

CCR3 RECEPTOR ANTAGONISTS

The invention relates to certain disubstituted piperidinyl and piperazinyl compounds, in which one of the substituents is a bicyclo-heterocyclalkyl group, that are useful as CCR-3 receptor antagonists, as well as pharmaceutical compositions containing them and their use for treating CCR-3 mediated diseases such as asthma.

Tissue eosinophilia is a feature of a number of pathological conditions such as asthma, rhinitis, eczema and parasitic infections (*see* Bousquet, J. *et al.*, N. Eng. J. Med. 323: 1033-1039 (1990) and Kay, A. B. *et al.*, Br. Med. Bull. 48:51-64 (1992)). In asthma, eosinophil accumulation and activation are associated with damage to bronchial epithelium and hyperresponsiveness to constrictor mediators. Chemokines such as RANTES, eotaxin, and MCP-3 are known to activate eosinophils (*see* Baggiolini, M. *et al.*, Immunol. Today, 15:127-133 (1994), Rot, A. M. *et al.*, J. Exp. Med. 176, 1489-1495 (1992) and Ponath, P. D. *et al.*, J. Clin. Invest., Vol. 97, No. 3, pp. 604-612 (1996)). However, unlike RANTES and MCP-3 which also induce the migration of other leukocyte cell types, eotaxin is selectively chemotactic for eosinophils (*see* Griffith-Johnson, D. A. *et al.*, Biochem. Biophys. Res. Commun. Vol. 197, 1167 (1993), and Jose, P. J. *et al.*, Biochem. Biophys. Res. Commun., Vol. 207, 788 (1994)). Specific eosinophil accumulation was observed at the site of administration of eotaxin whether by intradermal or intraperitoneal injection or aerosol inhalation (*see* Griffith-Johnson, D. A. *et al.*, Biochem. Biophys. Res. Commun., 197:1167 (1993); Jose, P. J. *et al.*, J. Exp. Med. 179, 881-887 (1994); Rothenberg, M. E. *et al.*, J. Exp. Med., 181, 1211 (1995), and Ponath, P. D., J. Clin. Invest., Vol. 97, No. 3, 604-612 (1996)).

Glucocorticoids such as dexamethasone, methprednisolone and hydrocortisone have been used for treating many eosinophil-related disorders, including bronchial asthma (R. P. Schleimer *et al.*, Am. Rev. Respir. Dis., 141, 559 (1990)). The glucocorticoids are believed to inhibit IL-5 and IL-3 mediated eosinophil survival in these diseases. However, prolonged use of glucocorticoids

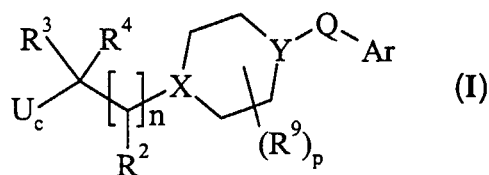
can lead to side effects in patients such as glaucoma, osteoporosis, and growth retardation (*see* Hanania, N. A. *et al.*, J. Allergy and Clin. Immunol., Vol. 96, 571-579 (1995) and Saha, M. T. *et al.*, Acta Paediatrica, Vol. 86, No. 2, 138-142 (1997)). It is desirable to have an alternative means of treating eosinophil-related diseases without incurring these undesirable side effects.

The CCR-3 receptor has been identified as a major chemokine receptor that eosinophils use for their response to eotaxin, RANTES and MCP-3. When transfected into a murine pre-beta lymphoma line, CCR-3 bound eotaxin, RANTES and MCP-3 conferred chemotactic responses on these cells to eotaxin, RANTES and MCP-3 (*see* Ponath, P. D. *et al.*, J. Exp. Med., 183, 2437-2448 (1996)). The CCR-3 receptor is expressed on the surface of eosinophils, T-cells (subtype Th-2), basophils and mast cells and is highly selective for eotaxin. Studies have shown that pretreatment of eosinophils with an anti-CCR-3 mAb completely inhibits eosinophil chemotaxis to eotaxin, RANTES and MCP-3 (*see* Heath, H. *et al.*, J. Clin. Invest., Vol. 99, No. 2, 178-184 (1997)). US patent application Serial No. 10/034,034, filed December 19, 2001, assigned to the present assignee, and U.S. Patent Nos. 6,140,344, 6,166,015, 6,323,223, 6,339,087, issued to the assignee herein, each describe compounds that are CCR-3 antagonists, and EP application EP903349, published March 24, 1999, discloses CCR-3 antagonists that inhibit eosinophilic recruitment by chemokine such as eotaxin.

Therefore, blocking the ability of the CCR-3 receptor to bind RANTES, MCP-3 and eotaxin and thereby preventing the recruitment of eosinophils should provide for the treatment of eosinophil-mediated inflammatory diseases.

The present invention is directed to piperdiny and piperziny-based compounds useful as CCR3 receptor antagonists which are capable of inhibiting the binding of eotaxin to the CCR-3 receptor and thereby provide a means of combating eosinophil induced diseases, such as asthma.

In a first aspect, this invention provides compounds of Formula (I):



wherein:

Ar is aryl or heteroaryl;

Q is $-C(=O)-$ or C_{1-2} alkylene;

X is N or $N^+R^{9a}Z^-$;

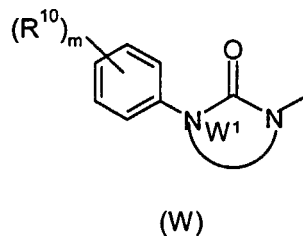
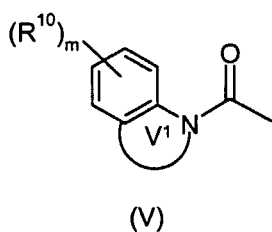
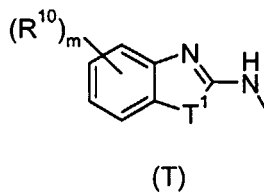
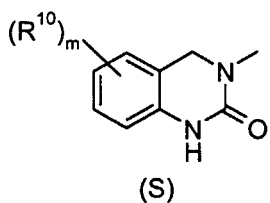
Y is CR^{9a} or N;

Z^- is a pharmaceutically acceptable anion;

R^2 is hydrogen or alkyl;

R^3 and R^4 are, independently of each other, hydrogen, alkyl, substituted alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroalkyl, $-(alkylene)-C(=O)-Z^1$, or $-(alkylene)-C(O)_2Z^1$, wherein Z^1 is alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, amino, alkylamino, aryl, arylalkyl, aryloxy, arylalkyloxy, heteroaryl, or heteroaryloxy;

U_e is selected from the group consisting of (S), (T), (V), and (W),

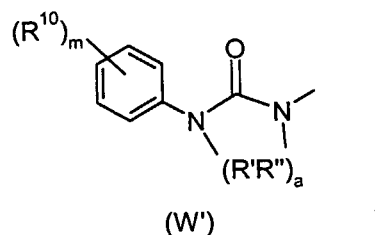
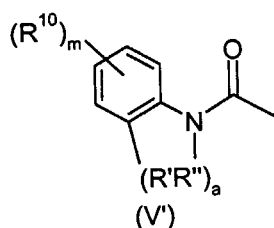
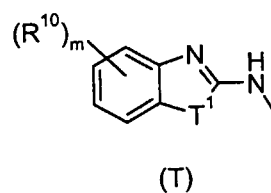
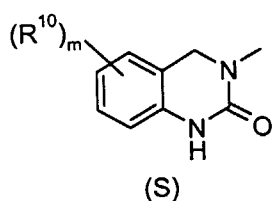


wherein T^1 is O, S, or NR^5 , wherein R^5 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, and heterocyclyl; and V^1 and W^1 define an optionally substituted five-to-six membered heterocyclo ring;

- provided that when U^c is T and T^1 is S, then at least one of R^3 and R^4 is not hydrogen, and provided that when both X and Y are N, then U_c is not T;
- R^9 is attached to any available carbon atom of the piperidinyl or piperazinyl ring and is selected from the group consisting of hydroxy, lower alkoxy, oxo (=O), halogen, cyano, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, and lower alkyl optionally substituted by one or two substituents independently selected from R^{15} ;
- R^{9a} and R^{9b} are independently selected from the group consisting of hydrogen and lower alkyl optionally substituted by one or two substituents independently selected from R^{15} ;
- R^{10} is attached to any available carbon atom of the benzo or phenyl ring and at each occurrence is independently selected from the group consisting of alkyl, substituted alkyl, hydroxy, alkoxy, halogen, cyano, haloalkoxy, amino, alkylamino, heterocyclyl, heteroaryl, cycloalkyl, or phenyl, said heterocyclyl, heteroaryl, cycloalkyl and phenyl being optionally substituted by one to three substituents independently selected from R^{16} ;
- R^{15} at each occurrence is independently selected from the group consisting of hydroxy, lower alkoxy, halo, cyano, trifluoromethyl, trifluoromethoxy, amino, and alkylamino;
- R^{16} at each occurrence is independently selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halo, cyano, trifluoromethyl, trifluoromethoxy, amino, and alkylamino;
- m is 0, 1, 2, 3, or 4;
- n is 0 or 1; and
- p is 0, 1, 2, 3 or 4;
- and, prodrugs, isomers, mixtures of isomers, or pharmaceutically-acceptable salts thereof.

Also, within the compounds as defined above [they will be referred to in the following under (i)], preferred are the following compounds:

- ii) The compound of (i), wherein U_c is selected from the group consisting of (S), (T), (V'), and (W'),



wherein R' and R'' at each occurrence are, independently of each other,
 5 hydrogrn, C₁₋₈ alkyl, hydroxy, C₁₋₈ alkoxy, halogen, cyano, halo C₁₋₈ alkoxy, amino
 or alkylamino, and a is an integer of 2 or 3.

(iii) The compound of any one of (i) and (ii), wherein U^c is T, and R⁴ is methyl,
 ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl.

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(iv) The compound of any one of (i) and (ii), wherein:

Ar is optionally-substituted phenyl or optionally substituted pyrimidinyl;

Q is CH₂;

R² is hydrogen;

15 R³ and R⁴ are, independently of each other, hydrogen, C₁₋₈ alkyl, hydroxyl C₁₋₈
 alkyl, or C₁₋₈ alkoxy C₁₋₈ alkyl;

R⁹ is selected from methyl, ethyl, hydroxy, methoxy, oxo (=O), halo, and cyano;

R^{9a} and R^{9b} are selected from hydrogen, methyl and ethyl;

n is 1; and

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p is 0 or 1.

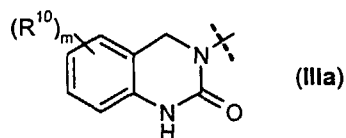
(v) The compound of any one of (i) to (iv), wherein X is N and Y is CR^{9b}.

(vi) The compound of any one of (i) to (iv), wherein both X and Y are N.

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(vii) The compound of any one of (i) to (iv), wherein X is $N^+R^{9a}Z^-$, and Y is CR^{9b} .

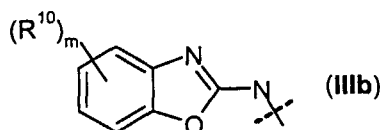
(viii) The compound of any one of (i) and (ii), wherein U_c is **IIIa**;



wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and m is 0, 1, or 2.

(ix) The compound of any one of (i) and (ii), wherein:

U_c is **IIIb**;



wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and m is 0, 1, or 2.

(x) The compound of (ix), wherein:

Ar is phenyl or pyrimidinyl optionally substituted by one, two or three groups selected from the group consisting of halo, C_{1-8} alkyl, heteroalkyl, C_{1-8} alkoxy, nitro, trifluoromethyl, C_{1-8} alkylsulfonyl, and optionally-substituted phenyl;

Q is CH_2 ;

R^2 is hydrogen;

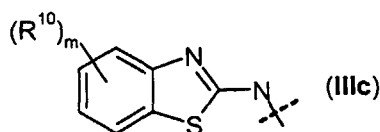
R^3 is hydrogen;

R^4 is methyl, ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl;

and

R^9 is selected from C_{1-4} alkyl, oxo ($=O$), halogen, and hydroxy.

(xi) The compound of any one of (i) and (ii), wherein U_c is **IIIc**;



wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and

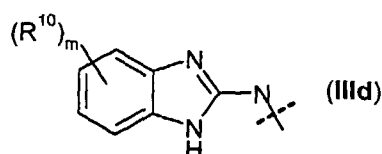
m is 0, 1, or 2.

(xii) The compound of (xi), wherein:

R^2 and R^3 are hydrogen; and

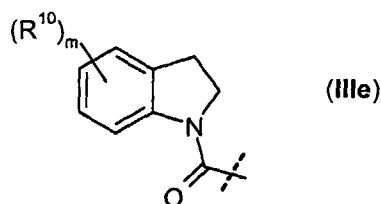
5 R^4 is methyl, ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl.

(xiii) The compound of any one of (i) and (ii), wherein U_c is **III d** ;



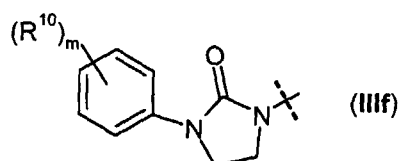
10 wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and m is 0, 1, or 2.

(xiv) The compound of any one of (i) and (ii), wherein U_c is **III e** ;



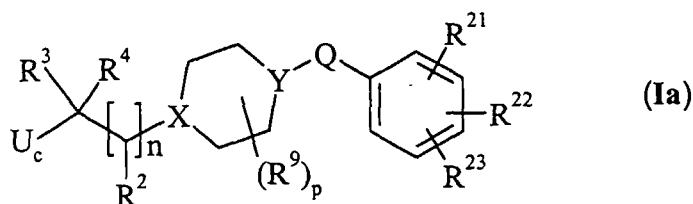
15 wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and m is 0, 1, or 2.

(xv) The compound of any one of (i) and (ii), wherein U_c is **III f**;



20 wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and m is 0, 1, or 2.

(xvi) The compound of any one of (i) and (ii), having Formula (Ia):



wherein,

X is N or $N^+R^{9a}Z^-$; Y is CR^{9a} or N;

Z is a pharmaceutically acceptable anion;

5 R^2 and R^3 are hydrogen;

R^{9a} is hydrogen or C_{1-4} alkyl;

R^{21} , R^{22} , and R^{23} are attached to any available carbon atom of the phenyl ring and are independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4} alkylsulfonyl, amino, and
10 alkylamino;

n is 1, and

U_c , Q, P, R^4 and R^9 are as defined in claim 1 or 2.

(xvii) The compound of (xvi), wherein Q is CH_2 .

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(xviii) The compound of any one of (xvi) and (xvii), wherein:

R^{21} , R^{22} , and R^{23} , and the phenyl ring to which they are attached, form 4-chlorophenyl or 3,4-dichlorophenyl;

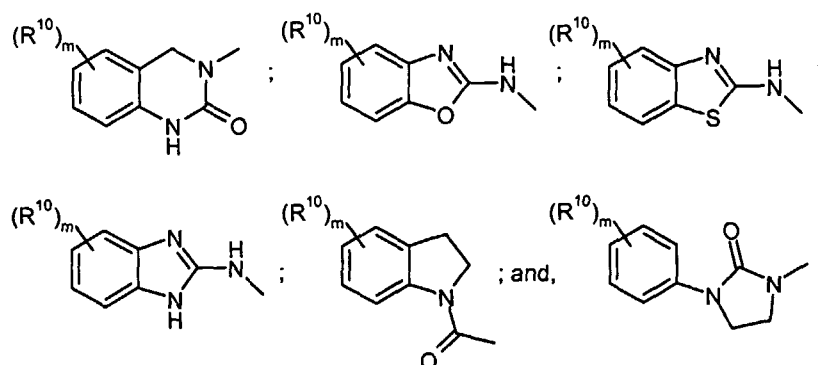
R^4 is methyl, ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl;

20 and

p is 0 or 1.

(xix) The compound of any one of (xvi), (xvii) and (xviii), in which U_c is selected from the group consisting of

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wherein R¹⁰ is selected from C₁₋₄ alkyl, halogen, cyano, and C₁₋₄ alkoxy; and *m* is 0, 1, or 2.

In a second aspect, this invention provides pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In a third aspect, this invention provides processes disclosed herein for preparing compounds of Formula (I).

In a forth aspect, this invention provides novel intermediates disclosed herein that are useful for preparing compounds of Formula (I).

In a fifth aspect, this invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in medical therapy or diagnosis, especially for use in the treatment of CCR-3 mediated diseases including respiratory diseases such as asthma.

In a sixth aspect, this invention provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament useful for treating a disease in a mammal treatable by administration of a CCR-3 receptor antagonist (e.g. asthma).

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below.

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to eight carbon atoms or a branched saturated monovalent hydrocarbon radical of three to eight carbon atoms, *e.g.*, methyl, ethyl, propyl, 2-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, pentyl. A "lower alkyl" is an alkyl group having one to four carbon atoms.

