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(54) Title:  4(SPIROPIPERIDINYL)METHYL SUBSTITUTED PYRROLIDINES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

(57) Abstract:  3-Substituted pyrrolidines having a spiroperidinylmethyl substituent on the 4-position of the ring are useful as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors CCR-3 and/or CCR-5.
4-(SPIROPIPERIDINYL)METHYL SUBSTITUTED PYRROLIDINES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation (reviewed in Schall, *Cytokine*, 3, 165-183 (1991) and Murphy, *Rev. Immun.*, 12, 593-633 (1994)). There are two classes of chemokines, C-X-C (α) and C-C (β), depending on whether the first two cysteines are separated by a single amino acid (C-X-C) or are adjacent (C-C). The α-chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils, whereas β-chemokines, such as RANTES, MIP-1α, MIP-1β, monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin are chemotactic for macrophages, T-cells, eosinophils and basophils (Deng, et al., *Nature*, 381, 661-666 (1996)).


Chemokine receptors, such as CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, CXCR-4, have been implicated as being important mediators of
inflammatory and immunoregulatory disorders and diseases, including asthma, rhinitis and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. A review of the role of chemokines in allergic inflammation is provided by Kita, H., et al., J. Exp. Med. 183, 2421-2426 (1996). An antagonist of the CCR3 receptor, Met-chemokine beta 7, has been proposed to be useful in ameliorating leukocyte infiltration associated with allergic inflammation (Nibbs, et al., J. Immunol., 164, 1488-1497 (2000)). Accordingly, agents which modulate chemokine receptors would be useful in such disorders and diseases. Compounds which modulate chemokine receptors would be especially useful in the treatment and prevention of atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and particularly bronchial asthma.

A retrovirus designated human immunodeficiency virus (HIV-1) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV.

Certain compounds have been demonstrated to inhibit the replication of HIV, including soluble CD4 protein and synthetic derivatives (Smith, et al., Science, 238, 1704-1707 (1987)), dextran sulfate, the dyes Direct Yellow 50, Evans Blue, and certain azo dyes (U.S. Patent No. 5,468,469). Some of these antiviral agents have been shown to act by blocking the binding of gp120, the coat protein of HIV, to its target, the CD4 glycoprotein of the cell.

Entry of HIV-1 into a target cell requires cell-surface CD4 and additional host cell cofactors. Fusin has been identified as a cofactor required for infection with virus adapted for growth in transformed T-cells, however, fusin does not promote entry of macrophagotropic viruses which are believed to be the key pathogenic strains of HIV in vivo. It has recently been recognized that for efficient entry into target cells, human immunodeficiency viruses require the chemokine receptors CCR-5 and CXCR-4, as well as the primary receptor CD4 (Levy, N. Engl. J. Med., 335(20), 1528-1530 (Nov. 14 1996)). The principal cofactor for entry mediated by the envelope glycoproteins of primary macrophage-trophic strains of HIV-1 is CCR5, a receptor for the β-chemokines RANTES, MIP-1α and MIP-1β (Deng, et al., Nature, 381, 661-666 (1996)). HIV attaches to the CD4 molecule on cells through a region of its envelope protein, gp120. It is believed that the CD-4 binding site on the gp120 of HIV interacts with the CD4 molecule on the cell surface, and undergoes conformational changes which allow it to bind to another cell-surface receptor, such as CCR5 and/or CXCR-4. This brings the viral envelope closer to the cell surface and allows interaction between gp41 on the viral envelope and a fusion domain on the cell surface, fusion with the cell membrane, and entry of the viral core into the cell. It has been shown that β-chemokine ligands prevent HIV-1 from fusing with the cell (Dragic, et al., Nature,
381, 667-673 (1996)). It has further been demonstrated that a complex of gp120 and soluble CD4 interacts specifically with CCR-5 and inhibits the binding of the natural CCR-5 ligands MIP-1α and MIP-1β (Wu, et al., Nature, 384, 179-183 (1996); Trkola, et al., Nature, 384, 184-187 (1996)).

Humans who are homozygous for mutant CCR-5 receptors which do not serve as co-receptors for HIV-1 in vitro appear to be unusually resistant to HIV-1 infection and are not immuno-compromised by the presence of this genetic variant (Nature, 382, 722-725 (1996)). Absence of CCR-5 appears to confer protection from HIV-1 infection (Nature, 382, 668-669 (1996)). Other chemokine receptors may be used by some strains of HIV-1 or may be favored by non-sexual routes of transmission. Although most HIV-1 isolates studied to date utilize CCR-5 or fusin, some can use both as well as the related CCR-2B and CCR-3 as co-receptors (Nature Medicine, 2(11), 1240-1243 (1996)). Nevertheless, drugs targeting chemokine receptors may not be unduly compromised by the genetic diversity of HIV-1 (Zhang, et al., Nature, 383, 768 (1996)). Accordingly, an agent which could block chemokine receptors in humans who possess normal chemokine receptors should prevent infection in healthy individuals and slow or halt viral progression in infected patients. By focusing on the host's cellular immune response to HIV infection, better therapies towards all subtypes of HIV may be provided. These results indicate that inhibition of chemokine receptors presents a viable method for the prevention or treatment of infection by HIV and the prevention or treatment of AIDS.

The peptides eotaxin, RANTES, MIP-1α, MIP-1β, MCP-1, and MCP-3 are known to bind to chemokine receptors. As noted above, the inhibitors of HIV-1 replication present in supernatants of CD8+ T cells have been characterized as the β-chemokines RANTES, MIP-1α and MIP-1β.

SUMMARY OF THE INVENTION

The present invention is directed to compounds which are modulators of chemokine receptor activity and are useful in the prevention or treatment of certain inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which chemokine receptors are involved.

