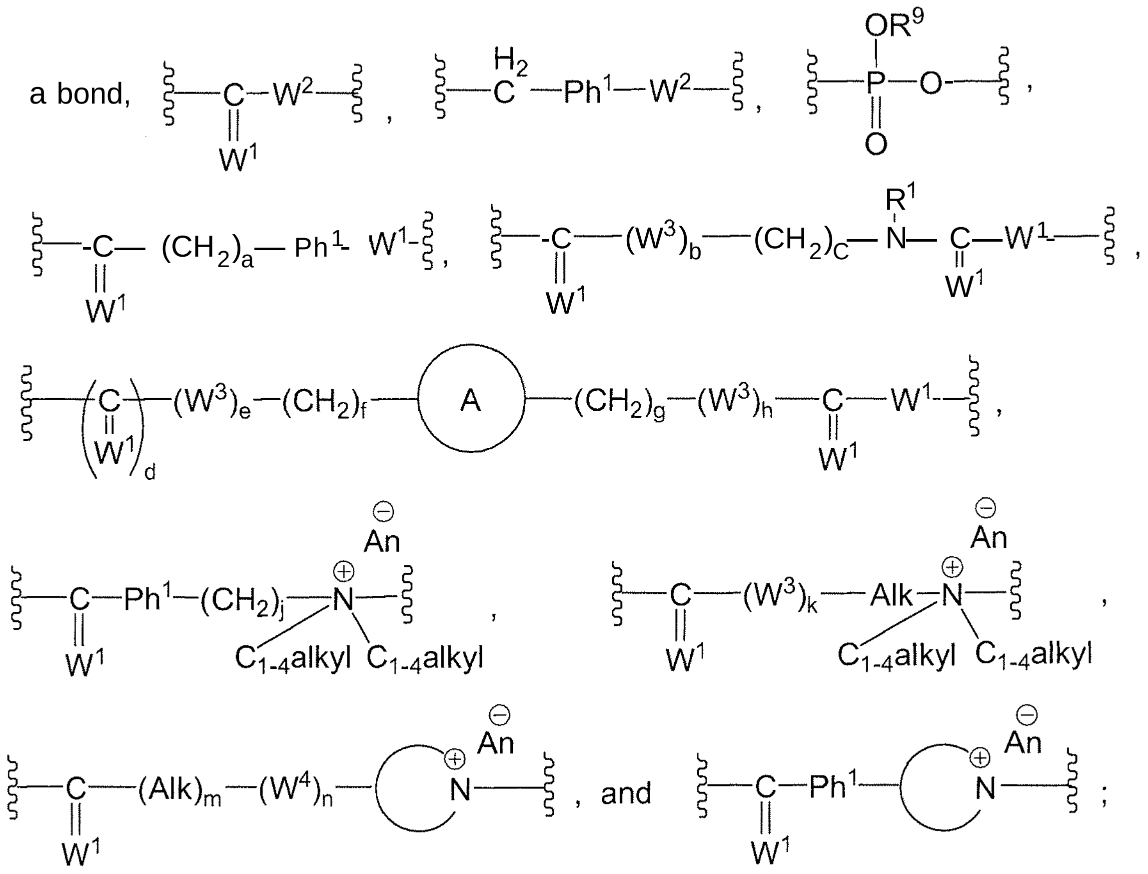


formula B;

wherein one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, $C_{1\text{-}10}$alkyl, C-2-1 0 alkenyl, $C_{2\text{-}}$i o alkynyl, optionally substituted C_3--iocycloalkyl, optionally substituted C_3.iocycloalkenyl, or optionally substituted 5-6 ring atom heterocycle wherein 1 or 2 ring atoms are selected from N, O and S, and wherein said cycloalkyl, cycloalkenyl, and said heterocycle are each optionally substituted 1, 2 or 3 times with a substituent selected from halo, C$_{1-4}$alkyl, and O-C$_{1-4}$alkyl;

L^1 is a selected from

a bond,



wherein:

each W^1 is the same or different and is O or S;

W^2 is O, S or N(R^1);

Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, C$_{1-4}$alkyl, OH, C$_{1-4}$alkoxyl, NH$_2$, N(H)C$_{1-4}$alkyl, and N(C$_{1-4}$alkyl)$_2$;

R^9 is H, C$_{1-4}$alkyl, or phenyl;

a is 0, 1, 2, 3, 4, 5 or 6;

each R^1 is the same or different and is independently H or C$_{1-4}$alkyl;

b is 0 and c is 1, 2, 3, 4, 5 or 6, or b is 1 and c is 2, 3, 4, 5 or 6;

each W^3 is the same or different and is independently -O- or -N(R^1)-;

d and e are both 0 and f is 1 or

d is 1, e is 0 or 1 and f is 0, 1, 2, 3, 4, 5 or 6;

Ring A is phenyl, pyridyl or pyrimidyl each optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, N(H)C_{1-4}alkyl, and N(C_{1-4}alkyl)$_2$;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0 or 1;

j is 0, 1, 2, 3, 4, 5 or 6;

k is 0 or 1;

each Alk is the same or different and is selected from

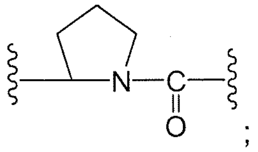
a C_{1-6}alkylene or C_{1-6}alkenylene each optionally substituted on nonadjacent carbons by 1, 2 or 3 substituents, selected from halo, OH, C_{1-4}alkoxyl, NH_2, N(H)C_{1-4}alkyl, or N(C_{1-4}alkyl)$_2$;

C_{3-6}cycloalkylene-C_{1-4}alkylene; and

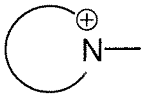
-CH(AA)- wherein AA is a proteinogenic amino acid side chain;

m is 0 or 1;

n is 0 or 1 and W^4 is -N(H)-C(O)-;

or (Alk)$_m$ and (W^4)$_n$ join to form: 

;



is a quaternary N-heteroaryl having 5 or 6 ring atoms wherein one ring atom is a quaternary N and optionally one additional ring atom is N; or a quaternary N-heterocycle having 5 or 6 ring atoms wherein one ring atom is a quaternary N-methyl and optionally one additional ring atom is N, wherein said N-heteroaryl and said N-heterocycle are optionally substituted on any available ring atom with C_{1-4}alkyl;

each $A\eta^{\theta}$ is a pharmaceutically acceptable counterion;

L^2 is a -O- or -O-CH_2-O-;

R^{15} is H, F, OH or methyl;

R^{16} is H, methyl or ethyl;

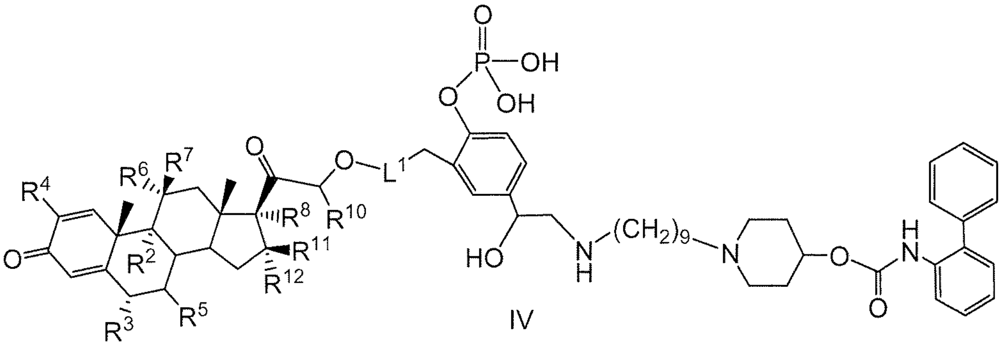
u is 2;

s and t are both 0 or 1;

Ring B is phenyl, thiophenyl, pyridyl or thiazolyl; and

each R^{19} is the same or different and is independently selected from halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, OH, O-Ci $_{-6}$alkyl, O-benzyl, CO_2H, CO_2C_{1-6}alkyl, S-C_{1-6}alkyl, SO_2C_{1-6}alkyl, NH_2, N(H)Ci $_{-6}$alkyl and N(C_{1-6}alkyl)$_2$ and CN.