"Alkenyl" means a linear monovalent hydrocarbon radical of two to eight carbon atoms or a branched monovalent hydrocarbon radical of three to eight carbon atoms, containing at least one double bond, *e.g.*, ethenyl, propenyl.

"Alkynyl" means a linear monovalent hydrocarbon radical of two to eight carbon atoms or a branched monovalent hydrocarbon radical of three to eight carbon atoms, containing at least one triple bond, *e.g.*, ethynyl, propynyl.

5 "Alkylene" means a linear saturated bivalent hydrocarbon radical of one to eight carbon atoms or a branched saturated bivalent hydrocarbon radical of three to eight carbon atoms, *e.g.*, methylene, ethylene, 2,2-dimethylethylene, 2-methylpropylene, pentylene. A "lower alkylene" is said bivalent radical having one to four carbon atoms.

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"Alkenylene" means a linear bivalent hydrocarbon radical of two to eight carbon atoms or a branched bivalent hydrocarbon radical of three to eight carbon atoms having at least one double bond, *e.g.*, methenylene, ethenylene, 2,2-dimethylethenylene, 2-methylpropylene, pentylene. A "lower alkenylene" is said
15 bivalent radical having two to four carbon atoms.

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"Substituted alkyl" means an alkyl group having one, two or three substituents selected from the group consisting of acyl, acylamino, hydroxy, alkoxy, haloalkoxy, cyano, amino, alkylamino, haloalkyl, halo, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylthio, aryl, cycloalkyl, heteroaryl and/or heterocyclyl, as defined herein. A substituted lower alkyl is an alkyl of one to four carbon atoms having one to three substituents selected from those recited for substituted alkyl, preferably from hydroxy, halo, lower alkoxy, cyano, and haloalkoxy.

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When the term "alkyl" is used as a suffix following another term, as in "phenylalkyl," or "hydroxyalkyl," this is intended to refer to an alkyl group, as defined above, being substituted with one to two substituents (preferably one substituent) selected from the other, specifically-named group. Thus, for example,
30 "phenylalkyl" refers to an alkyl group having one to two phenyl substituents, and thus includes benzyl, phenylethyl, and biphenyl. An "alkylaminoalkyl" is an alkyl group having one to two alkylamino substituents. "Hydroxyalkyl" includes 2-hydroxyethyl, 2-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 2,3-dihydroxybutyl, 2-(hydroxymethyl)-3-hydroxypropyl.

Accordingly, as used herein, the term "hydroxyalkyl" is used to define a subset of heteroalkyl groups defined below.

5 "Acyl" means a radical $-C(=O)R$, where R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl, or phenylalkyl, wherein the alkyl, cycloalkyl, cycloalkylalkyl, and phenylalkyl groups are as defined herein. Representative examples include, but are not limited to formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl.

10 "Acylamino" means a radical $-NR'C(=O)R$, where R' is hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl, wherein the alkyl, cycloalkyl, cycloalkylalkyl, and phenylalkyl groups are as defined herein. Representative examples include, but are not limited to formylamino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethyl-
15 carbonylamino, benzoylamino, benzylcarbonylamino.

"Alkoxy" means a radical $-OR$, where R is an alkyl as defined herein *e.g.*, methoxy, ethoxy, propoxy, butoxy. A "lower alkoxy" is an alkoxy group wherein the alkyl (R) group has one to four carbon atoms.

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When the term "oxy" is used as a suffix following another specifically-named group, as in "aryloxy", "heteroaryloxy," or "arylalkyloxy", this means that an oxygen atom is present as a linker to the other, specifically-named group. Thus, for example, "aryloxy" refers to the group $-O-R$, wherein R is aryl; "heteroaryloxy"
25 refers to the group $-O-R'$, wherein R' is heteroaryl.

"Alkoxycarbonyl" means a radical $-C(=O)R$, where R is alkoxy as defined herein.

30 "Alkylamino" means a radical $-NHR$ or $-NRR$ where R is selected from an alkyl, cycloalkyl or cycloalkylalkyl group as defined herein. Representative examples include, but are not limited to methylamino, ethylamino, isopropylamino, cyclohexylamino.

"Alkylsulfonyl" means a radical $-S(O)_2R$, where R is an alkyl, cycloalkyl or cycloalkylalkyl group as defined herein, *e.g.*, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, cyclohexylsulfonyl.

5 "Alkylsulfinyl" means a radical $-S(O)R$, where R is an alkyl, cycloalkyl or cycloalkylalkyl group as defined herein *e.g.*, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, cyclohexylsulfinyl.

"Alkylthio" means a radical $-SR$ where R, is an alkyl as defined above *e.g.*, methylthio, ethylthio, propylthio, butylthio. Mercapto is $-SH$.
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"Aryl" means a monocyclic or bicyclic aromatic hydrocarbon radical which is optionally substituted with one, two or three substituents selected from the group consisting of alkyl, heteroalkyl, acyl, acylamino, amino, alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, $-SO_2NR'R''$ (where R' and R'' are independently
15 hydrogen or alkyl), alkoxy, haloalkoxy, alkoxycarbonyl, carbamoyl, hydroxy, halo, nitro, cyano, mercapto, methylenedioxy, ethylenedioxy, acylalkyl, acylaminoalkyl, hydroxyalkyl, alkoxyalkyl, haloalkoxyalkyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, haloalkyl, haloalkyl(alkyl), alkoxycarbonylalkyl, alkylsulfonylalkyl, alkylsulfinylalkyl, alkylthioalkyl, or an optionally-substituted
20 phenyl as defined below. More specifically the term aryl includes, but is not limited to, phenyl, chlorophenyl, dichlorophenyl, fluorophenyl, methoxyphenyl, methylphenyl, dimethylphenyl, methylmethoxyphenyl, 1-naphthyl, 2-naphthyl.

25 "Carbamoyl" refers to a group $-C(=O)NRR'$, wherein R and R' are independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, or heterocyclyl.

"Cycloalkyl" refers to a saturated monovalent cyclic hydrocarbon radical of three to seven ring carbons *e.g.*, cyclopropyl, cyclobutyl, cyclohexyl, 4-methylcyclohexyl, and further includes such rings having a carbon-carbon bridge of one, two, or three bridgehead carbon atoms, and/or having a second ring fused thereto, with the understanding that in such cases the point of attachment will be to the non-aromatic carbocyclic ring moiety. Thus, the term "cycloalkyl" includes
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such rings as cyclopropyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl. Additionally, one or two carbon atoms of a cycloalkyl group may optionally contain a carbonyl oxygen group, *e.g.*, one or two atoms in the ring may be a moiety of the formula $-C(=O)-$.

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A "substituted cycloalkyl" is a cycloalkyl group as defined above having one to four (preferably one to two) substituents independently selected from the group of substituents recited above for aryl.

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"Halo" means fluoro, chloro, bromo, or iodo, preferably fluoro and chloro.

"Haloalkyl" means alkyl substituted with one or more same or different halo atoms, *e.g.*, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CCl_3$.

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"Haloalkoxy" means a group OR, wherein R is haloalkyl as defined above. Thus, it includes such groups as $-O-CHF_2$, $-O-CF_3$.

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"Heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that when the heteroaryl group is a bicyclic system, the point of attachment to the heteroaryl group will be to an aromatic ring containing at least one heteroatom.

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The heteroaryl ring is optionally substituted with one, two, three or four substituents, preferably one or two substituents, independently selected from alkyl, heteroalkyl, acyl, acylamino, amino, alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, $-SO_2NR'R''$ (where R' and R'' are independently hydrogen or alkyl), alkoxy, haloalkoxy, alkoxycarbonyl, carbamoyl, hydroxy, halo, nitro, cyano, mercapto, methylenedioxy, ethylenedioxy, acylalkyl, acylaminoalkyl, hydroxyalkyl, alkoxyalkyl, haloalkoxyalkyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, haloalkyl, haloalkyl(alkyl), alkoxycarbonylalkyl,

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alkylsulfonylalkyl, alkylsulfinylalkyl, and alkylthioalkyl, or optionally-substituted phenyl as defined below. More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidinyl, 5-(3,4-dimethoxyphenyl)-pyrimidin-2-

yl, 5-(4-methoxyphenyl)-pyrimidin-2-yl, 5-(3,4-methylenedioxyphenyl)-pyrimidin-2-yl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, tetrahydroquinolinyl, isoquinolyl, benzimidazolyl, benzisoxazolyl, benzothienyl
 5 and derivatives thereof.

"Heteroalkyl" means an alkyl radical as defined herein wherein one, two or three hydrogen atoms have been replaced with a substituent independently selected from the group consisting of $-OR^a$, $-NR^bR^c$, and $-S(O)_nR^d$ (where n is an integer
 10 from 0 to 2), with the understanding that the point of attachment of the heteroalkyl radical is through a carbon atom, wherein R^a is hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; R^b and R^c are independently of each other hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; and when n is 0, R^d is hydrogen, alkyl, cycloalkyl, or cycloalkylalkyl, and when n is 1 or 2, R^d is alkyl, cycloalkyl, cycloalkylalkyl,
 15 amino, acylamino, or alkylamino. Representative examples include, but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxypropyl, 1-hydroxymethylethyl, 3-hydroxybutyl, 2,3-dihydroxybutyl, 2-hydroxy-1-methylpropyl, 2-aminoethyl, 3-aminopropyl, 2-methylsulfonylethyl, aminosulfonylmethyl, aminosulfonylethyl, aminosulfonylpropyl,
 20 methylaminosulfonylmethyl, methylaminosulfonylethyl, methylaminosulfonylpropyl.

"Heterocyclyl" means a saturated or unsaturated non-aromatic cyclic radical of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from
 25 O, $S(O)_n$ (where n is an integer from 0 to 2), and NR^x , the remaining ring atoms being carbon atoms {wherein each R^x is independently hydrogen, alkyl, acyl, alkylsulfonyl, aminosulfonyl, (alkylamino)sulfonyl, carbamoyl, (alkylamino)carbonyl, (carbamoyl)alkyl, or (alkylamino)carbonylalkyl. The heterocyclyl ring may be optionally substituted with one, two, or three substituents
 30 independently selected as valence permits from alkyl, haloalkyl, heteroalkyl, halo, nitro, cyano, cyanoalkyl, hydroxy, hydroxyalkyl, amino, alkylamino, $-(X)_n-C(=O)R$ (where X is O or NR' , n is 0 or 1, R is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, amino, or alkylamino); $-alkylene-C(=O)R$ (where R is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, amino, or alkylamino); and/or $-S(O)_nR^d$ (where n is an integer

from 0 to 2, and R^d is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, amino, alkylamino, or hydroxyalkyl, provided that R^d is not hydrogen when *n* is 1 or 2). More specifically, the term heterocyclyl includes, but is not limited to, tetrahydropyranyl, piperidino, N-methylpiperidin-3-yl, piperazino, N-methylpyrrolidin-3-yl, 3-pyrrolidino, morpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, tetrahydrothiophenyl-S,S-dioxide, pyrrolinyl, imidazolinyl, and derivatives thereof.

“Leaving group” has the meaning conventionally associated with it in synthetic organic chemistry, *i.e.*, an atom or a group capable of being displaced by a nucleophile and includes halo (such as chloro, bromo, and iodo), alkanesulfonyloxy, arenesulfonyloxy, alkylcarbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, mesyloxy, tosyloxy, trifluoromethanesulfonyloxy, aryloxy (*e.g.*, 2,4-dinitrophenoxy), methoxy, N,O-dimethylhydroxylamino.

“Optional” or “optionally” means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “aryl optionally substituted with an alkyl” means that the alkyl may but need not be present, and the description includes situations where the aryl group is mono- or disubstituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

“Optionally-substituted phenyl” means a phenyl group which is optionally substituted with one, two or three substituents (preferably one to two) selected from alkyl, heteroalkyl, acyl, acylamino, amino, alkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, -SO₂NR'R'' (where R' and R'' are independently hydrogen or alkyl), alkoxy, haloalkoxy, alkoxycarbonyl, hydroxy, halo, nitro, cyano, mercapto, acylalkyl, acylaminoalkyl, hydroxyalkyl, alkoxyalkyl, haloalkoxyalkyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, haloalkyl, haloalkyl(alkyl), alkoxycarbonylalkyl, alkylsulfonylalkyl, alkylsulfinylalkyl, and alkylthioalkyl. More specifically the term includes, but is not limited to, phenyl, chlorophenyl, fluorophenyl, bromophenyl, methylphenyl, ethylphenyl, methoxyphenyl, cyanophenyl, 4-nitrophenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 3,4-difluorophenyl, 2,3-

dichlorophenyl, 3-methyl-4-nitrophenyl, 3-chloro-4-methylphenyl, 3-chloro-4-fluorophenyl or 3,4-dichlorophenyl and the derivatives thereof. An “optionally-substituted pyrimidinyl” means a pyrimidinyl ring optionally having one, two, or three (preferably one or two) substituents selected from those recited for optionally-substituted phenyl.

Preferred radicals for the chemical groups whose definitions are given above are those specifically exemplified in Examples.

“Pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

“Pharmaceutically-acceptable salt” of a compound means a salt that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as

ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine.

The term "pharmaceutically acceptable anion" as used herein means refers to the conjugate base of an inorganic acid or an organic acid used to form a pharmaceutically acceptable salt as defined above, such as Cl^- , I^- . When an acid releases a proton, the remaining species retains an electron pair to which the proton was formerly attached. This species can, in principle, reacquire a proton and is referred to as a conjugate base.

A "prodrug" of a compound of formula (I) herein refers to any compound which releases an active drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula I are prepared by modifying one or more functional group(s) present in the compound of Formula I in such a way that the modification(s) may be cleaved *in vivo* to release the compound of Formula I. Prodrugs include compounds of Formula I wherein a hydroxy, amino, or sulfhydryl group in a compound of Formula I is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, esters (*e.g.*, acetate, formate, and benzoate derivatives), carbamates (*e.g.*, N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formula I.

"Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Chemistry*, (Wiley, 2nd ed. 1991) and Harrison and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (Fmoc), nitro-veratryloxycarbonyl (NVOC), and the like. Representative hydroxy protecting groups include those where the hydroxy group is either acylated or alkylated such

as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

5 “Treating” or “treatment” of a disease includes: (1) preventing the disease, *i.e.*, causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; (2) inhibiting the disease, *i.e.*, arresting or reducing the development of the disease or its clinical symptoms; or (3) relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms.

10

“A therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc.,
15 of the mammal to be treated.

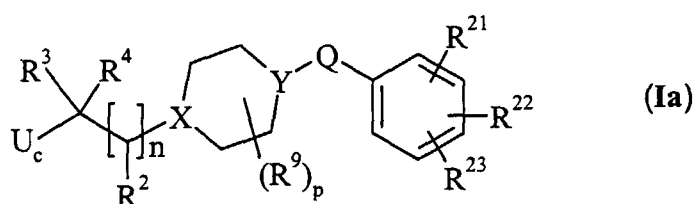
Compounds that have the same molecular Formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in
20 space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, if a carbon atom is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by
25 the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal
30 proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or

naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced
 5 Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

While the broadest definition of the invention is described before, certain compounds of Formula (I) are preferred.

For example, preferred compounds are compounds of Formula (Ia),



wherein,

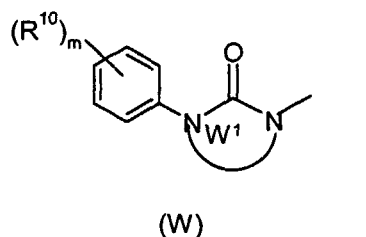
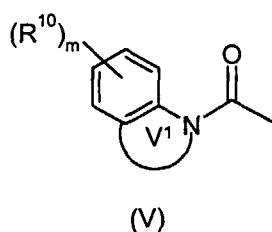
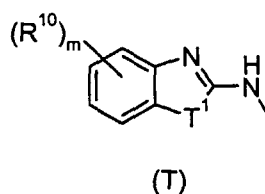
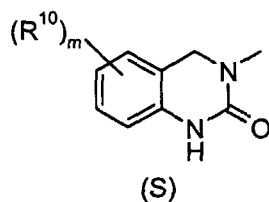
X is N or N⁺R^{9a} Z⁻;

Y is N or CR^{9b};

15 Z is a pharmaceutically acceptable anion;

Q is CH₂;

U_c is selected from one of (S), (T), (V), and (W),



20

wherein T¹ is O, S, or NR⁵, wherein R⁵ is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl and heterocyclyl; and V¹ and W¹ define an optionally

substituted five-to-six membered heterocyclo ring; provided that when U_c is T and T^1 is S, then at least one of R^3 and R^4 is not hydrogen, and provided that when both X and Y are N, then U_c is not T;

R^2 and R^3 are hydrogen;

5 R^4 is hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl;

R^9 is selected from lower alkyl, hydroxy, lower alkoxy and oxo (=O);

R^{9a} is lower alkyl;

R^{9b} is selected from hydrogen, methyl, and ethyl;

10 R^{21} , R^{22} , and R^{23} are attached to any available carbon atom of the phenyl ring and are independently selected from hydrogen, lower alkyl, lower alkoxy, halogen, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4} alkylsulfonyl, amino, or alkylamino; and

n is 1;

p is 0, 1, or 2.