The present invention is further concerned with compounds which inhibit the entry of human immunodeficiency virus (HIV) into target cells and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the prevention and/or treatment of the
resulting acquired immune deficiency syndrome (AIDS). The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the prevention and treatment of AIDS and viral infection by HIV.

5

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of formula I:

\[
\text{I}
\]

wherein

X is selected from (1) \(-(\text{CH}_2)_m\)-, wherein m is 1, 2 or 3, (2) -CO-, and (3) -CH(\text{C}_1-\text{C}_6 \text{ alkyl})-,

one of Y\text{1} and Y\text{2} is O and the other is C(R\text{5}R\text{6});

R\text{1} is selected from (1) hydrogen, (2) \text{C}_1-10 \text{ alkyl}, (3) \text{C}_2-10 \text{ alkenyl}, (4) CH(R\text{8})-Ar, (5) C(O)-Ar, (6) Ar, and (7) CO_2R\text{4c}; wherein alkyl and alkenyl are each unsubstituted or substituted with OR\text{4c}, CN, CO_2R\text{4c}, OC(O)(\text{C}_1-\text{C}_6 \text{ alkyl}), OC(O)(\text{halo substituted C}_1-\text{C}_6 \text{ alkyl}), \text{C}_3-7 \text{ cycloalkyl};

Ar is phenyl, pyridyl or imidazolyl wherein each is unsubstituted or substituted with halogen, OH, \text{C}_1-\text{C}_6 \text{ alkyl} optionally substituted with halogen, or OC\text{1-6} \text{ alkyl} optionally substituted with halogen;

R\text{8} is H or OR\text{9};

R\text{2} is selected from (1) hydrogen, (2) \text{C}_1-\text{C}_6 \text{ alkyl}, (3) \text{C}_2-\text{C}_6 \text{ alkenyl}, and (4) benzyl; or

R\text{1} and R\text{2} taken together represent (1) \(\text{CR}_4\text{C}R\text{4d}\), (2) \(-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\)-, or (3) \(-\text{CH}_2\text{CH}(\text{CH}_3)\text{OCH}(\text{CH}_3)\text{CH}_2\)-;

R\text{3} is selected from (1) phenyl, (2) heterocycl, (3) \text{C}_1-6 \text{ alkyl}, (4) \text{C}_2-6 \text{ alkenyl}, (5) \text{C}_2-6 \text{ alkylnyl},

(6) \text{C}_3-6 \text{ cycloalkyl}, (7) \text{CO}_2\text{R}\text{9}, (8) \text{CONR}\text{9R}\text{9}, (9) \text{CH}(\text{R}\text{8})-\text{heterocycl}, (10) \text{CN}, (11) \text{C(O)R}\text{9}, (12) \text{OCOR}\text{9}, (13) \text{OCO}_2\text{R}\text{9} and (14) \text{OCONR}\text{9R}\text{10}, wherein phenyl, heterocycl, alkyl, alkenyl, alkylnyl and cycloalkyl are unsubstituted or substituted, and the substituent(s) are
selected from halogen, CN, C1-6alkyl, (CH2)0-1OR\textsuperscript{4c}, OC3-6alkenyl, (CH2)0-1C(O)2R\textsuperscript{4c},
OC(O)2R\textsuperscript{4c}, OC(O)R\textsuperscript{4c}, OC(O)NR\textsuperscript{4c}R\textsuperscript{4d}, C(O)R\textsuperscript{4c}, SO\textsubscript{2}C1-6alkyl, phenyl, heterocycl,
trifluoromethyl and trifluoromethoxy;
R\textsuperscript{4c}, R\textsuperscript{4d}, and R\textsuperscript{4f} are independently selected from hydrogen and C1-6 alkyl;
R\textsuperscript{5} is selected from (1) hydrogen, (2) C1-6 alkyl, (3) C2-6 alkenyl, (4) CN, (5) CO\textsubscript{2}R\textsuperscript{4c}, and (6) OH; wherein alkyl and alkenyl are unsubstituted or substituted with OR\textsuperscript{4c}, CO\textsubscript{2}R\textsuperscript{4c} or CN;
R\textsuperscript{6} is selected from (1) hydrogen, (2) C1-6 alkyl, and (3) C2-6 alkenyl; or
R\textsuperscript{5} and R\textsuperscript{6} together represent oxo;
R\textsuperscript{7} is selected from phenyl, naphthyl, biphenyl, fluorenyl, indenyl, indanyl, dihydronaphthyl,
tetrahydronaphthyl, octahydronaphthyl, adamantyl, and heterocycle, each of which is
unsubstituted or substituted, where the substituents are independently selected from:

(a) C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, O-C1-6 alkyl, O-C2-6 alkenyl,
O-C2-6 alkynyl wherein the alkyl, alkenyl, and alkynyl moieties are each
unsubstituted or substituted, wherein the substituents are independently
selected from

(i) hydroxy,
(ii) halogen,
(iii) -NR\textsuperscript{9}R\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are independently selected from
hydrogen, C1-6 alkyl, C2-6 alkenyl, and C2-6 alkynyl, wherein the
alkyl, alkenyl, and alkynyl are each unsubstituted or substituted,
wherein the substituents are independently selected from (A)
phenyl, naphthyl and heterocycle each of which is unsubstituted or
substituted, and wherein the substituents are independently
selected from halogen, hydroxy, C1-6alkyl, C1-6alkoxy,

-CO\textsubscript{2}(C1-6 alkyl), -NR\textsuperscript{4c}R\textsuperscript{4d}, and trifluoromethyl, (B) -OR\textsuperscript{4c},
(C) -CO\textsubscript{2}(C1-6 alkyl), (D) -S(O)\textsubscript{n}-(C1-6 alkyl), wherein n is an
integer selected from 0, 1 and 2, (E) halogen, and (I) -NR\textsuperscript{4c}R\textsuperscript{4d},