35. The compound according to any of Claims 1-32 or a pharmaceutically acceptable salt thereof, which is a compound of Formula IV:


IV

or a pharmaceutically acceptable salt thereof, wherein:

each R^2, R^3, R^4, and R^5 are the same or different and are independently H, C_{1-4}alkyl or halo;

R^6 and R^7 are the same or different and are independently H or OH; or R^6 and R^7 taken together with the carbon to which they are attached form a >C=O group;

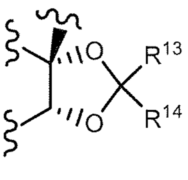
R^8 is H, OH, O(CO)C_{1-4}alkyl, or O(CO)OC_{1-4}alkyl;

each R^{10} and R^{11} is the same or different and is independently H or C_{1-4}alkyl;

R^{12} is H, OH, or C_{1-4}alkyl; or

R^{11} and R^{12} taken together with the carbon to which they are attached form a >=CH_2 group; or

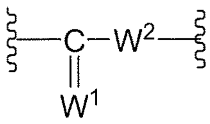
R^{12} and R^8 taken together with the carbons to which they are attached form a 1,3-dioxolane ring represented by formula B:


formula B;

wherein one of R^{13} and R^{14} is H, methyl or ethyl and the other is H, Ci-i $_0$alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-}iocycloalkenyl, or optionally substituted 5-6 ring atom heterocycle wherein 1 or 2 ring atoms are selected from N, O and S, and wherein said cycloalkyi, cycloalkenyl, and said heterocycle are each optionally substituted 1, 2 or 3 times with a substituent selected from halo, Ci_{-4}alkyl, and O-Ci_{-4}alkyl;

L^1 is a selected from

a bond,



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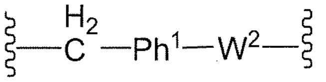

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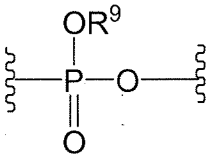

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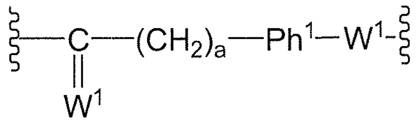

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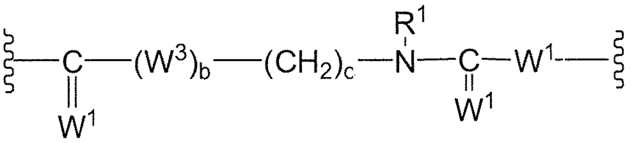

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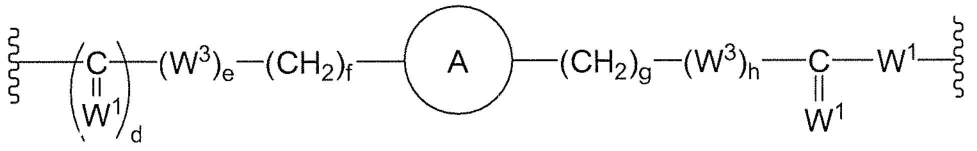

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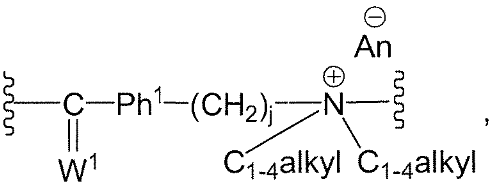

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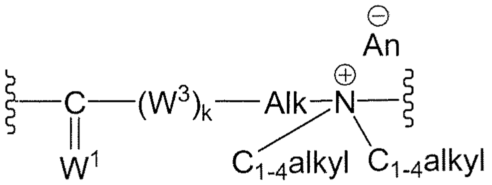