15

More preferred are compounds of Formula (Ia), as defined immediately above, wherein,

R^4 is alkyl, especially methyl, ethyl, 1-methylethyl, isopropyl, or hydroxyalkyl, especially 1-hydroxyethyl or 2-hydroxyethyl;

20 R^9 is selected from methyl, ethyl, oxo (=O), and hydroxy;

R^{9a} is lower alkyl;

R^{9b} is selected from hydrogen, methyl, and ethyl; and

p is 0 or 1.

25

In compounds of Formula (Ia), above, preferably R^{21} is hydrogen, and R^{22} and R^{23} are selected from hydrogen, halogen, methyl, and methoxy. More preferred are compounds wherein R^{21} , R^{22} , and R^{23} and the phenyl ring to which they are attached form mono or di chloro substituted phenyl, especially 4-chlorophenyl or 3,4-dichlorophenyl.

30

According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein U_c is T, and R^4 is methyl, ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl.

According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein Q is $-\text{CH}_2-$.

5 According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein R^2 is hydrogen; and R^3 and R^4 are, independently of each other, hydrogen, alkyl, hydroxyalkyl, or alkoxyalkyl.

10 According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein R^9 is selected from methyl, ethyl, hydroxy, methoxy, oxo ($=\text{O}$), halo, and cyano; and R^{9a} and R^{9b} are selected from hydrogen, methyl and ethyl.

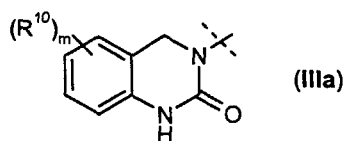
15 According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein n is 1.

According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein p is 0.

20 According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (Ia), above, wherein Y is N.

According to another aspect of the invention, a preferred group of compounds are those compounds of

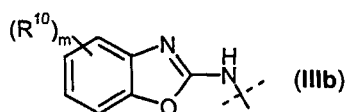
Formula (I) or (Ia), wherein U_c is (IIIa).



R^{10} is selected from lower alkyl, halogen, cyano, and lower alkoxy; and m is 0, 1, or 2.

5

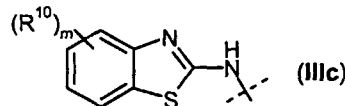
According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein U_c is (IIIb);



R^{10} is selected from lower alkyl, halogen, cyano, and lower alkoxy; and m is 0, 1, or 2.

10

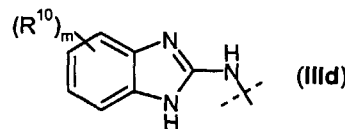
According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein U_c is (IIIc);



R^{10} is selected from lower alkyl, halogen, cyano, and lower alkoxy; and m is 0, 1, or 2

15

According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein U_c is (IIId);



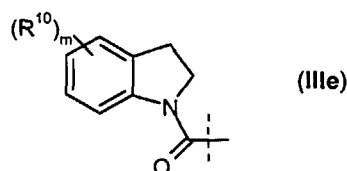
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R^{10} is selected from lower alkyl, halogen, cyano, and lower alkoxy; and m is 0, 1, or 2

According to another aspect of the invention, a preferred group of compounds are those compounds of Formula (I) or (Ia), wherein U_c is (IIIe);

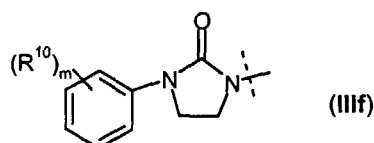
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23



R^{10} is selected from lower alkyl, halogen, cyano, and lower alkoxy; and
 m is 0, 1, or 2

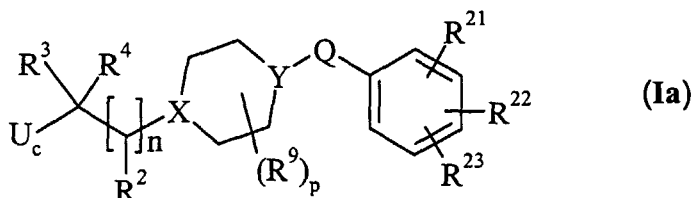
5 According to another aspect of the invention, a preferred group of
 compounds are those compounds of Formula (I) or (Ia), wherein U_c is (IIIf);



R^{10} is selected from lower alkyl, halogen, cyano, and lower alkoxy; and
 m is 0, 1, or 2

10

Other combinations of preferred groups, and/or particularly preferred
 groups, may form still other groups of preferred compounds. For example, also
 preferred are compounds having the Formula (Ia):



15

wherein,

X is N or $N^+R^{9a}Z^-$;

Y is N or CR^{9b} ;

Z is a pharmaceutically acceptable anion;

20 R^2 and R^3 are hydrogen;

R^4 is methyl, ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl;

R^9 is selected from methyl, ethyl, hydroxy, methoxy, oxo ($=O$), halo, and cyano;

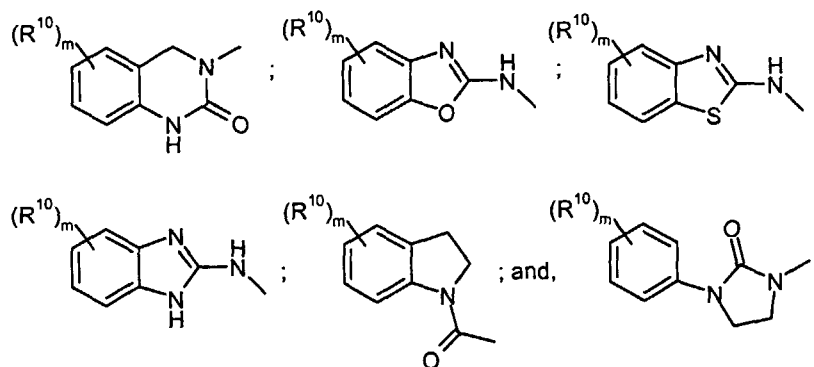
R^{9a} is lower alkyl;

R^{9b} is hydrogen, methyl or ethyl;

25 R^{21} , R^{22} , and R^{23} are attached to any available carbon atom of the phenyl ring and
 are independently selected from hydrogen, lower alkyl, lower alkoxy,

halogen, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₄alkylsulfonyl, amino, and alkylamino.

U_c is selected from one of,



5 wherein R¹⁰ is selected from lower alkyl, halogen, cyano, and lower alkoxy; and
 m is 0, 1, or 2;
 n is 1; and,
 p is 0 or 1.

10 Other more preferred embodiments are compounds as immediately defined
 above wherein Q is CH₂.

Even more preferred are compounds as immediately defined above, wherein
 R²¹, R²², and R²³, and the phenyl ring to which they are attached, form 4-
 15 chlorophenyl or 3,4-dichlorophenyl.

The compounds of the invention are CCR-3 receptor antagonists and inhibit
 eosinophil recruitment by CCR-3 chemokines such as RANTES, eotaxin, MCP-2,
 MCP-3 and MCP-4. Compounds of this invention and compositions containing
 20 them are useful in the treatment of eosinophil-induced diseases including
 inflammatory or allergic diseases, such as inflammatory bowel diseases (*e.g.*,
 Crohn's disease and ulcerative colitis); psoriasis and inflammatory dermatoses
 (*e.g.*, dermatitis and eczema), as well as respiratory allergic diseases such as
 asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity
 25 pneumonitis, and eosinophilic pneumonias (*e.g.*, chronic eosinophilic pneumonia).

In general, the compounds of this invention can be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of this invention, *i.e.*, the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Therapeutically effective amounts of compounds of Formula (I) may range from approximately 0.01-20 mg per kilogram body weight of the recipient per day; preferably about 0.1-10 mg/kg/day. Thus, for administration to a 70 kg person, the dosage range would most preferably be about 7 mg to 0.7 g per day.

In general, compounds of this invention will be administered as pharmaceutical compositions by any one of the following routes: oral, transdermal, inhalation (*e.g.*, intranasal or oral inhalation) or parenteral (*e.g.*, intramuscular, intravenous or subcutaneous) administration. A preferred manner of administration is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, liposomes, elixirs, or any other appropriate compositions. Another preferred manner for administering compounds of this invention is inhalation. This is an effective means for delivering a therapeutic agent directly to the respiratory tract for the treatment of diseases such as asthma and other similar or related respiratory tract disorders (*see, e.g.*, U.S. Pat. No. 5,607,915).

The choice of formulation depends on various factors such as the mode of drug administration and the bioavailability of the drug substance. For delivery via inhalation, the compound can be formulated as liquid solutions or suspensions, aerosol propellants or dry powder and loaded into a suitable dispenser for administration. There are three types of pharmaceutical inhalation devices--nebulizer inhalers, metered-dose inhalers (MDI) and dry powder inhalers (DPI). Nebulizer devices produce a stream of high velocity air that causes the therapeutic agents (which has been formulated in a liquid form) to spray as a mist which is

carried into the patient's respiratory tract. MDI's typically have the formulation packaged with a compressed gas. Upon actuation, the device discharges a measured amount of therapeutic agent by compressed gas, thus affording a reliable method of administering a set amount of agent. DPI's administer therapeutic agents in the form of a free flowing powder that can be dispersed in the patient's inspiratory air-stream during breathing by the device. In order to achieve a free flowing powder, the therapeutic agent is formulated with an excipient, such as lactose. A measured amount of the therapeutic is stored in a capsule form and is dispensed to the patient with each actuation. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area *i.e.*, decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability. The compositions are comprised of a compound of Formula (I) in combination with at least one pharmaceutically-acceptable excipient, as defined above. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, *e.g.*, peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

For liposomal formulations of the drug for parenteral or oral delivery the drug and the lipids are dissolved in a suitable organic solvent *e.g.* tert-butanol, cyclohexane (1% ethanol). The solution is lyophilized and the lipid mixture is
5 suspended in an aqueous buffer and allowed to form a liposome. If necessary, the liposome size can be reduced by sonification. (see Frank Szoka, Jr. and Demetrios Papahadjopoulos, "Comparative Properties and Methods of Preparation of Lipid Vesicles (Liposomes)", *Ann. Rev. Biophys. Bioeng.*, 9:467-508 (1980), and D. D. Lasic, "Novel Applications of Liposomes", *Trends in Biotech.*, 16:467-608,
10 (1998)).

Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

15

The level of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compound of Formula (I) based on the total formulation, with the balance being one or more
20 suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt %. Representative pharmaceutical formulations containing a compound of Formula (I) are described below.

The CCR-3 antagonistic activity of the compounds of this invention can be
25 measured by *in vitro* assays such as ligand binding and chemotaxis assays as described in more detail below. *In vivo* activity can be assayed in the Ovalbumin induced Asthma in Balb/c Mice Model as described in more detail below.

For ease of reference, the following abbreviations are used in the Schemes
30 and Examples below:

MeOH = methanol

EtOH = ethanol

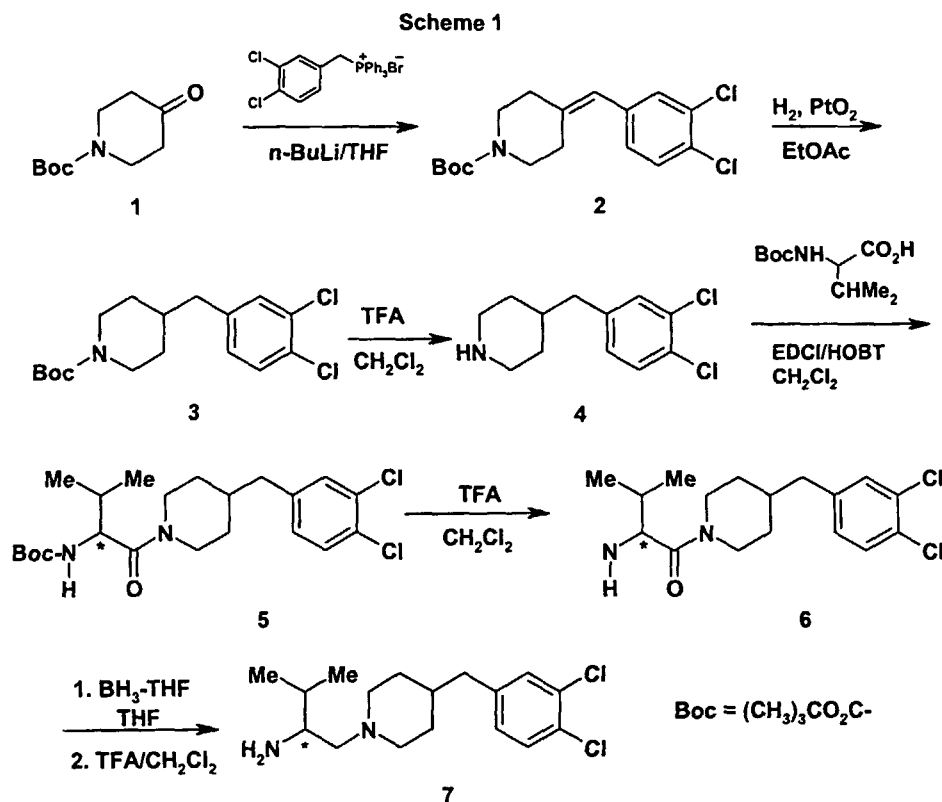
- EtOAc = ethyl acetate
HOAc = acetic acid
DCE = 1,2-dichloroethane
DCM = dichloromethane
5 DMF = dimethylformamide
EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et = ethyl
Me = methyl
i-Pr = *iso*-propyl
10 PCC = pyridinium chlorochromate
PDC = pyridinium dichromate
TEA or Et₃N = triethylamine
THF = tetrahydrofuran
TFA = trifluoroacetic acid
15 rt. = room temperature

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art. Preferred methods include, but are not limited to, the general synthetic procedures described below.

20

The starting materials and reagents used are either available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis., USA), Bachem (Torrance, Calif., USA), Enika Chemie or Sigma (St. Louis, Mo., USA), Maybridge (Dist: Ryan Scientific, P.O. Box 6496, Columbia, S.C. 92960), etc.; or
25 are prepared by methods known to those skilled in the art following procedures set forth in the literature such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced
30 Organic Chemistry, (John Wiley and Sons, 1992); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative and various modifications to these schemes can be made and will be suggested to one skilled in the art.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data. In the Schemes, the variables X, Y, Q, Ar, R⁴, R²¹, R²², R²³, p, q, etc., are defined as set forth in the claims.



Scheme 1 illustrates a general procedure for preparing piperidinyl intermediates (7), which can then be converted to compounds of Formula (I).. 4-Oxo-piperidine-1-carboxylic acid tert-butyl ester (1) is a suitable starting material to introduce the C-4 substituent. A Wittig condensation with a triphenyl(optionally substituted)benzylphosphonium halide converts the C-4 ketone into a (optionally substituted)phenylalkylidene 2 substituent. Several variants of the Wittig reaction are well known within the art and each can be adapted to the preparation of compounds of the present invention (see, e.g., *J. March Advanced Organic Chemistry* 4th ed., John Wiley & Sons, New York, 1992, pp. 956-963; A. Maercker, *Organic Reactions*, John Wiley, New York 1965 v. 14 p 270-490; phosphoryl-stabilized carbanions, W. S. Wadsworth Jr. *Organic Reactions* John Wiley & Sons, New York, v. 25, 1977, pp. 74-257; Peterson olefination, D. Ager, *Organic Reactions* John Wiley & Sons, New York, v. 38, 1990, pp. 1-224). The Wittig

Reaction is generally run by treating a phosphonium salt dissolved or suspended in an inert solvent with a strong base, *e.g.*, *n*-butyl lithium or lithium diisopropylamide at from -78 to 0° C. The ylide thus formed is added to 1 and stirred at a temperature ranging from -78 to 0° C until the reaction is completed and the product is purified by standard techniques. The requisite phosphonium salts are prepared by contacting a (optionally substituted) benzyl halide with triphenylphosphine. Benzyl halides are readily available by free radical-induced benzylic halogenation. In the exemplified process 3,4-dichlorotoluene is commercially available from the Sigma-Aldrich (catalog # 16,136-5).

Reduction of the olefin can be readily achieved by a variety of methods including catalytic hydrogenation and removal of the boc protecting group from the nitrogen atom is accomplished by standard protocols (T. W. Greene and P. G. M. Wuts, *supra*). The boc protecting group is acid sensitive and protocols for cleavage of the boc group typically contact the carbamate with trifluoroacetic acid and methylene chloride at temperatures ranging from 0° C to room temperature. Alternatively other acids such as hydrochloric acid also will readily cleave the boc group.