(iv) -NR\textsuperscript{9}.COR\textsuperscript{10},
(v) -NR\textsuperscript{9}.CO\textsubscript{2}R\textsuperscript{10},

30 (vi) -NR\textsuperscript{9}CO-NR\textsuperscript{9}R\textsuperscript{10},
(vii) -NR\textsuperscript{9}S(O)\textsubscript{2}-R\textsuperscript{10},
(viii) -NR\textsuperscript{9}S(O)\textsubscript{2}-NR\textsuperscript{9}R\textsuperscript{10},
(ix) -O-R\textsuperscript{9},
(x) -O(C1-6 alkyl)-O-R\textsuperscript{9},
(xi) -OCO-R^9,
(xii) -OCO_2-R^9, and
(xiii) -OCO-NR^9R^{10},
(xiv) -S(O)_2-NR^9R^{10}, wherein n is an integer selected from 0, 1 and 2,
(xv) -S(O)_n-R^9,
(xvi) methyl substituted with 1 to 3 fluorine atoms,
(xvii) R^{11} wherein R^{11} is phenyl, naphthyl, indenyl, indanyl, or heterocycle,
(xviii) -CO-R^{11},
(xix) -CO-R^9, and
(vx) -CO-NR^9R^{10},
(c) -NO_2,
(d) halogen,
(e) methyl substituted with 1 to 3 fluorine atoms,
(f) -NR^9R^{10},
(g) -NR^9-COR^{10},
(h) -NR^9-CO_2R^{10},
(i) -NR^9CO-NR^9R^{10},
(j) -NR^9S(O)_2-R^{10},
(k) -NR^9S(O)_2-NR^9R^{10},
(l) -CO-NR^9R^{10},
(m) -CO-R^9,
(n) OH,
(o) -OCO-NR^9R^{10},
(p) -OCO-R^9,
(q) -OCO_2-R^9,
(r) -S(O)_2-NR^9R^{10}, and
(s) -S(O)_n-R^9; or

X- R^7 is optionally substituted indanyl, wherein the substituents are as above for R^7;
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

In one subset of formula I are compounds wherein R^3 is thienyl, thiazolyl, thiadiazolyl, pyrazolyl, isoxazolyl or furanyl. In one embodiment thereof R^3 is thienyl.
In another subset of formula I are compounds wherein X-R^7 is CH_2-phenyl wherein said phenyl is optionally substituted with one to three substituents selected from the list under formula I. In one embodiment the substituents are independently selected from halogen.

In another subset of formula I are compounds wherein Y^1 is O, and Y^2 is C(R^5R^6), and R^5 and R^6 are as defined under formula I. In one embodiment R^5 and R^6 together represent oxo. In another embodiment, R^5 is CO_2R^4c, and R^6 is as defined under formula I.

In another subset of formula I are compounds of the formula Ia:

In another subset of formula I are compounds having the formula Ib:

The compounds of the instant invention have at least two asymmetric centers at the ring junction of the substituents bearing the piperidinyl ring and R^3. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended
that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The relative configurations of the most preferred compounds of this invention are of the trans orientation, i.e. as depicted:

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

As appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo. Similarly, \( C_1 \)-alkyl as in \( C_1 \)-alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbons in a linear or branched arrangement, such that \( C_1 \)-alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl, heptyl and octyl. Likewise, \( C_0 \), as in \( C_0 \)-alkyl is defined to identify the presence of a direct covalent bond.

The term "heterocycle" as used herein is intended to include the following groups:

- benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzodioxolanyl, benzothienyl, benzoxazolyl, benzothiazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, furazanyl, imidazolyl, indolyl, indolizinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazoliny, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, thienothienyl, triazolyl, azetidinyl, 1,4-dioxanyl, 1,3-dioxolanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydromidazolyl, dihydroindolyl, dihydroisoaxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl,
dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methyleneoxyphenyl, tetrahydropyranyl, tetrahydrofuranyl, and tetrahydrothienyl.

Representative compounds within the present invention include those exemplified herein as well as those in the following table:

![Chemical structure](image)

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^5/R^6$</th>
<th>$R^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_2$(2-F-Ph)</td>
<td>H</td>
<td>=O</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH$_2$(4-OCF$_3$-Ph)</td>
<td>H</td>
<td>=O</td>
<td>3-thienyl</td>
</tr>
<tr>
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<td>H/H</td>
<td>3-thienyl</td>
</tr>
<tr>
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<td>H</td>
<td>H/H</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH$_2$(4-Cl-Ph)</td>
<td>H</td>
<td>=O</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>CH$_3$</td>
<td>=O</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH$_2$(2-F-Ph)</td>
<td>H</td>
<td>H/H</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH$_2$(2-Cl-Ph)</td>
<td>H</td>
<td>H/H</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH$_2$(4-CH$_3$-Ph)</td>
<td>H</td>
<td>H/H</td>
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</tr>
<tr>
<td>CH$_2$(2-Cl-Ph)</td>
<td>H</td>
<td>=O</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH$_2$(4-CH$_3$-Ph)</td>
<td>H</td>
<td>=O</td>
<td>3-thienyl</td>
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<tr>
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<td>=O</td>
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</tr>
<tr>
<td>CH$_2$(4-OCCH$_3$-Ph)</td>
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<td>H/H</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH(OH)-Ph</td>
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<td>3-thienyl</td>
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<td>$R^1$+$R^2$ = CHPh</td>
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<td>3-thienyl</td>
</tr>
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<td>=O</td>
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<td>H/H</td>
<td>3-thienyl</td>
</tr>
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<td>=O</td>
<td>3-thienyl</td>
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<td>$\text{R}^3$</td>
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<tr>
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<td>H/H</td>
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<td>H/H</td>
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<td>CH$_2$Ph</td>
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<td>3-thienyl</td>
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<tr>
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<td>CH$_3$</td>
<td>H/H</td>
<td>CH=NN(CH$_3$)$_2$</td>
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<tr>
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<td>CH$_3$</td>
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<tr>
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<td>H/H</td>
<td>COH</td>
</tr>
<tr>
<td>CH(OH)CH$_2$CH$_2$CH$_3$</td>
<td>H</td>
<td>=O</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>R$^1$+R$^2$ = CH$_2$CH$_2$CH$_3$</td>
<td>H/H</td>
<td>3-thienyl</td>
<td></td>
</tr>
<tr>
<td>CH(CN)CH$_2$CH$_2$CH$_3$</td>
<td>H</td>
<td>H/H</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>R$^1$ + R$^2$ = -CH$_2$CH(CH$_3$)OC(CH$_3$)CH$_2$-</td>
<td>CO$_2$H/H</td>
<td>3-thienyl</td>
<td></td>
</tr>
<tr>
<td>CO$_2$H</td>
<td>CH$_2$CH$_3$</td>
<td>H/H</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH$_2$CH$_3$</td>
<td>CH$_2$CH$_3$</td>
<td>CN/H</td>
<td>3-thienyl</td>
</tr>
<tr>
<td>CH$_2$Ph</td>
<td>H</td>
<td>H/H</td>
<td>CO$_2$CH$_3$</td>
</tr>
</tbody>
</table>