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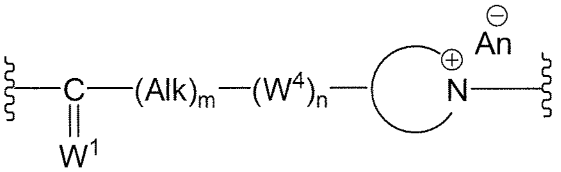
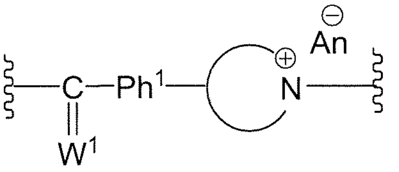


, and



;

wherein:

each W^1 is the same or different and is O or S;

W^2 is O, S or $N(R^1)$;

Ph^1 is phenyl optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, $N(H)C_{1-4}$alkyl, and $N(Ci_{-4}alkyl)_2$;

R^9 is H, C_{1-4}alkyl, or phenyl;

a is 0, 1, 2, 3, 4, 5 or 6;

each R^1 is the same or different and is independently H or C_{1-4}alkyl;

b is 0 and c is 1, 2, 3, 4, 5 or 6, or b is 1 and c is 2, 3, 4, 5 or 6;

each W^3 is the same or different and is independently -O- or -N(R ^{1})-;

d and e are both 0 and f is 1 or

d is 1, e is 0 or 1 and f is 0, 1, 2, 3, 4, 5 or 6;

Ring A is phenyl, pyridyl or pyrimidyl each optionally substituted on any available carbon with a substituent selected from halo, C_{1-4}alkyl, OH, C_{1-4}alkoxyl, NH_2, N(H)Ci$_{-4}$alkyl, and N(C_{1-4}alkyl)$_2$;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0 or 1;

j is 0, 1, 2, 3, 4, 5 or 6;

k is 0 or 1;

each Alk is the same or different and is selected from

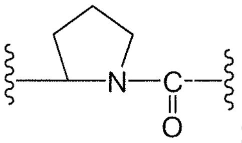
c$_{1-6}$alkylene or C_{1}-$_{6}$alkenylene each optionally substituted on nonadjacent carbons by 1, 2 or 3 substituents, selected from halo, OH, C_{1-4}alkoxyl, NH_2, N(H)Ci$_{-4}$alkyl, or N(Ci-$_4$alkyl)$_2$;

C_{3-6}cycloalkylene-C $_{1-4}$alkylene; and

-CH(AA)- wherein AA is a proteinogenic amino acid side chain;

m is 0 or 1;

n is 0 or 1 and W^4 is -N(H)-C(O)-;

or $(Alk)_m$ and $(W^4)_n$ join to form: 

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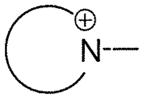
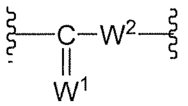


is a quaternary N-heteroaryl having 5 or 6 ring atoms wherein one ring atom is a quaternary N and optionally one additional ring atom is N; or a quaternary N-heterocycle having 5 or 6 ring atoms wherein one ring atom is a quaternary N-methyl and optionally one additional ring atom is N, wherein said N-heteroaryl and said N-heterocycle are optionally substituted on any available ring atom with C_{1-4}alkyl;

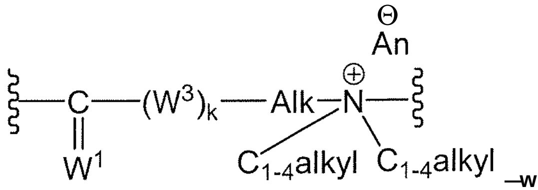
each $A\eta^{\theta}$ is a pharmaceutically acceptable counterion;