Substitution of the piperidinyll nitrogen is readily accomplished by a two-step sequence comprising acylation and reduction of the resulting amide (see also Scheme 2). Acylation of the nitrogen is readily accomplished utilizing the amine acylation protocols developed for peptide synthesis which produce high chemical yields of an amide without racemization of the adjacent chiral center to yield 6.

Prior to carrying out the acylation with an amino acid, the amino group of the amino acid must be protected to prevent undesirable amide formation. Numerous N-protecting groups have been developed which can be selectively cleaved under a variety of conditions. Protection strategies for coupling amino acids have been extensively reviewed (see *e.g.*, M. Bodanszky, *Principles of Peptide Synthesis*, Springer Verlag, New York 1993; P. Lloyd-Williams and F. Albericio *Chemical Methods for the Synthesis of Peptides and Proteins* CRC Press, Boca Raton, FL 1997). These references are incorporated herein in their entirety. The various amino-protecting groups useful in this invention include N-benzyloxy-

carbonyl- (cbz), *tert*-butoxy-carbonyl (Boc), N-formyl- and N-urethane-N-carboxy anhydrides which are all commercially available (SNPE Inc., Princeton, N.J., Aldrich Chemical Co., Milwaukee, Wis., and Sigma Chemical Co., St. Louis, Mo.) N-urethane amino-protected cyclic amino acid anhydrides are also described in the literature (William D. Fuller *et al.*, *J. Am. Chem. Soc.* **1990** 112:7414-7416) which is incorporated herein by reference. While many of these could be effectively employed in the present process, preferred urethane protecting groups include the *tert*-butoxycarbonyl or the benzyloxycarbonyl.

Protocols for efficient coupling of N-protected amino acids have extensively optimized (M. Bodanszky *supra*; P. Lloyd-Williams and F. Albericio *supra*). At least 1 equivalent of the protected amino acid and 1 equivalent of a suitable coupling agent or dehydrating agent, *e.g.*, 1,3-dicyclohexylcarbodiimide or salts of such diimides with basic groups, N-ethyl-N'-(3-(dimethylamino) propyl)carbodiimide hydrochloride, should be employed from the start. Other dehydrating agents such as N,N'-carbonyldiimidazole, trifluoroacetic anhydride, mixed anhydrides, acid chlorides may be used. Numerous additives have been identified which improve the coupling efficiency and limit racemization of the alpha-amino acid including, 1-hydroxybenzotriazole and 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (W. König and R. Geiger *Chem. Ber.* **1970** 788:2024 and 2034), N-hydroxysuccinimide (E. Wunsch and F. Drees, *Chem. Ber.* **1966** 99:110), 1-hydroxy-7-azabenzotriazole (L. A. Carpino *J. Am. Chem. Soc.* **1993** 115:4397-4398). Aminium /uronium- and phosphonium HOBt/HOAt-based coupling reagents have been developed, *e.g.* based peptide coupling reagents, *e.g.*, 1-benzotriazol-1-yloxy-bis(pyrrolidino)uronium hexafluorophosphate (J. Xu and S. Chen *Tetrahedron Lett.* **1992** 33:647), 1-benzotriazol-1-yloxy-N,N-dimethylmethananiminium hexachloroantimonate (P. Li and J. Xu, *Tetrahedron Lett.* **1999** 40:3606), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethylammoniumuronium hexafluorophosphate (L. A. Carpino, *J. Am. Chem. Soc.* **1993** 115:4397), O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis-(tetramethylene)uronium hexafluorophosphate (A. Erlich *et al. Tetrahedron Lett.* **1993** 34:4781), 2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (R. Knorr *et al. Tetrahedron Lett.* **1989** 30:1927), 7-azobenzotriazol-yoxy-*tris*-(pyrrolidino) hexafluorophosphate (F.

Albericio *et al.*, *Tetrahedron Lett.* **1997** 38:4853), 1-benzotriazolyloxy-*tris*-(dimethylamino)phosphonium hexafluorophosphate (B. Castro *et al.* *Tetrahedron Lett.* **1976** 14:1219) and, 1-benzotriazolyloxy-*tris*-pyrrolidinophosphonium hexafluorophosphate (J. Coste *et al.* *Tetrahedron Lett.* **1990** 31:205).

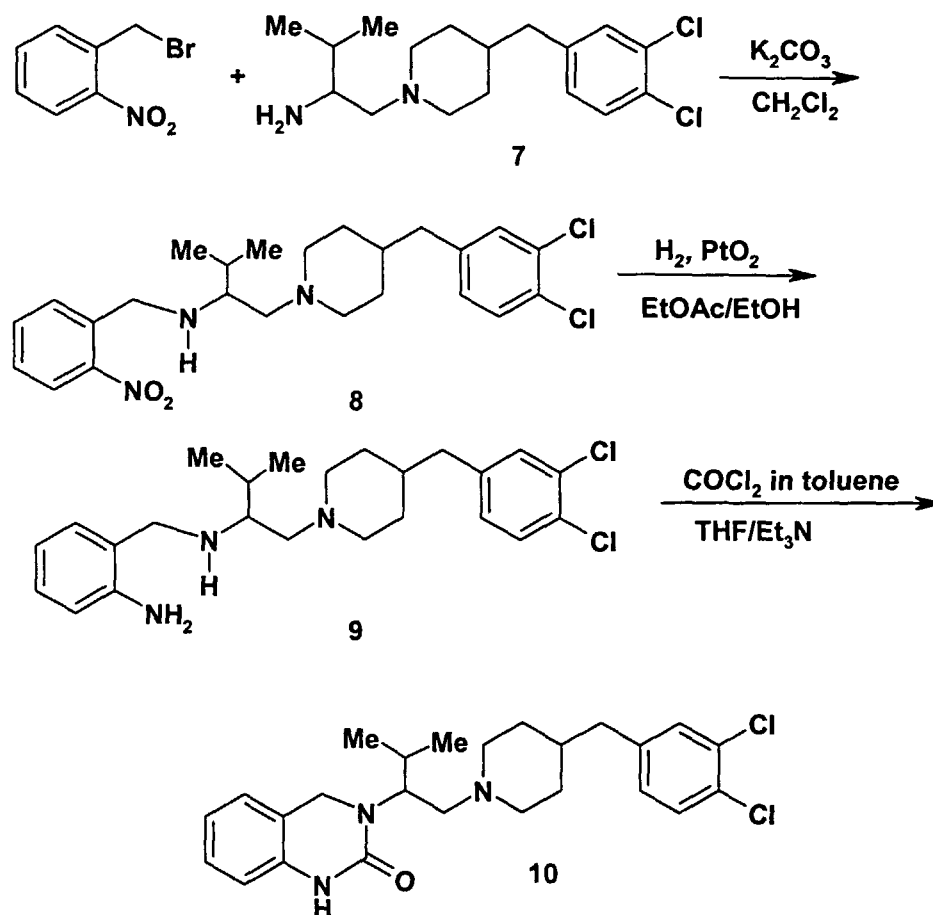
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Removal of the boc protecting group in an analogous manner to that described above affords **7** which can be converted to the compounds of the present invention. Reduction of **6** is typically carried out with a solution of diborane in THF in a manner well known to those of skill in the art (e.g. the reaction is run under inert conditions with an inert solvent, typically cyclic or acyclic ethers at about -20° C to 70° C). Alternate reducing agents are well known in the art (J. March, *supra* p. 1212-1213; A. G. M. Barrett *Reduction of Carboxylic Acid Derivatives to Alcohols, Ethers and Amines* in *Comprehensive Organic Synthesis* vol. 8, I. Fleming (Ed) **1991** 248-251). An alternative procedure to the two-step acylation and reduction sequence is direct alkylation of the piperidinyl nitrogen which may be advantageous depending on the nature of the amine and the alkylating agent. (Gibson in *The Chemistry of the Amino Group* S. Patai (ed), John Wiley, New York, 1968 p. 45-55).

10

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Scheme 2



The preparation of 3-{1-[4-(3,4-dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-3,4-dihydro-1H-quinazolin-2-one (10) shown in Scheme 2

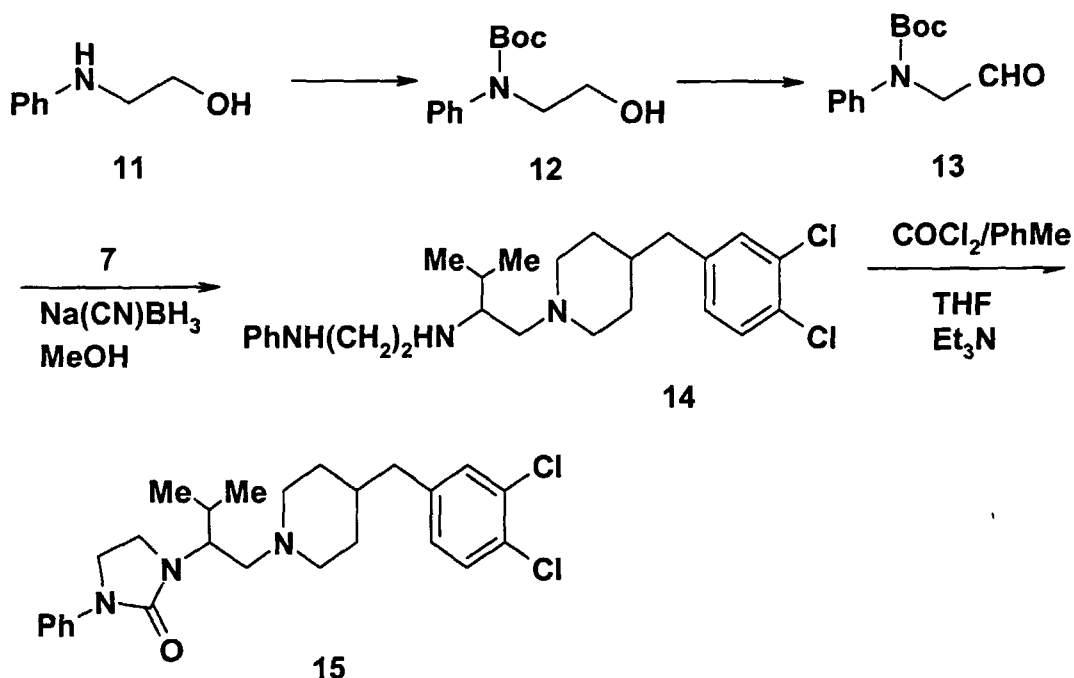
illustrates the the primary amine into a cyclic urea, and specifically a 4-dihydro-1H-quinazolin-2-one. Alkylation of amine 7 with 1-bromomethyl-2-nitrobenzene affords 8. Reduction of the nitro group to a primary amine was accomplished by

catalytic hydrogenation to yield 9. Alternative procedures for reduction of a nitro group are well know and can also be adapted to the preparation of the compounds

of the present invention (J. March, *supra*, p. 1216-1217) Intramolecular cyclization of the primary and secondary amines with phosgene or a phosgene equivalent such as diimidazole carbonyl afforded the urea 10 (A. F. Katritzky and A. F. Pozharskii *Handbook of Heterocyclic Chemistry*, 2nd Ed. Pergamon Press, Oxford 2000, p.573; A. F. Hegarty and L. J. Diennen, *Functions Containing Carbonyl Groups and Two Heteroatoms other than a Halogen of a Chalcone in Comprehensive Organic Functional Group Transformations*, T. L. Gilchrist (ed.) v. 6 chapter 6.16,

Pergamon Press, Oxford 1995 pp. 506-507; see pp. 500-501 for corresponding intermolecular process).

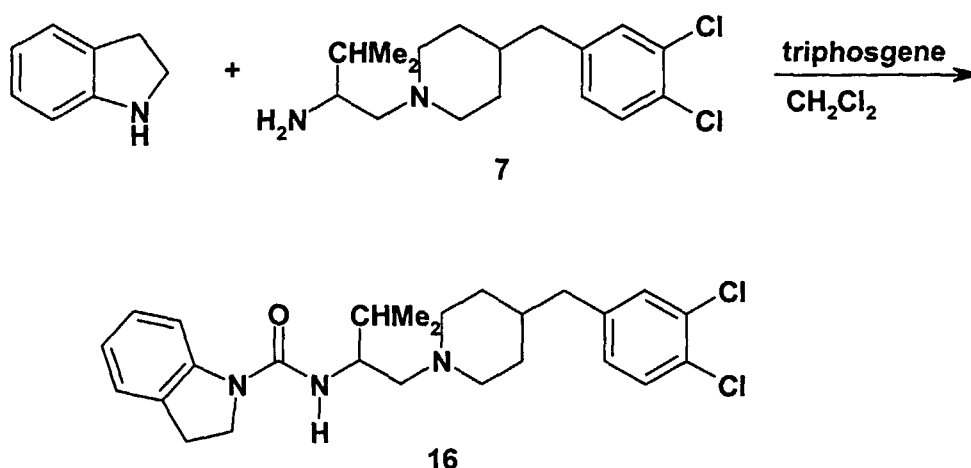
Scheme 3



An alternative to the amine acylation/reduction or alkylation sequences to substitute the piperdinyll nitrogen of 4 is reductive amination. Scheme 3 is an adaptation of the process to the synthesis of a 3-phenyl-imidazolidin-2-one. 2-Phenylaminoethanol (11) is treated with di-*tert*-butyl-dicarbonate to introduce the Boc protecting group and subsequently converted to 13 by oxidation with pyridinium dichromate to afford 13. Reductive amination (R. M. Hutchings and M. K. Hutchings *Reduction of C=N to CHNH by Metal Hydrides* in *Comprehensive Organic Synthesis* col. 8, I. Fleming (Ed) Pergamon, Oxford 1991 pp. 47-54) of 7 with piperidine 7 affords the triamine 14 which is subjected to intramolecular cyclization with phosgene to yield 1-{1-[4-(3,4-dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-3-phenyl-imidazolidin-2-one (15).

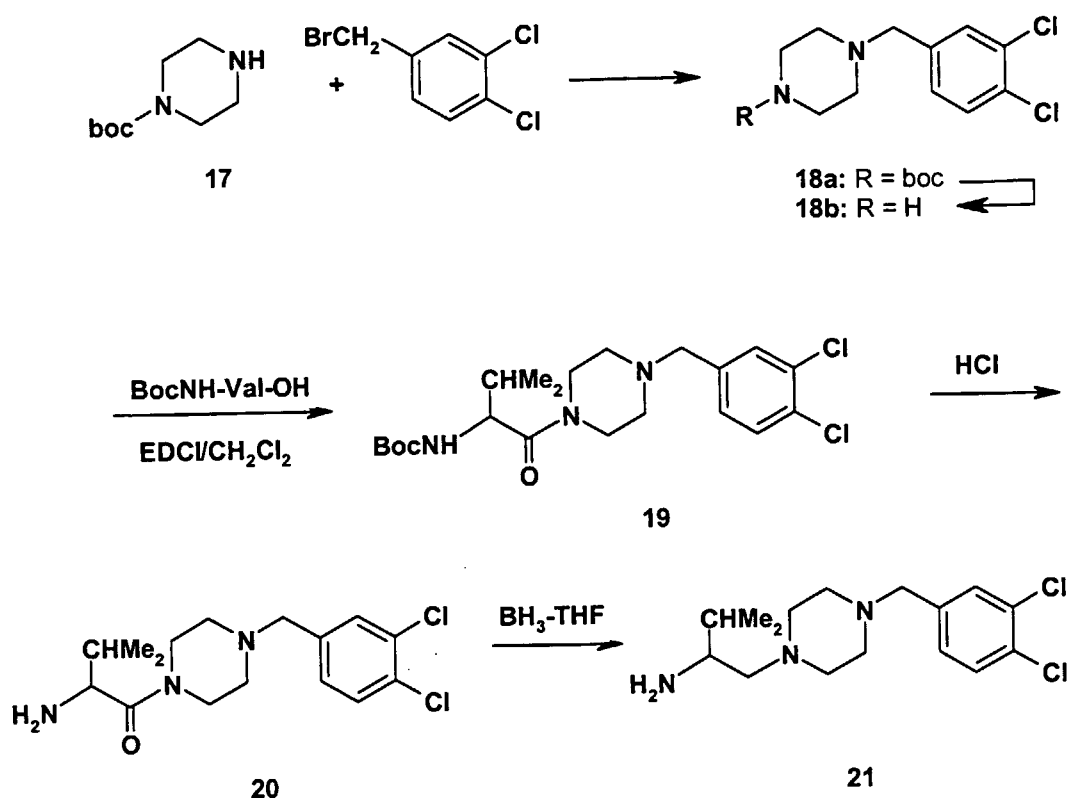
Scheme 4 depicts the phosgene-mediated intermolecular coupling of two amines, 7 and 2,3-dihydroindole to afford urea 16.