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

Abbreviations used herein include: Me = methyl; Et = ethyl; Bu = butyl; Ph = phenyl; cPr/cBu/cHex = cyclopropyl/cyclobutyl/cyclohexyl; Pyr = pyridyl; Ac = acetyl; BOC = t-butyloxycarbonyl; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; TFA = trifluoro-acetic acid; Bn = benzyl; LAH = lithium aluminum hydride; Ms = methanesulfonyl (mesyl); THF
The subject compounds are useful in a method of modulating chemokine receptor activity in a patient in need of such modulation comprising the administration of an effective amount of the compound.

The present invention is directed to the use of the foregoing spiro-substituted azacycles as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors, including CCR-3 and/or CCR-5.

The utility of the compounds in accordance with the present invention as modulators of chemokine receptor activity may be demonstrated by methodology known in the art, such as the assay for CCR-5 binding as disclosed by Van Riper, et al., J. Exp. Med., 177, 851-856 (1993), and the assay for CCR-3 binding as disclosed by Daugherty, et al., J. Exp. Med., 183, 2349-2354 (1996). Cell lines for expressing the receptor of interest include those naturally expressing the receptor, such as EOL-3 or THP-1, or a cell engineered to express a recombinant receptor, such as CHO, RBL-2H3, HEK-293. For example, a CCR3 transfected AML14.3D10 cell line has been placed on restricted deposit with American Type Culture Collection in Rockville, Maryland as ATCC No. CRL-12079, on April 5, 1996. The utility of the compounds in accordance with the present invention as inhibitors of the spread of HIV infection in cells may be demonstrated by methodology known in the art, such as the HIV quantitation assay disclosed by Nunberg, et al., J. Virology, 65 (9), 4887-4892 (1991).

In particular, the compounds of the following examples had activity in binding to the CCR-3 or the CCR-5 receptor in the aforementioned assays, generally with an IC50 of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

Mammalian chemokine receptors provide a target for interfering with or promoting eosinophil and/or lymphocyte function in a mammal, such as a human. Compounds which inhibit or promote chemokine receptor function, are particularly useful for modulating eosinophil and/or lymphocyte function for therapeutic purposes. Accordingly, the present invention is directed to compounds which are useful in the prevention and/or treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to
inhibit (i.e., reduce or prevent) inflammation. As a result, one or more inflammatory processes, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is inhibited. For example, eosinophilic infiltration to inflammatory sites (e.g., in asthma) can be inhibited according to the present method.

Similarly, an instant compound which promotes one or more functions of a mammalian chemokine receptor (e.g., a human chemokine) is administered to stimulate (induce or enhance) an inflammatory response, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, resulting in the beneficial stimulation of inflammatory processes. For example, eosinophils can be recruited to combat parasitic infections.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the method of the present invention. In a preferred embodiment, the disease or condition is one in which the actions of eosinophils and/or lymphocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

Diseases or conditions of humans or other species which can be treated with inhibitors of chemokine receptor function, include, but are not limited to: inflammatory or allergic diseases and conditions, including respiratory allergic diseases such as asthma, particularly bronchial asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), delayed-type hypersensitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g.,
necrotizing, cutaneous, and hypersensitivity vasculitis); eosinophilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis.

Diseases or conditions of humans or other species which can be treated with promoters of chemokine receptor function, include, but are not limited to: immunosuppression, such as that in individuals with immunodeficiency syndromes such as AIDS, individuals undergoing radiation therapy, chemotherapy, therapy for autoimmune disease or other drug therapy (e.g., corticosteroid therapy), which causes immunosuppression; immunosuppression due congenital deficiency in receptor function or other causes; and infectious diseases, such as parasitic diseases, including, but not limited to helminth infections, such as nematodes (round worms); (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis); trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms)

(Echinococciosis, Taeniasis saginata, Cysticercosis); visceral worms, visceral larva migrans (e.g., Toxocara), eosinophilic gastroenteritis (e.g., Anisaki spp., *Phocanema spp.*), cutaneous larva migrans (*Ancylostoma braziliense*, *Ancylostoma caninum*).

The compounds of the present invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic conditions, atopic conditions, as well as autoimmune pathologies.