35. The compound according to Claim 34 or a pharmaceutically acceptable salt thereof, wherein L^1 is:



$-C(=W^1)-W^2-$

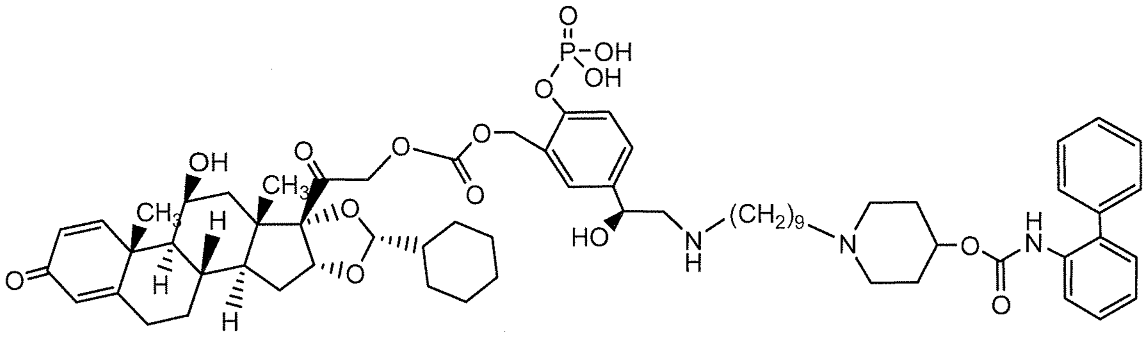
, wherein **W^1** is **O,** and **W^2** is **O, N(H),** or $N(CH_3)$; or



$-C(=W^1)-(W^3)_k-\mathrm{Alk}-N^{\oplus}(C_{1-4}\mathrm{alkyl})(C_{1-4}\mathrm{alkyl})-\ \ \mathrm{An}^{\ominus}$

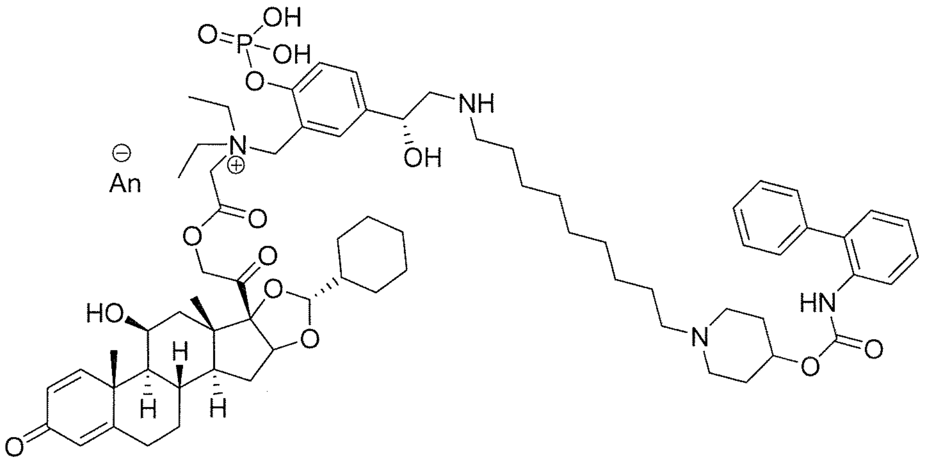
—wherein W^1 is O, k is 0, and Alk is C_{1-4}alkylene and $\mathrm{An}^{®}$ is a pharmaceutically acceptable counterion.

36. The compound



or a pharmaceutically acceptable salt thereof.