Scheme 4



Piperazine derivatives of the present invention can be prepared from the commercially available 1-boc-piperazine (Fluka; catalog number 15502). The unprotected amine can be substituted by direct alkylation of the amine or by an acylation/reduction sequence as described above. (Scheme 5). In the exemplified synthesis the amine is alkylated by 3,4-dichloro-bromomethyl-benzene. Removal of the boc protecting group with acid affords **18b**. The N-(2-amino-3-methylbutyl) substituent is incorporated by acylation/reduction analogously to the sequence described in Scheme 1. Coupling of **18a** with Boc-NH-Val-OH affords amide **19** which is deprotected by TFA treatment and subsequently reduced with diborane-THF to afford 1-[4-(3,4-dichloro-benzyl)-piperazin-1-ylmethyl]-2-methyl-propylamine (**21**). Intra-molecular cyclization of the primary amine with phosgene or an equivalent afforded N-carbamoyl, 3,4-dihydro-1H-quinazolin-2-one and imidazolidin-2-one derivatives as previously exemplified in Schemes 2 and 3.

Scheme 5

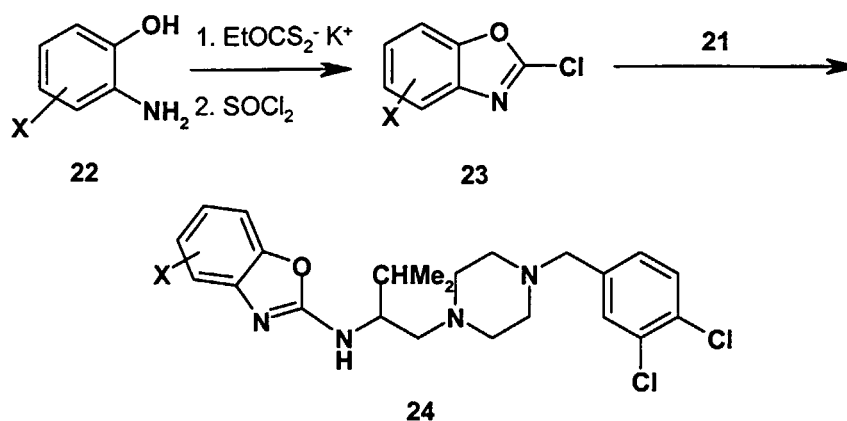


Heterocycle-substituted amines were prepared by contacting **21** with an optionally substituted heterocyclic ring susceptible to attack by nucleophiles. 2-Chlorobenzoxazole derivatives **23** are susceptible to attack by nucleophilic amines with subsequent expulsion of chloride ion to afford 2-aminobenzoxazoles compounds. Reacting **21** with **23** affords benzoxazol-2-yl-{1-[4-(3,4-dichlorobenzyl)-piperazin-1-ylmethyl]-2-methyl-propyl}-amine (**24**). 2-chlorobenzoxazoles (Scheme 6) are prepared by sequential treatment with potassium ethoxydithiocarbonate and thionyl chloride to afford **23**. The preparation of benzoxazoles has been reviewed (G. V. Boyd *Comprehensive Heterocyclic Chemistry*, K. T. Potts (ed.) v. 6, part 4B pp. 216-227)

Benzothiazoles and benzimidazoles of the present invention can be prepared analogously from benzothiazoles and benzimidazoles from suitable precursors. The synthesis of benzothiazoles and benzimidazoles is well known in the art (Benzothiazoles; J. Metzger, *Thiazoles and their Benzo Derivatives* in *Comprehensive Heterocyclic Chemistry* K. T. Potts (ed) v. 6, part 4B, Pergamon Press, Oxford pp. 321-326; A. Dondoni and P. Merino, *Comprehensive*

Heterocyclic Chemistry II v. 3, I. Shinkai (ed) Pergamon Press Oxford, 1996, pp. 431-452 ; Benzimidazoles, M. R. Grimmett *Imidazole and their Benzo Derivatives* (iii) *Synthesis and Applications in Comprehensive Heterocyclic Chemistry* K. T. Potts (ed.) Pergamon Press, Oxford v. 5, pp. 457-496; M.R. Grimmett *Imidazole and their Benzo Derivatives* (iii) *Synthesis and Applications in Comprehensive Heterocyclic Chemistry II* I. Shinkai (ed.) v. 3, Pergamon Press, Oxford, 1996, pp. 185-213).

Scheme 6



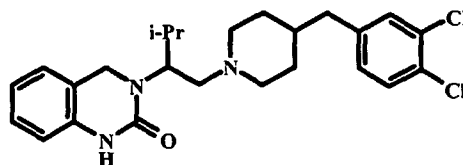
EXAMPLES

The following preparations and examples are provided to enable those skilled in the art to more clearly understand and to practice the present invention. However, these Examples should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

In general, the nomenclature used in this Application is based on AUTONOMTM v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. For convenience and consistency, acid addition salts are depicted with the piperidinyll nitrogen protonated. This is not intended to be a limitation and in individual cases protonation of other nitrogen atoms can occur and any protonated species is within the scope of the invention.

Example 1

3-{1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-3,4-dihydro-1H-quinazolin-2-one

**Step 1**

n-Butyl lithium (43.2 ml, 2M in pentane, 108 mmol) was slowly added to an ice-cooled suspension of 3,4-dichlorobenzyl triphenylphosphonium bromide (54 g, 108 mmol) (prepared by stirring equimolar amounts of 3,4-dichlorobenzyl bromide and triphenylphosphine in THF at 65 °C overnight) in dry THF (500 ml) under an argon atmosphere. After 15 min., the reaction mixture was allowed to warm to room temperature and then was stirred for an additional 2 h. 1-tert-butoxycarbonyl-4-piperidone (21.4 g, 108 mmol) was added, and the stirring was continued overnight. Hexane (2 l) was added and the reaction was stirred and then filtered. The filtrate was concentrated *in vacuo* to give 41.8 g of an orange gum. Column purification with silica gel and 70% DCM in hexane, followed by 100% DCM and a gradient of 1% MeOH/DCM through 5% MeOH/DCM gave 1-tert-butoxycarbonyl-4-(3,4-dichlorobenzylidene)piperidine (29 g) as a light tan oil.

Step 2

Platinum oxide (0.3 g) was added to a solution of 1-(tert-butoxycarbonyl)-3,4-dichlorobenzylidene)piperidine (29 g, 85 mmol) in EtOAc (500 ml), and the mixture was stirred under a hydrogen atmosphere overnight. The reaction mixture was filtered through a celite bed and the filtrate was concentrated to give 1-(tert-butoxycarbonyl)-3,4-dichlorobenzyl)piperidine (30 g) as an oil.

Step 3

TFA (50 ml) was added to a solution of 1-(tert-butoxycarbonyl)-3,4-dichlorobenzyl)piperidine (24 g, 70 mmol) in DCM (150 ml), and the reaction mixture was stirred for 1 h. The solvent was removed *in vacuo*, followed by addition of EtOAc (200 ml), and the resulting mixture was made basic with 1N

aqueous sodium hydroxide. The organic layer was separated, dried over magnesium sulfate, and the solvent was removed *in vacuo* to give 4-(3,4-dichlorobenzyl)piperidine (17 g) as light brown solid.

5 Step 4

To a solution of 4-(3,4-dichlorobenzyl)piperidine (23 g, 1.3 eq.) were added D-BOC-Valine (20 g, 82 mmol), EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) (20.3 g, 1.3 eq.) and HOBT (Benzotriazol-1-ol, 2.2 g, 0.2 eq.). The resulting mixture was stirred at rt. overnight. Volatile was removed and the residue was partitioned between EtOAc and aqueous NaHCO₃. The organic layer was washed with saturated brine and dried over Na₂SO₄. The crude product was purified on a silica gel column with 20% EtOAc in hexane to give 36 g of {1-[4-(3,4-Dichloro-benzyl)-piperidine-1-carbonyl]-2-methyl-propyl}-carbamic acid tert-butyl ester as a white forming [foaming?] material.

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Step 5

To a solution of {1-[4-(3,4-Dichloro-benzyl)-piperidine-1-carbonyl]-2-methyl-propyl}-carbamic acid tert-butyl ester (36 g, 0.08 mol) in 100 ml of CH₂Cl₂ was added TFA (35 ml, 0.45 mol). After the mixture was stirred at room temperature for 16 h, the volatile was removed and the residue was partitioned between EtOAc and KOH (20 g) in 100 ml of water. The organic layer was separated and washed with water, brine, and dried over Na₂SO₄. Concentration gave 28 g of 2-Amino-1-[4-(3,4-dichloro-benzyl)piperidin-1-yl]-3-methyl-butan-1-one.

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Step 6

2-Amino-1-[4-(3,4-dichloro-benzyl)piperidin-1-yl]-3-methyl-butan-1-one (28 g, 0.08 mol) was dissolved in 250 ml of THF and mixed with 500 ml of BH₃-THF (1.0 M). The reaction mixture was heated to reflux for 3h, then allowed to cool to room temperature, then cooled to an ice bath temperature. The solution was acidified with the dropwise addition of 3N HCl until pH<3. Volatile was removed and the residue was reconstituted in 100 ml of EtOH and 300 ml of 3N HCl. After the resulting mixture was heated to 82 °C for 1.5 h, it was cooled to room temperature and then basified with NaOH (aq.). The product was extracted with

30

EtOAc and the organic layer was washed with NaCl (sat.) and dried over Na₂SO₄. Column purification on silica gel with 2.5% to 5% of (10% NH₄OH in MeOH) in CH₂Cl₂ gave 24 g of 1-[4-(3,4-dichloro-benzyl)-piperidin-1-ylmethyl]-2-methylpropylamine.

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Step 7

2-Nitrobenzyl bromide (69 mg, 1.05 eq.) was mixed up with 1-[4-(3,4-dichloro-benzyl)-piperidin-1-ylmethyl]-2-methylpropylamine (100 mg, 0.3 mmol) in 5 ml of CH₂Cl₂ in the presence of K₂CO₃ (84 mg, 2 eq.). After the mixture was stirred at room temperature overnight, it was quenched with water and extracted with EtOAc. The organic layer was separated, washed with brine, and dried over Na₂SO₄. Column purification on silica gel with 25% acetone, 25% CH₂Cl₂ in hexane gave 100 mg of {1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-(2-nitro-benzyl)-amine as an oil.

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Step 8

{1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-(2-nitro-benzyl)-amine (90 mg, 0.19 mmol) was reduced under 1 atm of H₂ in EtOH/EtOAc (5 ml/5 ml) in the presence of PtO₂. After stirring for 2h, it was filtered through a celite bed and concentrated to give 89 mg of 2-({1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propylamino}-methyl)-phenylamine.

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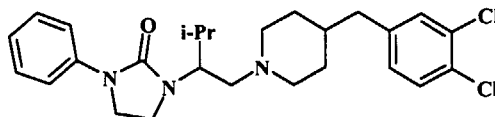
Step 9

To a solution of 2-({1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propylamino}-methyl)-phenylamine (80 mg, 0.18 mmol) in 10 ml of dry THF was added Et₃N (0.094 ml, 3.7 eq.), followed by the addition of 20% phosgene in toluene (0.087 ml, 0.18 mmol). After the mixture was stirred at room temperature for 2h, the volatile was removed. The residue was partitioned between water and CH₂Cl₂. The organic layer was washed with water, NaCl (sat.) and dried over Na₂SO₄. Column purification with 5% MeOH in CH₂Cl₂ gave 70 mg of the desired product, 3-{1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-3,4-dihydro-1H-quinazolin-2-one.

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Example 2

1-{1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-3-phenyl-imidazolidin-2-one

**Step 1**

5 2-Phenylamino-ethanol (5.0 g, 36 mmol) and di-t-butyl-dicarbonate (1.9 g, 1.5 eq.) in 50 ml of THF was heated to 55°C for 7 h. Volatile was then removed *in vacuo*. The crude product was recrystallized from CH₂Cl₂ and hexane to give 8.1 g of white crystalline material ((2-Hydroxy-ethyl)-phenyl-carbamic acid tert-butyl ester).

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Step 2

 (2-Hydroxy-ethyl)-phenyl-carbamic acid tert-butyl ester (3.0 g, 13 mmol) was mixed with PDC (5.3 g, 1.1 eq.) in 50 ml of CH₂Cl₂ and stirred at room temperature for 16 h. The reaction mixture was then diluted with Et₂O, filtered
15 through florisil, and the colorless filtrate was concentrated. The residue was purified on a silica gel column with 15% EtOAc in hexane to give 1.6 g of (2-Oxo-ethyl)-phenyl-carbamic acid tert-butyl ester as a colorless oil.

Step 3

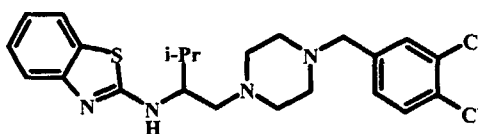
20 A mixture of (2-Oxo-ethyl)-phenyl-carbamic acid tert-butyl ester (0.5 g, 2.13 mmol) and 1-[4-(3,4-dichloro-benzyl)-piperidin-1-ylmethyl]-2-methylpropylamine (0.7 g, 1 eq.) in 30 ml of MeOH was stirred with 3 Å molecular sieves (10 g) for 0.5 h. NaCNBH₃ (0.081 g, 0.6 eq.) was then added and the mixture was stirred for another 3 h. The reaction was quenched with a few drops of
25 3N HCl and filtered through a celite bed. The crude product was purified on a silica gel column with 3% (10% NH₄OH in MeOH) in CH₂Cl₂ to give 0.35 g of N-{1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-N'-phenyl-ethane-1,2-diamine.

Step 4

To a solution of N-{1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-N'-phenyl-ethane-1,2-diamine (0.2 g, 0.45 mmol) and Et₃N (0.22 ml, 3.5 eq.) in 25 ml of THF was added 20% phosgene in toluene (0.42 ml, 0.85 mmol) dropwise. The solution was stirred for 1 h at room temperature, and the volatile was removed. The residue was partitioned between EtOAc and NaHCO₃ (aq.), and the organic layer was separated, washed with brine, and dried over Na₂SO₄. Preparative TLC with 5% MeOH, 2.5 % hexane in CH₂Cl₂ gave 0.12 g of Example 2, i.e., 1-{1-[4-(3,4-Dichloro-benzyl)-piperidin-1-ylmethyl]-2-methyl-propyl}-3-phenyl-imidazolidin-2-one, which was converted to HCl salt.

Referential Example 1

Benzothiazol-2-yl-{1-[4-(3,4-dichloro-benzyl)-piperazin-1-ylmethyl]-2-methyl-propyl}-amine



Step 1

3,4-Dichlorobenzyl bromide (35.2 g, 150 mmol) was added to a solution of N-(tert-butoxycarbonyl)piperazine (24.8 g, 130 mmol) and triethylamine (21 mL, 150 mmol) in DCM (100 mL) over 30 min. After 1h, the reaction mixture was diluted with EtOAc, and the product precipitated out as the hydrochloride salt with addition of 1N aqueous hydrogen chloride solution. The solid product was filtered, washed with water, and then resuspended in EtOAc. Two equivalents of 1N aqueous sodium hydroxide solution was added and the free amine was extracted into EtOAc. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated to provide 1-(tert-butoxycarbonyl)-4-(3,4-dichlorobenzyl)piperazine (45 g).

Step 2

TFA (75 ml, 0.97 mol) was added to a solution of 1-(tert-butoxycarbonyl)-4-(3,4-dichlorobenzyl)piperazine (45 g, 0.13 mol) in DCM (75 ml). The mixture was stirred for 1h at room temperature and then made basic with a sodium

hydroxide solution. The product was extracted into EtOAc and the organic layer was washed with sodium bicarbonate solution, dried over magnesium sulfate, and concentrated *in vacuo* to give 1-(3,4-dichlorobenzyl)piperazine (35.8 g) as a solid.

5 Step 3

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.08 g, 26.5 mmol) was added to a solution of 1-(3,4-dichlorobenzyl)piperazine (5 g, 20.4 mmol) and (D,L)-Boc-valine (5.76 g, 26.5 mmol) in DCM. After 2h, the product was extracted into EtOAc. The organic layer was washed with sodium bicarbonate solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography with hexane/EtOAc (1:1) gave 1-[4-(3,4-dichlorobenzyl)piperazin-1-ylcarbonyl]-N-(tert-butoxycarbonyl)-2-methylpropylamine (5.46 g) as a form.[or foam?]