In another aspect, the instant invention may be used to evaluate putative specific agonists or antagonists of chemokine receptors, including CCR-3 and/or CCR-5. Accordingly, the present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds which modulate the activity of chemokine receptors. For example, the compounds of this invention are useful for isolating receptor mutants, which are excellent screening tools for more potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to chemokine receptors, e.g., by competitive inhibition. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the chemokine receptors, including CCR-3 and/or CCR-5. As appreciated in the art, thorough evaluation of specific agonists and antagonists of the above chemokine receptors has been hampered by the lack of availability of non-peptidyl (metabolically resistant) compounds with high binding affinity for these receptors. Thus the compounds of this invention are commercial products to be sold for these purposes.
The present invention is further directed to a method for the manufacture of a medicament for modulating chemokine receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The present invention is further directed to the use of these compounds in the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV) and the treatment of, and delaying of the onset of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

In a preferred aspect of the present invention, a subject compound may be used in a method of inhibiting the binding of a chemokine to a chemokine receptor, such as CCR-3 or CCR-5, of a target cell, which comprises contacting the target cell with an amount of the compound which is effective at inhibiting the binding of the chemokine to the chemokine receptor.

The subject treated in the methods above is a mammal, preferably a human being, male or female, in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism. In a preferred aspect of the present invention, modulation refers to antagonism of chemokine receptor activity. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.
Combined therapy to modulate chemokine receptor activity and thereby prevent and treat inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis, and those pathologies noted above is illustrated by the combination of the compounds of this invention and other compounds which are known for such utilities.

For example, in the treatment or prevention of inflammation, the present compounds may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipooxygenase inhibitor, such as an inhibitor of 5-lipooxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphone, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanil, sulindac, tenidap, and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dexamethorphan; a diuretic; and a sedating or non-sedating antihistamine.

Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention. Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists such as those described in US 5,510,332, WO95/15973, WO96/01644, WO96/06108, WO96/20216, WO96/22966, WO96/31206, WO96/40781, WO97/03094, WO97/02289, WO 98/42656, WO98/53814, WO98/53817, WO98/53818, WO98/54207, and WO98/58902; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such
as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) anti-
histamines (H1-histamine antagonists) such as brompheniramine, chlorpheniramine, dexchlor-
pheniramine, tripolidine, clemastine, diphenhydramine, diphenylpyraline, triphenylmethyl,
hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cypromethazine, antazoline,
pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, desca-
ebroxoythylamine cetratadine, and the like; (e) non-steroidal anti-asthmatics such as β2-agonists (terbutaline,
metaproterenol, fenoterol, isothoramine, albuterol, bitolterol, and pirbuterol), theophylline,
cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast,
montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors
(zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic
acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen,
fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin,
pirprofen, pronoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives
(indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid,
fentiazac, furofenac, ibufenac, isooxepac, oxpinac, sulindac, tioproin, tolmetin, zidometacin, and
zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid,
niflumic acid and tolafenamic acid), biphenylcarboxylic acid derivatives (diflunisal and
flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic
acid, sulfasalazine) and the pyrazolones (apazine, bezpiperylon, feprazone, mopbutazone,
oxphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of
phosphodiesterase type IV (PDE-IV); (i) other antagonists of the chemokine receptors, especially
CCR-1, CCR-2, CCR-3 and CCR-5; (j) cholesterol lowering agents such as HMG-CoA
reductase inhibitors (lovastatin, simvastatin and pravastatin, fluavastatin, atorvastatin, and other
statins), sequestrants (cholesteryramine and colestipol), nicotinic acid, fenofibrate acid derivatives
(gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-diabetic agents such
as insulin, sulfonylureas, biguanides (metformin), α-glucosidase inhibitors (acarbose) and
glitazones (troglitazone and pioglitazone); (l) preparations of interferon beta (interferon beta-1α,
interferon beta-1β); (m) other compounds such as 5-aminosalicylic acid and prodrugs thereof,
antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemothera-
peutic agents. The weight ratio of the compound of the compound of the present invention to the
second active ingredient may be varied and will depend upon the effective dose of each
ingredient. Generally, an effective dose of each will be used. Thus, for example, when a
compound of the present invention is combined with an NSAID the weight ratio of the
compound of the present invention to the NSAID will generally range from about 1000:1 to
about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the
present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The present invention is further directed to combinations of the present compounds with one or more agents useful in the prevention or treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art. Representative agents are provided in US Patent 6,489,354 columns 36 - 39, which is hereby incorporated by reference.

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments of with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or dDI. Preferred agents for combination therapy include: Zidovudine, Lamivudine, Stavudine, Efavirenz, Ritonavir, Nelfinavir, Abacavir, Indinavir, 141-W94 (4-amino-N-(2 syn,3S)-2-hydroxy-4-phenyl-3-((S)-tetrahydrofuran-3-yloxy carbonylamino)-butyl)-N-isobutyl-benzenesulfonamide), N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(2-benzo[b]furanyl-methyl)-2(S)-N'-(t-butylycarbox-amido)-piperazinyl))-pentaneamid, and Delavirdine. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylycarbo-xamido)-piperazinyl))-pentane-amide ethanolate, and is synthesized according to U.S. Patent 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred inhibitors of HIV protease include nelfinavir and ritonavir. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include (-) 6-chloro-4(S)-cyclopropylethynyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, which may be prepared by methods disclosed in EP 0,582,455. The preparation of ddC, dDI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations with the compounds of the present invention include the following: (1) Zidovudine and Lamivudine; (2) Stavudine and Lamivudine; (3) Efavirenz; (4) Ritoavir; (5) Nelfinavir; (6) Abacavir; (7) Indinavir; (8) 141-W94; and (9) Delavirdine. Preferred combinations with the compounds of the present invention further
include the following (1) indinavir, with efavirenz or (-) 6-chloro-4(S)-cyclopentylnyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be...
for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting
agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.
In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods suitable for preparing the compounds of this invention are provided in US Patent 6,489,354, the disclosures thereof are hereby incorporated by reference. The various piperidine derivatives, when not commercially available, are prepared as described in the following Schemes.