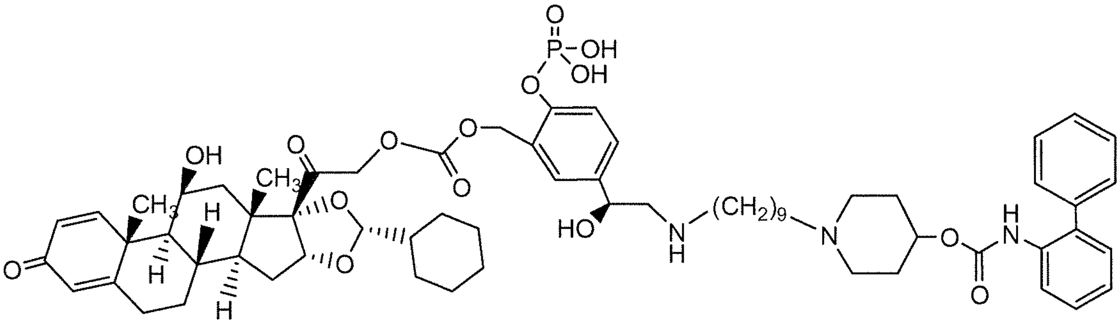
37. The compound



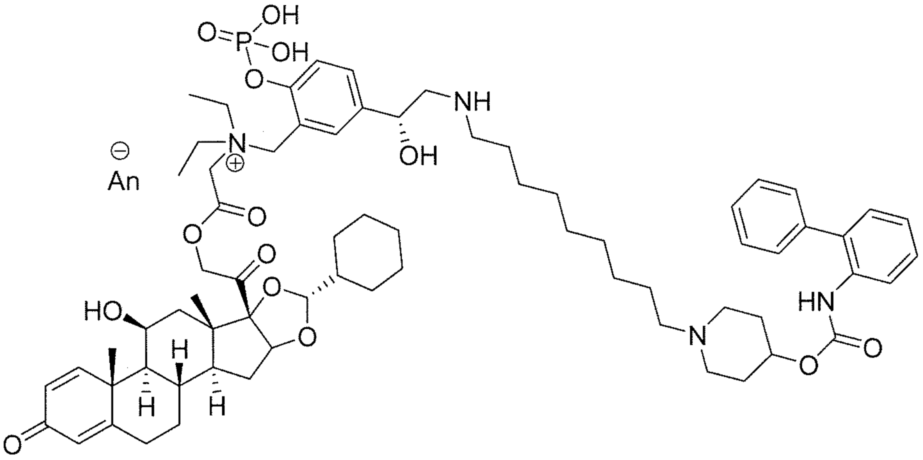
or a pharmaceutically acceptable salt thereof, wherein $\mathrm{An}^{\ominus}$ is a pharmaceutically acceptable counterion.

38. A composition comprising a compound according to any one of claims 1-37 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, diluent or carrier.

39. The composition according to claim 38 wherein the compound is



or



or a pharmaceutically acceptable salt thereof.

40. The composition according to any of Claims 38-39 wherein said composition is suitable for inhalation.

41. The composition according to any of claims 38-40 wherein said composition is a solution for aerosolization and administration by nebulizer.

42. The composition according to any of claims 38-40 wherein said composition is suitable for administration by metered dose inhaler or dry powder inhaler.

43. The composition according to any of claims 38-40 wherein said composition is a dry powder.

44. The composition according to any of claims 38-40 further comprising a therapeutically active agent selected from anti-inflammatory agents, anticholinergic agents, β-agonists, peroxisome proliferator-activated receptor agonists, epithelial sodium channel blockers, kinase inhibitors, antiinfective agents and antihistamines.

45. The composition according to Claim 44, wherein said therapeutically active agent is a corticosteroid.

46. The composition according to Claim 45, wherein said corticosteroid is ciclesonide, desisobutyryl ciclesonide, budesonide mometasone, fluticasone propionate, or fluticasone furoate.

47. The composition according to Claim 44, wherein said therapeutically active agent is a PDE4 inhibitor.

48. The composition according to Claim 44, wherein said therapeutically active agent is tiotropium.

49. The composition according to Claim 44, wherein said therapeutically active agent is salmeterol or R-salmeterol.

50. The composition according to Claim 44, wherein said therapeutically active agent is a peroxisome proliferator-activated receptor gamma agonist.

51. A method comprising administering to a human, an effective amount of a compound according to any of Claims 1-37 or a pharmaceutically acceptable salt thereof.

52. A method for the treatment of pulmonary inflammation or bronchoconstriction in a human in need thereof, comprising administering to said human an effective amount of a compound according to any of Claims 1-37 or a pharmaceutically acceptable salt thereof.

53. A method for the treatment of a disease associated with reversible airway obstruction in a human in need thereof, comprising administering to said human an effective amount of a compound according to any of Claims 1-37 or a pharmaceutically acceptable salt thereof.

54. A method for the treatment of asthma in a human in need thereof, comprising administering to said human an effective amount of a compound according to any of Claims 1-37 or a pharmaceutically acceptable salt thereof.

55. A method for the treatment of COPD in a human in need thereof, comprising administering to said human an effective amount of a compound according to any of Claims 1-37 or a pharmaceutically acceptable salt thereof.