15 Step 4

Ethereal hydrogen chloride solution (80 ml, 80 mmol) was added to a solution of 1-[4-(3,4-dichlorobenzyl)piperazin-1-ylcarbonyl]-N-(tert-butoxycarbonyl)-2-methylpropylamine (4.28 g, 9.64 mmol) in MeOH (50 ml) and the mixture was heated at 70°C. After 2.5 h, the reaction mixture was concentrated and the solid was suspended in ether and filtered to give 1-[4-(3,4-dichlorobenzyl)piperazin-1-ylcarbonyl]-2-methylpropylamine as the hydrochloride salt. The product was dissolved in water, treated with Triethylamine (4 ml) and the free amine was extracted into EtOAc, The EtOAc layer was dried over magnesium sulfate, filtered, and concentrated to give 1-[4-(3,4-dichlorobenzyl)piperazin-1-ylcarbonyl]-2-methylpropylamine (3.2 g) as the free amine.

25 Step 5

A 1.0 M diborane solution in THF (65.2 ml, 65.2 mmol) was added to a solution of 1-[4-(3,4-dichlorobenzyl)piperazin-1-ylcarbonyl]-2-methylpropylamine (3.2 g, 9.3 mmol) in THF (15 ml). The mixture was heated at reflux under nitrogen for 2h and then concentrated *in vacuo*. The residue was dissolved in MeOH, acidified with 6 N hydrogen chloride solution (50 ml), and then reheated to 70°C. After 1h, the reaction mixture was cooled and basified with a sodium hydroxide solution and the product was extracted into EtOAc. The EtOAc layer was washed

with sodium bicarbonate solution, dried over magnesium sulfate, filtered and concentrated to provide 1-[4-(3,4-dichlorobenzyl)piperazin-1-ylmethyl]-2-methylpropylamine (3.53 g) as an oil.

5 Step 6

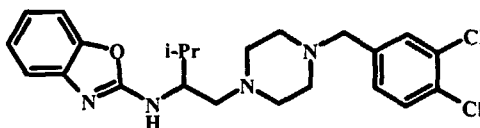
To a solution of 2-methylsulfanyl-benzothiazole (1.22, 6.7 mmol) dissolved in 15 mL of acetic acid was added potassium permanganate (1.81 g, 1.7 eq.) in 17 mL of H₂O. The resulting mixture was heated for 30 min and stirred at rt. for over 48 h. The reaction was quenched with NaHSO₃, and the pH of the solution was
10 adjusted to 8 with NH₄OH. The reaction was extracted with EtOAc, the EtOAc layer was washed with H₂O, dried over Na₂SO₄ and concentrated to give the desired product, 2-methanesulfonyl-benzothiazole. M⁺: 213.

Step 7

15 2-Methanesulfonylbenzothiazole (0.055 g, 0.25 mmol) and 1-[4-(3,4-dichlorobenzyl)piperazin-1-ylmethyl]-2-methylpropylamine (84 mg, 0.25 mmol) were heated to 130°C under argon. After 90 min, the mixture was cooled. It was then purified on a silica gel column with 40% EtOAc in hexane first, followed by 1% i-PrNH₂, 10% MeOH in EtOAc to give benzothiazol-2-yl-{1-[4-(3,4-dichloro-
20 benzyl)-piperazin-1-ylmethyl]-2-methyl-propyl}-amine (39%). M⁺: 462.

Referential Example 2

Benzooxazol-2-yl-{1-[4-(3,4-dichloro-benzyl)-piperazin-1-ylmethyl]-2-methylpropyl}amine



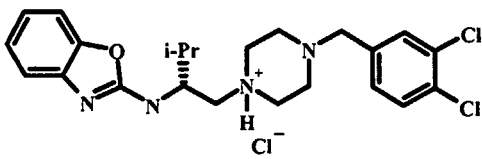
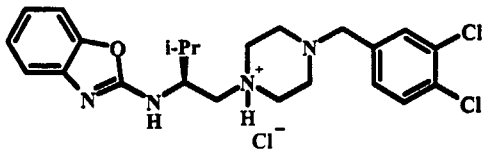
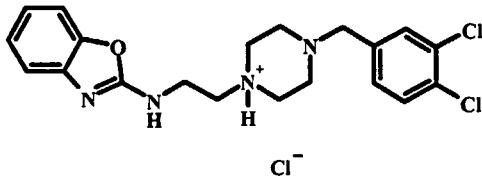
25

To a solution of 1-[4-(3,4-dichlorobenzyl)piperazin-1-ylmethyl]-2-methylpropylamine (0.108 g, 0.33 mmol) and diisopropylethylamine (0.17 ml, 3eq.) in 1.5 ml of THF was added dropwise 2-chloro-benzooxazole (0.04 ml, 0.36 mmol) in 0.36 ml of THF at 0°C. The resulting mixture was stirred at 0°C for 2h
30 and then allowed to warm to room temperature, where it was stirred for an

additional 2h. Volatile was removed *in vacuo* and the residue was partitioned between EtOAc and water. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified on a silica gel column with 40% EtOAc in hexane first, followed by 1% *i*-PrNH₂, 10% MeOH in EtOAc to give benzooxazol-2-yl- $\{1-[4-(3,4\text{-dichloro-benzyl})\text{-piperazin-1-ylmethyl}]\text{-2-methyl-propyl}\}$ amine (85%), M^+ : 446.

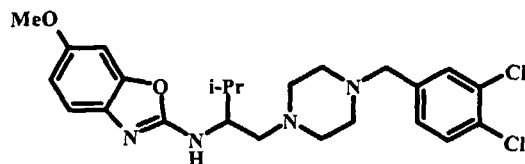
Examples 3-5

The compounds described in Table 1 were prepared following the procedure described in Referential Example 1, Steps 1-5 and Referential Example 2 above, but substituting BOC-valine with the desired amino acid, i.e., L-BOC-valine (Ex. 3), D-BOC-valine (Ex. 4), and BOC-glycine (Ex. 5).

TABLE 1				
Ex. No	Structure	Compound Name	(MW) MS m.p.	CCR3 IC ₅₀
3		1-[(R)-2-(Benzooxazol-2-ylamino)-3-methylbutyl]-4-(3,4-dichlorobenzyl)-piperazin-1-ium; chloride RO1164829-001	447.41	
4		1-[(S)-2-(Benzooxazol-2-ylamino)-3-methylbutyl]-4-(3,4-dichlorobenzyl)-piperazin-1-ium; chloride RO4002895-001	447.41 M^+ =446	4.35
5		1-[2-(Benzooxazol-2-ylamino)-ethyl]-4-(3,4-dichlorobenzyl)-piperazin-1-ium; chloride RO1164827-001	405.33 M^+ =404	

Referential Example 3

{1-[4-(3,4-Dichloro-benzyl)-piperazin-1-ylmethyl]-2-methyl-propyl}-(6-methoxy-benzooxazol-2-yl)-amine

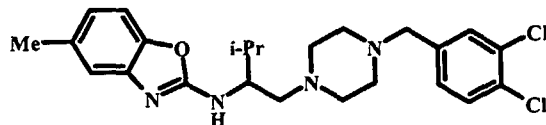


5 **Step 1**

2-Amino-5-methoxy-phenol hydrochloride salt (0.203 g, 1.2 mmol) and potassium salt of dithiocarbonic acid O-ethyl ester were dissolved in 4 ml of pyridine and heated to reflux for 2h. The reaction mixture was cooled to room temperature and quenched by pouring into 5 ml of water (ice cold). To the mixture, 0.22 ml of conc. HCl was added and stirred for 30 min. Solid was filtered, washed with water, and dried *in vacuo* overnight. To the above product was added SOCl₂ (0.55 ml, 7.6 mmol) and 2 drops of DMF. After the reaction was heated to 70 °C for 30 min, it was cooled room temperature. Excess SOCl₂ was removed *in vacuo* and the residue was purified on a silica gel column with 5% MeOH in CH₂Cl₂ to give {1-[4-(3,4-Dichloro-benzyl)-piperazin-1-ylmethyl]-2-methyl-propyl}-(6-methoxy-benzooxazol-2-yl)-amine.

Referential Example 4

{1-[4-(3,4-Dichloro-benzyl)-piperazin-1-ylmethyl]-2-methyl-propyl}-(5-methyl-benzooxazol-2-yl)-amine



20 **Step 1**

To a solution of 2-amino-p-cresol (1.81 g, 0.015 mol) and KOH (1.2 eq. 0.99 g) in 30 ml of EtOH was added methanedithione (18 ml). The resulting mixture was heated to reflux for 18 h. Upon cooling, the volatile was removed *in vacuo* and the residue was partitioned between EtOAc and 18 ml of 1N HCl. The

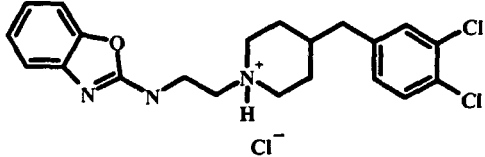
organic layer was separated, washed with water, dried over sodium sulfate, and concentrated to give 5-Methyl-3H-benzooxazole-2-thione (1.2 g, M+1: 165).

Step 2

5-Methyl-3H-benzooxazole-2-thione (0.539 g, 1.64 mmol) and 1-[4-(3,4-dichlorobenzyl)piperazin-1-ylmethyl]-2-methylpropylamine (0.225 g, 1.64 mmol) were dissolved in 1.5 ml of toluene and heated to reflux for 2h. The reaction mixture was cooled to room temperature and the volatile removed *in vacuo*. The crude product was purified on a silica gel column with 40% EtOAc in hexane, followed by 1% i-PrOH, 9% MeOH in EtOAc to give 0.25 g of {1-[4-(3,4-Dichloro-benzyl)-piperazin-1-ylmethyl]-2-methyl-propyl}-(5-methyl-benzooxazol-2-yl)-amine. M.p. 155.3-156.9 °C; MS: M⁺+1: 461.

Examples 6

The compounds described in Table 2 were prepared following the procedure described in Example 1, Steps 1-6 and Referential Example 1, but substituting BOC-valine with the desired amino acid BOC-glycine (Example 6).

TABLE 2			
Ex. No.	Structure	Compound Name	(MW) MS mp (°C)
6		1-[2-(Benzooxazol-2-ylamino)-ethyl] -4-(3,4-dichloro-benzyl)-piperidinium; chloride	404 M ⁺ = 404 217- 233

Examples 7-25

Examples 7 -25 as described in Table 3 were prepared following the same or similar methods described above for Examples 1 through 6 and Referential Example 1 through 4.

5

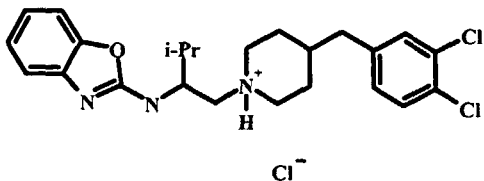
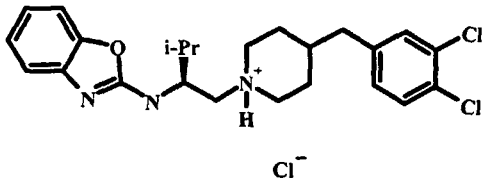
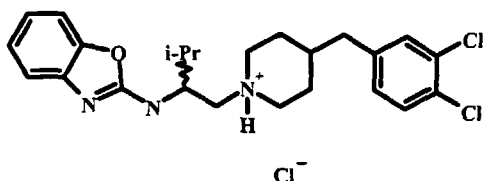
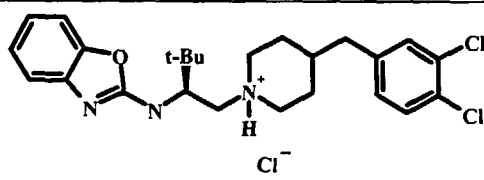
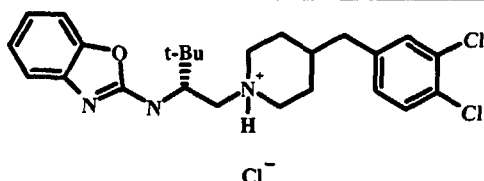
TABLE 3			
Ex No	Structure	Compound Name	(MW) M+H mp
7		1-[2-(Benzooxazol-2-ylamino)-3-methyl-butyl]-4-(3,4-dichloro-benzyl)-piperidinium; chloride	446.42 446 151-156
8		1-[(S)-2-(Benzooxazol-2-ylamino)-3-methyl-butyl]-4-(3,4-dichloro-benzyl)-piperidinium; chloride	
9		1-[2-(Benzooxazol-2-ylamino)-3-methyl-butyl]-4-(3,4-dichloro-benzyl)-piperidinium; chloride	446.42 M ⁺ =446 6
10		1-[(S)-2-(benzooxazol-2-ylamino)-3,3-dimethyl-butyl]-4-(3,4-dichloro-benzyl)-piperidinium; chloride	460.45 460 253-258
11		1-[(R)-2-(benzooxazol-2-ylamino)-3,3-dimethyl-butyl]-4-(3,4-dichloro-benzyl)-piperidinium; chloride	460.45 460

TABLE 3

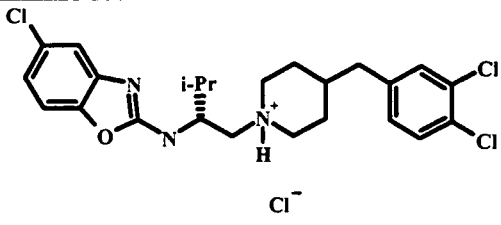
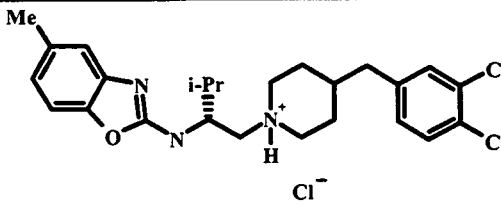
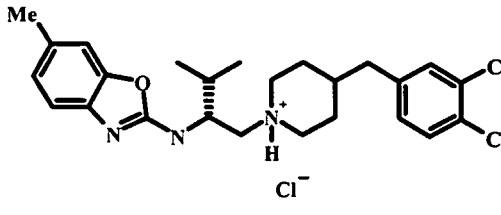
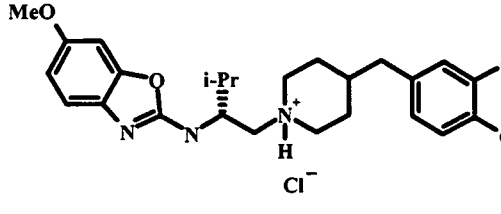
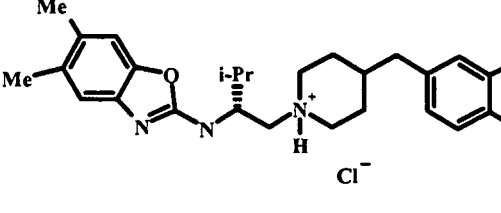
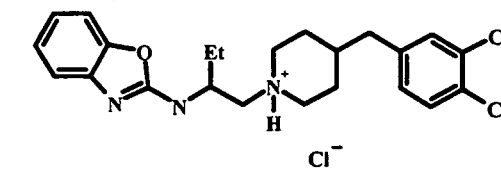
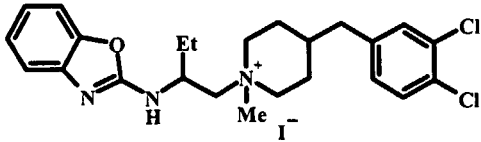
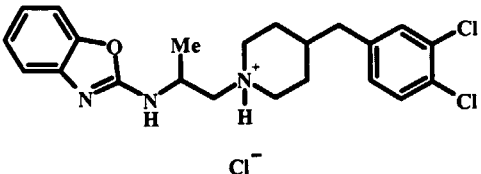
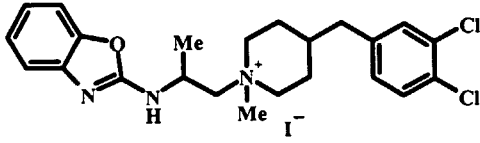
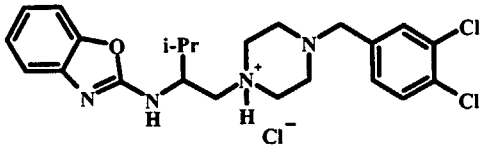
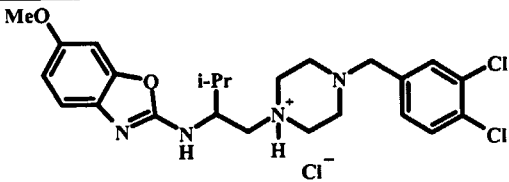
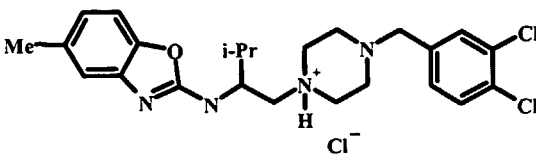
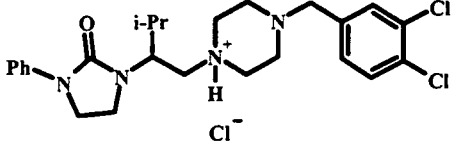
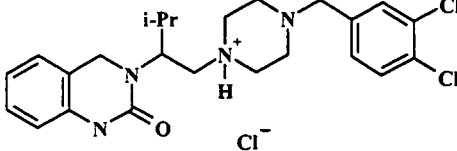
Ex No	Structure	Compound Name	(MW) M+H mp
12		1-[(R)-2-(6-chloro-benzooxazol-2-ylamino)-3-methyl-butyl]-4-(3,4-dichloro-benzyl)-piperidinium; chloride	480.86 480 215- 224
13		4-(3,4-Dichloro-benzyl)-1-[(R)-3-methyl-2-(5-methyl-benzooxazol-2-ylamino)-butyl]-piperidinium; chloride	460.45 460 141.0- 144.5
14		4-(3,4-Dichloro-benzyl)-1-[(R)-3-methyl-2-(6-methyl-benzooxazol-2-ylamino)-butyl]-piperidinium; chloride	460.45 M ⁺ =45 9
15		4-(3,4-Dichloro-benzyl)-1-[(R)-2-(6-methoxy-benzooxazol-2-ylamino)-3-methyl-butyl]-piperidinium; chloride	476.45 476
16		4-(3,4-Dichloro-benzyl)-1-[(R)-2-(5,6-dimethyl-benzooxazol-2-ylamino)-3-methyl-butyl]-piperidinium; chloride	474.47 M ⁺ =47 3 145- 1533
17		1-[2-(Benzooxazol-2-ylamino)-butyl]-4-(3,4-dichloro-benzyl)-piperidinium; chloride	432.39 432