The spiropiperidine 34 is prepared from the commercially available N-BOC-4-oxopiperidine 30. Deprotonation of trimethylsulfonium iodide with a strong base like NaH in
DMSO affords a sulfur ylid that reacts with the 4-carbonyl group of 30 to form epoxide 31. The oxirane is opened by a nucleophile such as the sodium salt of dimethyl malonate and the resulting hydroxy diester is cyclized and decarboxylated during acidic workup to form the spirolactone 32. The lactone 32 is treated with a strong base such as LDA or LHMDS at low temperatures and the resulting enolate is reacted with an electrophile such as an alkyl iodide to give the alkylated lactone 33. Removal of the N-BOC group with a strong acid such as HCl or TFA in solvents such as dichloromethane and dioxane gives the amine 34.

**SCHEME 2**

Alternatively, the alkylated lactone 33 is deprotonated with a strong base such as LDA or LHMDS at low temperatures. The lactone enolate reacts with an electrophile such as the same or a different alkyl iodide to afford the disubstituted lactone 35. The BOC group is removed by treatment with a strong acid such as HCl or TFA in solvents such as dichloromethane and dioxane to give the amine 36.

**SCHEME 3**

The lactone carbonyl group of 37 is partially reduced with an agent such as DIBAIH in toluene or lithium tri-tert-butoxyalumimum hydride in THF to form lactol 38. Lactol
38 is deoxygenated by treatment with a trialkylsilane and a Lewis Acid such as trimethylsilane and boron trifluoride etherate, and the product ester is treated with a strong acid such as HCl or TFA in solvents such as dichloromethane and dioxane to provide amine 39. Similarly, treating 38 with cyanotrimethylsilane or allyltrimethylsilane provides the amine 40 or 41, respectively.

**SCHEME 4**

Bis-deprotonation of commercially available N-BOC-piperidine-4-carboxylic acid 43 with a strong base such as LDA or LHMDS at low temperature affords the enolate which reacts with electrophiles such as an oxirane to form lactone 44. The transformation of 44 to the amine 47 may be accomplished as described in Scheme 3.

**SCHEME 5**

The BOC group of nitrile 40 is not compatible with the acidic conditions required for the transformation of a nitrile to its corresponding carboxylic acid. In such cases, the amine may be attached to the pyrrolidine fragment prior to hydrolysis or protected with a benzyl group. The nitrile can be solvolyzed to the methyl ester 49 by treatment with a strong acid such as HCl in
methanol, or the it may be hydrolyzed directly to the carboxylic acid 50 by treatment with a strong acid such as HCl in dioxane. “P” in this case represents the pyrrolidine fragment of formula I or a protecting group such as N-benzyl.

The nitrogen of the spiropiiperidines may also be benzyl protected. The hydroxy group of lactol 52 is converted to a nitrile as in Scheme 3. Nitrile 53 is solvolyzed with HCl in methanol to give the methyl ester 54, which is deprotonated by treatment with a strong base such as LDA or LHMDS. The resulting ester enolate reacts with an electrophile such as an alkyl iodide to afford the ester 55. The benzyl group of 55 is removed by treatment with ammonium formate and Pd(OH)2 in a solvent such as methanol to afford amine 56.

A carboxy group is installed on the sidechain at the 3 position by modification of an allyl substituent on the N-benzyl piperidine 57. Oxidation of the olefin 57 with osmium...
tetroxide and a co-oxidant such as Jones Reagent forms the acid, which is converted to the methyl ester 58 under acidic conditions such as thionyl chloride in methanol. The ester is deprotonated with a strong base such as LDA or LHMDS and the resulting ester enolate reacts with an electrophile such as an alkyl iodide to afford the alkylated product 59. The benzyl group of 59 is removed by catalytic hydrogenation with ammonium formate and palladium hydroxide in a solvent such as methanol to afford the amine 60.

A carboxy group is installed on the sidechain at the 2 position by modification of a carboxy substituent on the N-benzyl spiropiperidine 61. The carboxy group is converted to the hydroxy group with a strong reducing agent such LAH in THF. The hydroxy group of 62 is activated with a sulfonyl chloride such as methanesulfonyl chloride in the presence of a base such as triethylamine and the intermediate mesylate is displaced with a nucleophile such as KCN to form 63, which upon treatment with a strong acid such as HCl in an alcohol solvent such as methanol provides the ester 64. Deprotonation of 64 with a strong base such as LDA or LHMDS followed by reaction with an electrophile such as an alkyl iodide affords alkyl analog 65. The benzyl group of 65 is removed by catalytic hydrogenation with ammonium formate and palladium hydroxide in a solvent such as methanol to afford the amine 66.
The preparation of enantiomerically pure acid analogs is accomplished by chromatographic separation. The racemic acid 67 is converted to the p-methoxybenzyl (PMB) ester 68 by treatment with 4-methoxybenzyl chloride and a base such as CsCO₃ in a polar, aprotic solvent such as DMF. The racemic ester 68 is separated into its individual enantiomers 69 by chromatography on a chiral support such as ChiralPak AD or ChiralPak OD using a solvent such as 5% ethanol in heptane. The 4-methoxybenzyl ester of each enantiomer 69 is then removed by treatment with an acid such as formic acid to afford the enantiomerically pure 70.

The various R³ groups in formula I are prepared in a similar manner to that shown in Scheme 10. The various aldehyde such as 75 are either commercially available or synthetically prepared as described in Schemes 11 to 16. In some instances, the procedure used
to generate 74 is used to transform a commercially available acrylic acid to N-methoxy-N-methylacrylamides in the likeness of 76. The aldehyde 75 is prepared by cyclizing 71 with the required thioamide to form thiazole 72, which upon interconversion of the ethyl ester to the N-methoxy-N-methylamide provided 75 after reduction. Treatment of 75 with the commercially available stabilized ylide provides the acrylamide 76, which forms the pyrrolidine 77 as described in US Patent 6,489,354 and J. Org. Chem. 1987, 52, 235. The intermediate 77 can be elaborated into compounds of this invention using procedures described in US Patent 6,489,354 and the following examples.