56. A method for the treatment of bronchiectasis in a human in need thereof, comprising administering to said human an effective amount of a compound according to any of Claims 1-37 or a pharmaceutically acceptable salt thereof.

57. A method for the treatment of emphysema in a human in need thereof, comprising administering to said human an effective amount of a compound according to any of Claims 1-37 or a pharmaceutically acceptable salt thereof.

58. A compound according to any of claims 1-37 or a pharmaceutically acceptable salt thereof for use as a medicament.

59. A compound according to any of claims 1-37 or a pharmaceutically acceptable salt thereof for use in the treatment of pulmonary inflammation or bronchoconstriction in a human.

60. A compound according to any of claims 1-37 or a pharmaceutically acceptable salt thereof for use in the treatment of a disease associated with reversible airway obstruction, asthma, COPD, bronchiectasis, or emphysema in a human.

61. A compound according to any of claims 1-37 or a pharmaceutically acceptable salt thereof for use in the treatment of asthma or COPD in a human.

62. The use of a compound according to any one of claims 1-37 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of pulmonary inflammation or bronchoconstriction in a human.

63. The use of a compound according to any one of claims 1-37 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a disease associated with reversible airway obstruction, asthma, COPD, bronchiectasis, or emphysema in a human.

64. A composition comprising a compound according to any one of claims 1-37 or a pharmaceutically acceptable salt thereof for use in the preparation of a medicament for the treatment of pulmonary inflammation or bronchoconstriction in a human.

65. A composition comprising a compound according to any one of claims 1-37 or a pharmaceutically acceptable salt thereof for use in the preparation of a medicament for the treatment of reversible airway obstruction, asthma, COPD, bronchiectasis, or emphysema in a human.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US201Q/06Q312

A. CLASSIFICATION OF SUBJECT MATTER
INV. CO7J51/00 A61K31/573 A61P11/06 A61P11/08 A61P5/44
ADD.

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)
C07J 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 , BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE, 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	WO 2006/138212 AI (CORUS PHARMA INC [US] ; BAKER WILLIAM R [US] ; STASIAK MARCIN [US] ; GIRT) 28 December 2006 (2006-12-28) cited in the application page 4, last paragraph; claim 1; examples 111, 113, 115, 117 -----	1-65
Y	WO 2005/063777 AI (CORUS PHARMA [US] ; BAKER WILLIAM R [US] ; STASIAK MARCIN [US]) 14 July 2005 (2005-07-14) cited in the application examples 37,38 page 4, last paragraph page 34, paragraph 2 page 3, last paragraph ----- -/--	1-65

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

☒ See patent family 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

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"&" document member of the same patent family

Date of the actual completion of the international search 4 May 2011	Date of mailing of the international search report 11/05/2011
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Watchorn, Peter

INTERNATIONAL SEARCH REPORT

International application No

PCT/US201Q/06Q312

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 2008/076269 A2 (GILEAD SCIENCES INC [US]; BAKER WILLIAM R [US]; STASIAK MARCIN [US]; S) 26 June 2008 (2008-06-26) cited in the application page 1, paragraph 2; claim 1; examples 29-84 -----	1-65
Y	EP 1 894 568 Al (NOVARTIS AG [CH]) 5 March 2008 (2008-03-05) page 1, paragraph 1-4 -----	1-65
Y	W0 2009/036243 Al (GLAXO GROUP LTD [GB]; LAINE DRAMANE IBRAHIM [US]) 19 March 2009 (2009-03-19) claims 1,14,36,37 -----	1-65
Y, P	W0 2009/152171 Al (GILEAD SCIENCES INC [US]; BAKER WILLIAM [US]; KIM MUSONG [US]; RUDOLPH) 17 December 2009 (2009-12-17) page 2, lines 23-29; claim 1; examples 46-135 -----	1-65
Y, P	W0 2010/126953 Al (GILEAD SCIENCES INC [US]; BAKER WILLIAM R [US]; KIM MUSONG [US]; PHILL) 4 November 2010 (2010-11-04) page 8, paragraph 2-3; claim 1; examples 1-10 -----	1-65

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US201Q/06Q312

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WO 2010126953 Al	04-11--2010	NONE	