TABLE 3

Ex No	Structure	Compound Name	(MW) M+H mp
			123- 130
18		1-[2-(Benzooxazol-2-ylamino)-butyl]-4-(3,4-dichloro-benzyl)-1-methyl-piperidinium; iodide	447.43 M ⁺ =44 6 123.0- 128.5
19		1-[2-(Benzooxazol-2-ylamino)-propyl]-4-(3,4-dichloro-benzyl)-piperidinium; chloride	418.37 418
20		1-[2-(Benzooxazol-2-ylamino)-propyl]-4-(3,4-dichloro-benzyl)-1-methyl-piperidinium iodide	433.40 432 129.0- 137.5
21		1-[2-(Benzooxazol-2-ylamino)-3-methyl-butyl]-4-(3,4-dichloro-benzyl)-piperazin-1-ium; chloride	447.41 446
22		4-(3,4-Dichloro-benzyl)-1-[2-(6-methoxy-benzooxazol-2-ylamino)-3-methyl-butyl]-piperazin-1-ium; chloride	477.43 476
23		4-(3,4-Dichloro-benzyl)-1-[3-methyl-2-(5-methyl-benzooxazol-2-ylamino)-butyl]-piperazin-1-ium; chloride	461.43 461

24		4-(3,4-Dichloro-benzyl)- 1-[3-methyl-2-(2-oxo-3- phenyl-imidazolidin-1-yl)- butyl]-piperazin-1-ium; chloride	474.47 474
25		4-(3,4-Dichloro-benzyl)- 1-[3-methyl-2-(2-oxo-1,4- dihydro-2H-quinazolin-3- yl)-butyl]-piperazin-1- ium; chloride	460.45 460

Example 26-Formulation Examples

The following are representative pharmaceutical formulations containing a
5 compound of Formula (I).

Tablet Formulation

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

10

Ingredient	Quantity per tablet, mg
compound of this invention	400
Cornstarch	50
croscarmellose sodium	25
Lactose	120
magnesium stearate	5

Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

5

Suspension Formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbit (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
distilled water	q.s. to 100 ml

10

Injectable Formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	0.2 g
sodium acetate buffer solution	0.4M 2.0 ml
HCl (1N) or NaOH (1N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 ml

15

Liposomal Formulation

The following ingredients are mixed to form a liposomal formulation.

Ingredient	Amount
compound of this invention	10 mg
L-.alpha.-phosphatidylcholine	150 mg
tert-butanol	4 ml
Freeze dry the sample and lyophilize overnight. Reconstitute the sample with 1 ml 0.9% saline solution. Liposome size can be reduced by sonication.	

20

Example 27**CCR-3 Receptor Binding Assay--*In Vitro***

The CCR-3 antagonistic activity of the compounds of the invention was determined by their ability to inhibit the binding of ^{125}I eotaxin to CCR-3 L1.2 transfectant cells (see Ponath, P. D. et al., J. Exp. Med., Vol. 183, 2437-2448, (1996)).

The assay was performed in Costar 96-well polypropylene round bottom plates. Test compounds were dissolved in DMSO and then diluted with binding buffer (50 mM HEPES, 1 mM CaCl_2 , 5 mM MgCl_2 , 0.5% bovine serum albumin (BSA), 0.02% sodium azide, pH 7.24) such that the final DMSO concentration was 2%. 25 μl of the test solution or only buffer with DMSO (control samples) was added to each well, followed by the addition of 25 μl of ^{125}I -eotaxin (100 pmol) (NEX314, New England Nuclear, Boston, Mass.) and 1.5×10^5 of the CCR-3 L1.2 transfected cells in 25 μl binding buffer. The final reaction volume was 75 μl .

After incubating the reaction mixture for 1 hour at rt., the reaction was terminated by filtering the reaction mixture through polyethylenimine treated Packard Unifilter GF/C filter plate (Packard, Chicago, Ill.). The filters were washed four times with ice cold wash buffer containing 10 mM HEPES and 0.5M sodium chloride (pH 7.2) and dried at 65°C for approximately 10 minutes. 25 μl /well of Microscint-20® scintillation fluid (Packard) was added and the radioactivity retained on the filters was determined by using the Packard TopCount®. Compounds of this invention were tested and found to have a measurable level of activity in this assay.

Example	CCR3 Binding IC_{50} (μM)
11	0.15
21	0.97

Example 28**Inhibition of Eotaxin Mediated Chemotaxis of CCR-3 L1.2 Transfected Cells--*In Vitro* Assay**

5 The CCR-3 antagonistic activity of the compounds of this invention can be determined by measuring the inhibition of eotaxin mediated chemotaxis of the CCR-3 L1.2 transfectant cells, using a slight modification of the method described in Ponath, P. D. et al., J. Clin. Invest. 97: 604-612 (1996). The assay is performed in a 24-well chemotaxis plate (Costar Corp., Cambridge, Mass.). CCR-3 L1.2
10 transfectant cells are grown in culture medium containing RPMI 1640, 10% Hyclone® fetal calf serum, 55 mM 2-mercaptoethanol and Geneticin 418 (0.8 mg/ml). 18-24 hours before the assay, the transfected cells are treated with n-butyric acid at a final concentration of 5 mM/1x10⁶ cells/ml, isolated and resuspended at 1x10⁷ cells/ml in assay medium containing equal parts of RPMI
15 1640 and Medium 199 (M 199) with 0.5% bovine serum albumin.

 Human eotaxin suspended in phosphate buffered saline at 1 mg/ml is added to bottom chamber in a final concentration of 100 nm. Transwell culture inserts (Costar Corp., Cambridge, Mass.) having 3 micron pore size are inserted into each
20 well and L1.2 cells (1x10⁶) are added to the top chamber in a final volume of 100 µl. Test compounds in DMSO are added both to the top and bottom chambers such that the final DMSO volume is 0.5%. The assay is performed against two sets of controls. The positive control contained cells with no test compound in the top chamber and only eotaxin in the lower chamber. The negative control contains
25 cells with no test compound in the top chamber and neither eotaxin nor test compound in lower chamber. The plate is incubated at 37 °C. After 4 hours, the inserts are removed from the chambers and the cells that have migrated to the bottom chamber are counted by pipetting out 500 µl of the cell suspension from the lower chamber to 1.2 ml Cluster tubes (Costar) and counting them on a FACS for
30 30 seconds.

Example 29**Inhibition of Eotaxin Mediated Chemotaxis of Human Eosinophils—*In Vitro* Assay**

The ability of compounds of the invention to inhibit eotaxin mediated chemotaxis of human eosinophils can be assessed using a slight modification of procedure described in Carr, M. W. et al., Proc. Natl. Acad. Sci. USA, 91: 3652-3656 (1994). Experiments are performed using 24 well chemotaxis plates (Costar Corp., Cambridge, Mass.). Eosinophils are isolated from blood using the procedure described in PCT Application, Publication No. WO 96/22371. The endothelial cells used are the endothelial cell line ECV 304 obtained from European Collection of Animal Cell Cultures (Porton Down, Salisbury, U.K.). Endothelial cells are cultured on 6.5 mm diameter Biocoat.RTM. Transwell tissue culture inserts (Costar Corp., Cambridge, Mass.) with a 3.0 μ M pore size. Culture media for ECV 304 cells consists of M199, 10% Fetal Calf Serum, L-glutamine and antibiotics. Assay media consists of equal parts RPMI 1640 and M199, with 0.5% BSA. 24 hours before the assay 2×10^5 ECV 304 cells are plated on each insert of the 24-well chemotaxis plate and incubated at 37 °C. 20 nM of eotaxin diluted in assay medium is added to the bottom chamber. The final volume in bottom chamber is 600 μ l. The endothelial coated tissue culture inserts are inserted into each well. 10^6 eosinophil cells suspended in 100 μ l assay buffer are added to the top chamber. Test compounds dissolved in DMSO are added to both top and bottom chambers such that the final DMSO volume in each well was 0.5%. The assay is performed against two sets of controls. The positive control contains cells in the top chamber and eotaxin in the lower chamber. The negative control contains cells in the top chamber and only assay buffer in the lower chamber. The plates are incubated at 37 °C. in 5% CO₂ /95% air for 1-1.5 hours.

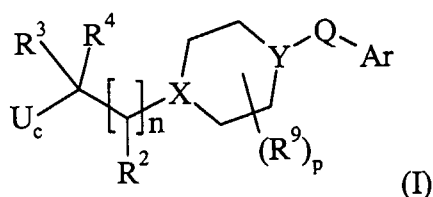
The cells that migrate to the bottom chamber are counted using flow cytometry. 500 μ l of the cell suspension from the lower chamber are placed in a tube, and relative cell counts are obtained by acquiring events for a set time period of 30 seconds.

Example 30**Inhibition of Eosinophil Influx Into the Lungs of Ovalbumin Sensitized Balb/c Mice by CCR-3 Antagonist--*In Vivo* Assay**

The ability of the compounds of the invention to inhibit leukocyte infiltration into the lungs can be determined by measuring the inhibition of eosinophil accumulation into the bronchioalveolar lavage (BAL) fluid of Ovalbumin (OA)-sensitized balb/c mice after antigen challenge by aerosol. Briefly, male balb/c mice weighing 20-25g are sensitized with OA (10 µg in 0.2 ml aluminum hydroxide solution) intraperitoneally on days 1 and 14. After a week, the mice are divided into ten groups. Test compound or only vehicle (control group) or anti-eotaxin antibody (positive control group) is administered either intraperitoneally, subcutaneously or orally. After 1 hour, the mice are placed in a Plexiglass box and exposed to OA aerosol generated by a PARISTAR.TM. nebulizer (PARI, Richmond, Va.) for 20 minutes. Mice which have not been sensitized or challenged are included as a negative control. After 24 or 72 hours, the mice are anesthetized (urethane, approx. 1 g/kg, i.p.), a tracheal cannula (PE 60 tubing) is inserted and the lungs are lavaged four times with 0.3 ml PBS. The BAL fluid is transferred into plastic tubes and kept on ice. Total leukocytes in a 20 µl aliquot of the BAL fluid is determined by Coulter Counter.TM. (Coulter, Miami, Fla.). Differential leukocyte counts are made on Cytospin.TM. preparations which have been stained with a modified Wright's stain (DiffQuick.TM.) by light microscopy using standard morphological criteria.

Claims

1. A compound of Formula (I):



wherein:

Ar is aryl or heteroaryl;

Q is $-C(=O)-$ or C_{1-2} alkylene;

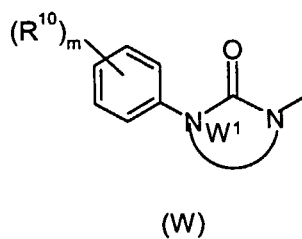
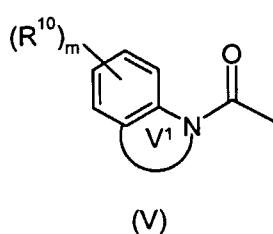
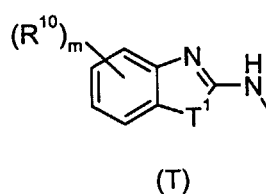
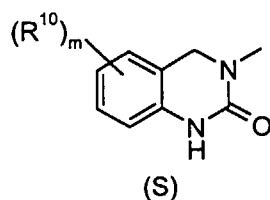
10 X is N or $N^+R^{9a}Z^-$; Y is CR^{9a} or N;

Z is a pharmaceutically acceptable anion;

R^2 is hydrogen or C_{1-8} alkyl;

15 R^3 and R^4 are, independently of each other, hydrogen, C_{1-8} alkyl, substituted C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-7} cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroalkyl, $-(C_{1-8} \text{ alkylene})-C(=O)-Z^1$, or $-(C_{1-8} \text{ alkylene})-C(O)_2Z^1$, wherein Z^1 is C_{1-8} alkyl, halo C_{1-8} alkyl, C_{1-8} alkoxy, halo C_{1-8} alkoxy, hydroxy, amino, alkylamino, aryl, aryl C_{1-8} alkyl, aryloxy, aryl C_{1-8} alkyloxy, heteroaryl, or heteroaryloxy;

U_c is selected from the group consisting of (S), (T), (V), and (W),



20 wherein T^1 is O, S, or NR^5 , wherein R^5 is selected from the group consisting of hydrogen, C_{1-8} alkyl, substituted C_{1-8} alkyl, C_{3-7} cycloalkyl, and

heterocyclyl; and V^1 and W^1 define an optionally substituted five-to-six membered heterocyclo ring, provided that when U_c is T and T^1 is S, then at least one of R^3 and R^4 is not hydrogen, and provided that when both X and Y are N, U_c is not T;

5 R^9 is attached to any available carbon atom of the piperidinyl or piperazinyl ring and is selected from the group consisting of hydroxy, C_{1-4} alkoxy, oxo (=O), halogen, cyano, halo C_{1-4} alkyl, halo C_{1-4} alkoxy, and C_{1-4} alkyl optionally substituted by one or two substituents independently selected from R^{15} ;

10 R^{9a} and R^{9b} are independently selected from the group consisting of hydrogen and C_{1-8} alkyl optionally substituted by one or two substituents independently selected from R^{15} ;

15 R^{10} is attached to any available carbon atom of the benzo or phenyl ring and at each occurrence is independently selected from the group consisting of C_{1-8} alkyl, substituted C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, halogen, cyano, halo C_{1-8} alkoxy, amino, alkylamino, heterocyclyl, heteroaryl, C_{3-7} cycloalkyl or phenyl, said heterocyclyl, heteroaryl, C_{3-7} cycloalkyl and phenyl being optionally substituted by one to three substituents independently selected from R^{16} ;

20 R^{15} at each occurrence is independently selected from the group consisting of hydroxy, C_{1-4} alkoxy, halo, cyano, trifluoromethyl, trifluoromethoxy, amino, and alkylamino;

R^{16} at each occurrence is independently selected from the group consisting of C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halo, cyano, trifluoromethyl, trifluoromethoxy, amino and alkylamino;