The syntheses of various N-methyl pyrazole aldehydes are shown in Scheme 11. The aldehydes 79 and 80 are prepared from commercially available 78 with DMF either under strongly basic or Lewis acidic conditions respectively. The aldehyde 83 is prepared from commercially available 81 via oxidation to the acid, N-methylation and reduction of the acid chloride.
SCHEME 12

Benzothiazole 84 is converted to 85 via deprotonation and formylation with DMF. The isoxazole aldehyde 86 is prepared via the cyclization of ethyl nitroacetate with acetylene and phenylisocyanate, followed by reduction of the ethyl ester. Tetrabromination of thiophene followed by debromination of the 2 and 5 postions and formylation of the mono anion with DMF provides 87.

SCHEME 13

Commercially available 4-methoxythiophene-3-carboxylic acid is converted to the aldehyde 88 via reduction to the alcohol and one-step oxidation using DMSO and sulfur trioxide pyridine complex as shown in Scheme 13.
SCHEME 14

![Chemical structure](image)

Acid 89 can be prepared by the oxidative degradation of benzothiodiazole to the vicinal diacid, which is subsequently mono-decarboxylated under thermal conditions. The furazane acid 91 is prepared by the cyclization of 90 with succinic anhydride and subsequent oxidation of one of the two vicinal methyl groups. N-Methylimidazole is substituted at the 2-position with ethyl chloroformate and saponified to provide the acid 92. The heterocyclic acids 89, 91 and 92 are reduced to their respective aldehydes using the methods to generate 75 and 88.

SCHEME 15

![Chemical structure](image)

The synthesis of acid 96 involves the cyclization of dimethylvinylethynylcarbinole (93) to 2,2-dimethyl tetrahydropyran-4-one (94). The pyrone is homologated to epoxyester 95, decarboxylated to the intermediate aldehyde and oxidized. The heterocyclic acid 96 is reduced to the aldehyde using the methods to generate 75 and 88.
Commercially available fumaric acid monoethyl ester is elaborated into intermediate 97 by the methods described above. Using standard protocols, complete reduction of the ethyl ester 97 to the alcohol 101 followed by oxidation provides the aldehyde intermediate 98. This aldehyde is converted to either the acetylene 99 or the nitrile 100. The intermediate alcohol 101 can also be elaborated into the nitrile homolog 102.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.
REFERENCE EXAMPLES

INTERMEDIATE 1. tert-butyl 3-benzyl-2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

Step 1.

To a solution of trimethylsulfonium iodide (12g, 54.5 mmol) in 100 ml of DMSO was added NaH (2.4g, 60 mmol) at 0 °C and the solution was allowed to warmed to rt over 1.5 h. A solution of tert-butyl 4-oxopiperidine-1-carboxylate (10g, 50.2 mmol) in 50 ml of DMSO was added. The resulting solution was heated at 50 °C for 2h and was poured into 500 ml of water. The solution was extracted with ether (3x200 ml) and the combined organic phase was dried over MgSO₄, filtered through celite and concentrated. The residue was purified by flash chromatography with EtOAc/hexane = 1:4 to give 4.92 g of tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate.

Step 2.

A solution of dimethyl malonate (3.5 ml, 23.05 mmol) in 20 ml of ethanol was added NaOMe (6ml as a 25% solution in methanol, 26.2 mmol) and the resulting solution was heated at reflux for 0.5 h. The compound of Step 1 (4.74g, 27.2 mmol) was added and the solution was heated at reflux for 3h. A solution of 15 ml of 15% NaOH was then added and the solution was heated at 100 °C overnight. 2N H₂SO₄ was added to bring the solution to pH = 4 and the solution was extracted with EtOAc (2x100mL). The organic layer was dried with MgSO₄, filtered through celite and concentrated. The residue was heated at 130 °C for 2.5h and was then purified by flash chromatography with EtOAc/hexane = 1:4 to 1:2 to give tert-butyl 2-oxo-1-oxa-8-azaspiro[4.5]-decane-8-carboxylate.

Step 3. A solution of the compound of Step 2 (0.35g, 1.38 mmol) in 10 mL of THF at -78 °C was added LDA (1.93 mmol, 0.96 mL). After 15 min, benzyl bromide (0.33 mL, 2.76 mmol) was added and the solution was stirred at -78 °C for 1.5 h. It was quenched with NH₄Cl solution (2 drops) and was dried with Na₂SO₄. Upon filtration through celite and removal of solvent, the residue was purified by flash chromatography (EtOAc:hexanes = 1:4) to give the title compound.

INTERMEDIATE 2. tert-butyl 3-benzyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate
A solution of Intermediate 1 (7.88g, 2.28 mmol) in a mixture of 10 ml of toluene and 5 ml of THF was added DIBAL-H (2.75 ml as 1M solution) at -70 °C. After 1.5 h, it was quenched with HOAc and was allowed to warm to 0 °C. The mixture was poured into 100 ml of saturated potassium sodium tartrate. The pH of the solution was adjusted to 8 with K₂CO₃ and was stirred for 20 min. The solution was extracted with EtOAc and the organic phase was dried with MgSO₄. Upon filtration through celite and removal of solvent, the residue was dissolved in 3 ml of CH₂Cl₂. To the solution was added 1 ml of Et₂SiH and 0.5 ml of BF₃·Et₂O at -78 °C. After 2h, it was poured in 20 ml of saturated NaHCO₃ and was extracted with EtOAc. The organic phase was dried with MgSO₄. Upon filtration through celite and removal of solvent, the residue was purified by flash chromatography (EtOAc:hexanes = 1:9) to give the title compound.