25 m is 0, 1, 2, 3, or 4;

n is 0 or 1; and

p is 0, 1, 2, 3 or 4; or a prodrug, isomer, mixture of isomers, or pharmaceutically-acceptable salt thereof;

wherein

30 the term "aryl" means a monocyclic or bicyclic aromatic hydrocarbon radical which is optionally substituted by one, two or three substituents selected from the group consisting of C_{1-8} alkyl, heteroalkyl, acyl, acylamino, amino, alkylamino, C_{1-8} alkylthio, alkylsulfinyl, alkylsulfonyl, $-SO_2NR'R''$ (where R' and R'' are independently hydrogen or C_{1-8} alkyl), C_{1-8} alkoxy, halo C_{1-8} alkoxy, C_{1-8}

alkoxycarbonyl, carbamoyl, hydroxy, halo, nitro, cyano, mercapto, methylenedioxy, ethylenedioxy, acyl C₁₋₈ alkyl, acylamino C₁₋₈ alkyl, hydroxyl C₁₋₈ alkyl, C₁₋₈ alkoxy C₁₋₈ alkyl, halo C₁₋₈ alkoxy C₁₋₈ alkyl, cyano C₁₋₈ alkyl, amino C₁₋₈ alkyl, alkylamino C₁₋₈ alkyl, halo C₁₋₈ alkyl, halo C₁₋₈ alkyl(C₁₋₈ alkyl), C₁₋₈ alkoxycarbonyl C₁₋₈ alkyl, alkylsulfonyl C₁₋₈ alkyl, alkylsulfinyl C₁₋₈ alkyl, C₁₋₈ alkylthio C₁₋₈ alkyl and an optionally-substituted phenyl;

the term "heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two or three ring heteroatoms selected from N, O and S, the remaining ring atoms being C, with the understanding that when the heteroaryl group is a bicyclic system, the point of attachment to the heteroaryl group will be to an aromatic ring containing at least one heteroatom, and the heteroaryl ring being optionally substituted by one, two, three or four substituents independently selected from C₁₋₈ alkyl, heteroalkyl, acyl, acylamino, amino, alkylamino, C₁₋₈ alkylthio, alkylsulfinyl, alkylsulfonyl, -SO₂NR'R'' (where R' and R'' are independently hydrogen or C₁₋₈ alkyl), C₁₋₈ alkoxy, halo C₁₋₈ alkoxy, C₁₋₈ alkoxycarbonyl, carbamoyl, hydroxy, halo, nitro, cyano, mercapto, methylenedioxy, ethylenedioxy, acyl C₁₋₈ alkyl, acylamino C₁₋₈ alkyl, hydroxyl C₁₋₈ alkyl, C₁₋₈ alkoxy C₁₋₈ alkyl, halo C₁₋₈ alkoxy C₁₋₈ alkyl, cyano C₁₋₈ alkyl, amino C₁₋₈ alkyl, alkylamino C₁₋₈ alkyl, halo C₁₋₈ alkyl, halo C₁₋₈ alkyl(C₁₋₈ alkyl), C₁₋₈ alkoxycarbonyl C₁₋₈ alkyl, alkylsulfonyl C₁₋₈ alkyl, alkylsulfinyl C₁₋₈ alkyl, and C₁₋₈ alkylthio C₁₋₈ alkyl, and optionally-substituted phenyl;

the term "substituted alkyl" means an alkyl group having one, two or three substituents selected from the group consisting of acyl, acylamino, hydroxy, C₁₋₈ alkoxy, halo C₁₋₈ alkoxy, cyano, amino, alkylamino, halo C₁₋₈ alkyl, halo, C₁₋₈ alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, C₁₋₈ alkylthio, aryl, C₃₋₇ cycloalkyl, heteroaryl and heterocyclyl;

the term "heterocyclyl" means a saturated or unsaturated non-aromatic cyclic radical of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from O, S(O)_n (where n is an integer from 0 to 2), and NR^x, the remaining ring atoms being carbon atoms {wherein each R^x is independently hydrogen, C₁₋₈ alkyl, acyl, alkylsulfonyl, aminosulfonyl, (alkylamino)sulfonyl, carbamoyl, (alkylamino)carbonyl, (carbamoyl) C₁₋₈ alkyl, or (alkylamino)carbonyl C₁₋₈ alkyl, and the heterocyclyl ring being optionally substituted by one, two, or three

substituents independently selected as valence permits from the group consisting of C₁₋₈ alkyl, halo C₁₋₈ alkyl, heteroalkyl, halo, nitro, cyano, cyano C₁₋₈ alkyl, hydroxy, hydroxyl C₁₋₈ alkyl, amino, alkylamino, -(X)_n-C(=O)R (where X is O or NR', *n* is 0 or 1, R is hydrogen, C₁₋₈ alkyl, halo C₁₋₈ alkyl, hydroxy, C₁₋₈ alkoxy, amino, or alkylamino); - C₁₋₈ alkylene-C(=O)R (where R is hydrogen, C₁₋₈ alkyl, halo C₁₋₈ alkyl, hydroxy, C₁₋₈ alkoxy, amino or alkylamino); and -S(O)_nR^d (where *n* is an integer from 0 to 2, and R^d is hydrogen, C₁₋₈ alkyl, halo C₁₋₈ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₈ alkyl, amino, alkylamino, or hydroxyl C₁₋₈ alkyl, provided that R^d is not hydrogen when *n* is 1 or 2);

the term "heteroalkyl" means an alkyl radical wherein one, two or three hydrogen atoms have been replaced with a substituent independently selected from the group consisting of -OR^a, -NR^bR^c, and -S(O)_nR^d (where *n* is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl radical is through a carbon atom, wherein R^a is hydrogen, acyl, C₁₋₈ alkyl, C₃₋₇ cycloalkyl, or C₃₋₇ cycloalkyl C₁₋₈ alkyl; R^b and R^c are independently of each other hydrogen, acyl, C₁₋₈ alkyl, C₃₋₇ cycloalkyl, or C₃₋₇ cycloalkyl C₁₋₈ alkyl; and when *n* is 0, R^d is hydrogen, C₁₋₈ alkyl, C₃₋₇ cycloalkyl, or C₃₋₇ cycloalkyl C₁₋₈ alkyl, and when *n* is 1 or 2, R^d is C₁₋₈ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₈ alkyl, amino, acylamino, or alkylamino;

the term "alkylamino" means a radical -NHR or -NRR where R is selected from an C₁₋₈ alkyl, C₃₋₇ cycloalkyl or C₃₋₇ cycloalkyl C₁₋₈ alkyl;

the term "acyl" means a radical -C(=O)R, where R is hydrogen, C₁₋₈ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₈ alkyl, phenyl, or phenyl C₁₋₈ alkyl;

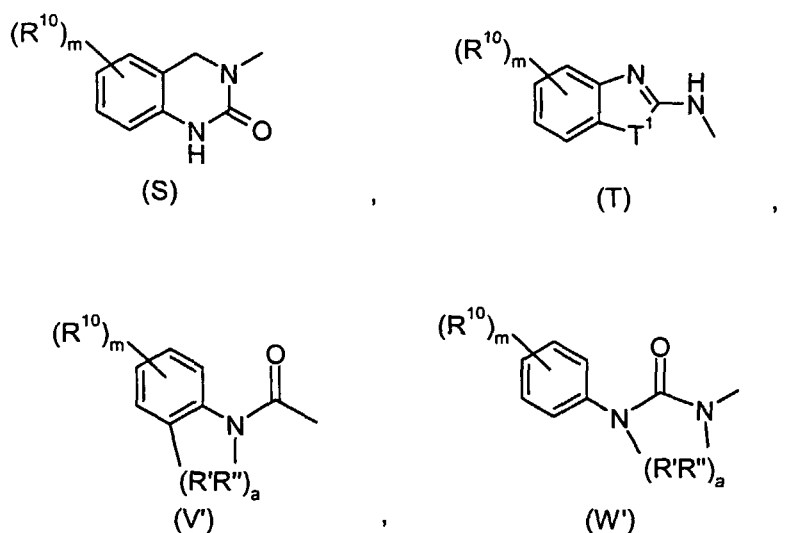
the term "optionally substituted phenyl" or "optionally substituted pyrimidinyl" mean a phenyl group or a pyrimidinyl group which is optionally substituted by one, two or three substituents selected from the group consisting of C₁₋₈ alkyl, heteroalkyl, acyl, acylamino, amino, alkylamino, C₁₋₈ alkylthio, alkylsulfinyl, alkylsulfonyl, -SO₂NR'R'' (where R' and R'' are independently hydrogen or C₁₋₈ alkyl), C₁₋₈ alkoxy, halo C₁₋₈ alkoxy, C₁₋₈ alkoxycarbonyl, hydroxy, halo, nitro, cyano, mercapto, acyl C₁₋₈ alkyl, acylamino C₁₋₈ alkyl, hydroxyl C₁₋₈ alkyl, C₁₋₈ alkoxy C₁₋₈ alkyl, halo C₁₋₈ alkoxy C₁₋₈ alkyl, cyano C₁₋₈ alkyl, amino C₁₋₈ alkyl, C₁₋₈ alkylamino C₁₋₈ alkyl, halo C₁₋₈ alkyl, halo C₁₋₈ alkyl(C₁₋₈ alkyl), C₁₋₈ alkoxycarbonyl C₁₋₈ alkyl, alkylsulfonyl C₁₋₈ alkyl, alkylsulfinyl C₁₋₈ alkyl, and C₁₋₈ alkylthio C₁₋₈ alkyl;

the term "alkylsulfonyl" means a radical $-S(O)_2R$, where R is C_{1-8} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl C_{1-8} alkyl group;

the term "alkylsulfinyl" means a radical $-S(O)R$, where R is C_{1-8} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl C_{1-8} alkyl group;

- 5 the term "carbamoyl" means a group $-C(=O)NRR'$, wherein R and R' are independently selected from hydrogen, C_{1-8} alkyl, substituted C_{1-8} alkyl, C_{3-7} cycloalkyl or heterocyclyl.

- 10 2. The compound according to claim 1 wherein U_c is selected from the group consisting of (S), (T), (V'), and (W'),



- 15 wherein R' and R'' at each occurrence are, independently of each other, hydrogen, C_{1-8} alkyl, hydroxy, C_{1-8} alkoxy, halogen, cyano, halo C_{1-8} alkoxy, amino or alkylamino, and a is an integer of 2 or 3.

3. The compound according to any one of claims 1 and 2, wherein U_c is T, and R^4 is methyl, ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl.

20

4. The compound according to any one of claims 1 and 2, wherein:
 Ar is optionally-substituted phenyl or optionally-substituted pyrimidinyl;
 Q is CH_2 ;
 25 R^2 is hydrogen;

R^3 and R^4 are, independently of each other, hydrogen, C_{1-8} alkyl, hydroxyl C_{1-8} alkyl, or C_{1-8} alkoxy C_{1-8} alkyl;

R^9 is selected from methyl, ethyl, hydroxy, methoxy, oxo (=O), halo, and cyano;

R^{9a} and R^{9b} are selected from hydrogen, methyl and ethyl;

5 n is 1; and

p is 0 or 1.

5. The compound according to any one of claims 1 to 4, wherein X is N and Y is CR^{9b} .

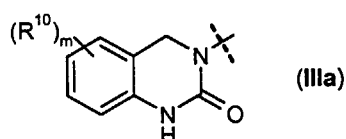
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6. The compound according to any one of claims 1 to 4, wherein both X and Y are N.

7. The compound according to any one of claims 1 to 4, wherein X is $N^+R^{9a}Z^-$, and Y is CR^{9b} .

15

8. The compound according to any one of claims 1 and 2, wherein U_c is **IIIa**;

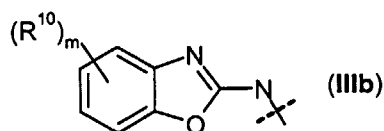


wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and

20 m is 0, 1, or 2.

9. The compound according to any one of claims 1 and 2, wherein:

U_c is **IIIb**;



25 wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and m is 0, 1, or 2.

10. The compound according to claim 9, wherein:

Ar is phenyl or pyrimidinyl optionally substituted by one, two or three groups

30 selected from the group consisting of halo, C_{1-8} alkyl, heteroalkyl, C_{1-8} alkoxy, nitro, trifluoromethyl, C_{1-8} alkylsulfonyl, and optionally-substituted phenyl;

Q is CH₂;

R² is hydrogen;

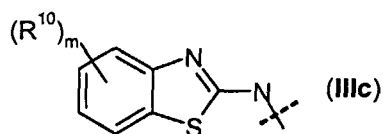
R³ is hydrogen;

R⁴ is methyl, ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl;

5 and

R⁹ is selected from C₁₋₄ alkyl, oxo (=O), halogen, and hydroxy.

11. The compound according to any one of claims 1 and 2, wherein U_c is **IIIc** ;



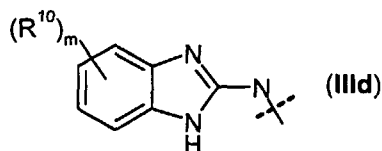
10 wherein R¹⁰ is selected from C₁₋₄ alkyl, halogen, cyano, and C₁₋₄ alkoxy; and
 m is 0, 1, or 2.

12. The compound according to claim 11, wherein:

R² and R³ are hydrogen; and

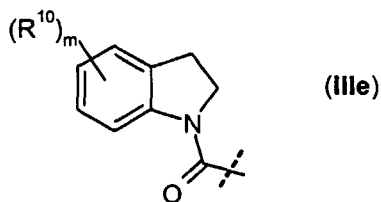
15 R⁴ is methyl, ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl.

13. The compound according to any one of claims 1 and 2, wherein U_c is **IIIId** ;



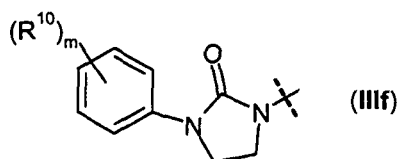
20 wherein R¹⁰ is selected from C₁₋₄ alkyl, halogen, cyano, and C₁₋₄ alkoxy; and
 m is 0, 1, or 2.

14. The compound according to any one of claims 1 and 2, wherein U_c is **IIIe** ;



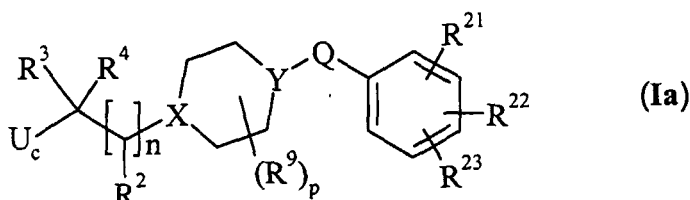
25 wherein R¹⁰ is selected from C₁₋₄ alkyl, halogen, cyano, and C₁₋₄ alkoxy; and
 m is 0, 1, or 2.

15. The compound according to any one of claims 1 and 2, wherein U_c is **III f**;



wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and
 5 m is 0, 1, or 2.

16. The compound according to any one of claims 1 and 2, having Formula
 (Ia):



10 wherein,

X is N or $N^+R^{9a}Z^-$; Y is CR^{9a} or N;

Z is a pharmaceutically acceptable anion;

R^2 and R^3 are hydrogen;

15 R^{9a} is hydrogen or C_{1-4} alkyl;

R^{21} , R^{22} , and R^{23} are attached to any available carbon atom of the phenyl ring and
 are independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen,
 cyano, trifluoromethyl, trifluoromethoxy, C_{1-4} alkylsulfonyl, amino, and
 alkylamino;

20 n is 1, and

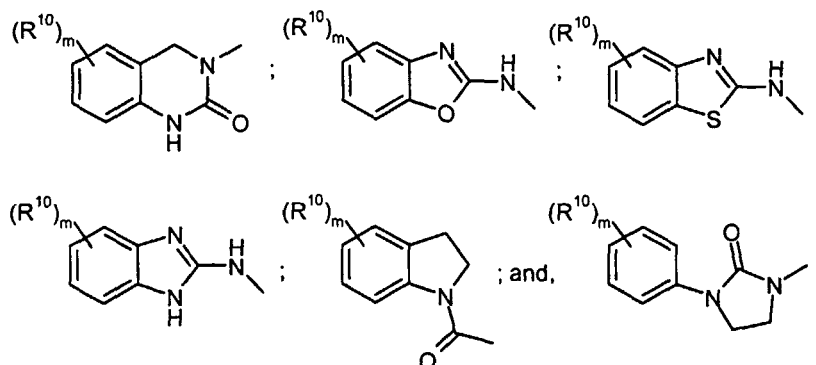
U_c , Q , P , R^4 and R^9 are as defined in claim 1 or 2.

17. The compound according to claim 16, wherein Q is CH_2 .

25 18. The compound according to any one of claims 16 and 17, wherein:
 R^{21} , R^{22} , and R^{23} , and the phenyl ring to which they are attached, form 4-
 chlorophenyl or 3,4-dichlorophenyl;

R^4 is methyl, ethyl, 1-methylethyl, isopropyl, 1-hydroxyethyl or 2-hydroxyethyl;
and
 p is 0 or 1.

19. The compound according to any one of claims 16, 17 and 18, in which U_c is selected from the group consisting of



wherein R^{10} is selected from C_{1-4} alkyl, halogen, cyano, and C_{1-4} alkoxy; and
 m is 0, 1, or 2.

10

20. A pharmaceutical composition comprising a therapeutically-effective amount of a compound according to any one of claims 1 to 19 or a salt thereof and a pharmaceutically-acceptable excipient.

21. A compound according to any one of claims 1 to 19 or a salt thereof for use in medical therapy or diagnosis.

22. A use of a compound of Formula (I) according to any one of claims 1 to 19 or a salt thereof for the manufacture of a medicament comprising one or more compounds according to any one of claims 1 to 19 or a salt thereof for the treatment of a disease treatable by a CCR-3 receptor antagonist.

23. The use according to claim 22, wherein the disease is asthma.

24. The invention as herein before described, particularly with reference to the new compounds, intermediates, medicaments, uses and processes.