INTERMEDIATE 3. tert-butyl 2-allyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

A solution of tert-butyl 2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (0.384g, 1.5 mmol) in of 10 ml of toluene was added LiAl(O'Bu)₃H (4 ml, 2.7 mmol) at -78 °C. It was allowed to warm to -5 °C over 3 h. The mixture was poured into 100 ml of saturated potassium sodium tartrate and was stirred for 20 min. The solution was extracted with EtOAc and the organic phase was dried with MgSO₄. Upon filtration through celite and removal of solvent, the residue was dissolved in 5 ml of CH₂Cl₂. To the solution was added 2.4 ml of allyltrimethylsilane and 0.48 ml of BF₃·Et₂O at -78 °C. It was allowed to warm to -40 °C for 2 h and it was poured into 20 ml of saturated NaHCO₃. The mixture was extracted with CH₂Cl₂. The organic phase was washed with brine and was dried with MgSO₄. Upon filtration through celite and removal of solvent, the residue was purified by flash chromatography (EtOAc: hexanes = 1:4) to give the title compound.

INTERMEDIATE 4. tert-butyl 2-propyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

A solution of Intermediate 3 (80 mg) in 20 ml of EtOAc was added 50 mg of 10% Pd-C and was hydrogenated under 40 PSI on Parr apparatus for 15h. The solution was filtered through celite and concentrated to afford the title compound.
INTERMEDIATE 5. tert-butyl 3-methyl-3-propyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

Step 1. The procedure described in Step 3 of Intermediate 1 was followed to provide tert-butyl 3-allyl-2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate.

Step 2. A solution of diisopropylamine (0.72 ml, 5.1 mmol) in 12 ml of THF was added nBuLi (3 ml as 1.6 M solution in hexanes) at 0 °C. After 25 min, it was cooled to -78 °C and was added a solution of the compound of Step 1 (1.0g, 3.4 mmol) in 5 ml of THF. After 20 min, it was added MeI (0.5 ml, 6.8 mmol) and the solution was allowed to warm to rt for 18 h. It was quenched with NH₄Cl and extracted EtOAc. Organic phase was washed with brine and was dried with MgSO₄. Upon filtration through celite and removal of solvent, the residue was purified by flash chromatography (EtOAc:hexanes = 1:4) to give tert-butyl 3-allyl-3-methyl-2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate.

Step 3. The procedure for Intermediate 2 was followed to provide tert-butyl 3-allyl-3-methyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate.

Step 4. The title compound was prepared from the compound of Step 3 with same procedure as described for Intermediate 4.

INTERMEDIATE 6. tert-butyl 1-oxo-3-phenyl-2-oxa-8-azaspiro[4.5]decane-8-carboxylate

A solution of diisopropylamine (3.51 ml, 25 mmol) in 40 ml of THF was added nBuLi (15 ml as 1.6 M solution in hexanes) at 0 °C. After 0.5 h, it was cooled to -78 °C and was added a solution of 1-Boc-piperidine-4-carboxylic acid (2.29g, 10 mmol) in 20 ml of THF. After 1h, it was added styrene oxide (1.25 ml, 11 mmol) and the solution was allowed to warm to rt for 18 h. It was diluted with 100 ml of EtOAc and organic phase was washed with brine and was dried with MgSO₄. Upon filtration through celite and removal of solvent, the residue was purified by flash chromatography (EtOAc : hexanes = 1:1) to give the title compound.

INTERMEDIATE 7. tert-butyl 3-phenyl-2-oxa-8-azaspiro[4.5]decane-8-carboxylate
The title compound was prepared from Intermediate 6 following the procedure described for Intermediate 2.

INTERMEDIATE 8. tert-butyl 3-((3-hydroxypropyl)-2-oxa-8-azaspiro[4.5]decane-8-carboxylate

A solution of tert-butyl 3-but-3-enyl-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (analogously prepared as Intermediates 7, 0.205g, 0.69 mmol) in mixture 10 ml of methanol and 10 ml of CH₂Cl₂ was cooled to -78 °C and treated with O₃ until it turned to blue color. The solution was purged with N₂ and was added Me₂S. It was allowed to warm to rt and volatiles were removed by vacuum. The residue was dissolved in 5 ml of EtOH and was added NaBH₄ (100 mg). After 1.5 h, it was quenched with H₂SO₄ and extracted with CH₂Cl₂. The combined organic phases were dried with MgSO₄, filtered and concentrated to afford the title compound.


Step 1. A solution of tert-butyl 2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (2.3g, 9.0 mmol) in 15 mL of 4 N HCl in dioxane was stirred at rt for 1h. Volatiles were removed and the residue was dissolved in 20 mL of CH₂Cl₂. To the solution was added benzaldehyde (1.09 mL, 10.7 mmol), Et₃N (5 mL, 35.9 mmol) and NaB(OAc)₃H (2.86 g, 13.5 mmol). After 14h, the mixture was poured into ether and the resulting solution was washed with NaHCO₃ and brine, dried with Na₂SO₄ and concentrated. The residue was purified by flash chromatography (acetone:hexanes = 1:3) to give 8-benzyl-1-oxa-8-azaspiro[4.5]decan-2-one.

Step 2. The product of Step 1 was converted to 8-benzyl-1-oxa-8-azaspiro[4.5]decane-2-carbonitrile by the same procedure as in Example 21.

Step 3. To the compound of Step 2 in 10 mL of dioxane was added 5 mL of concentrated HCl and the resulting solution was heated at reflux for 4h. To the solution was added methanol (20 mL) and the solution was heated at reflux for 1h. Volatiles were removed by vacuum and the residue was taken in ether. The ether layer was washed with NaHCO₃ and brine, dried over
Na₂SO₄ and concentrated. The residue was purified by flash chromatography (acetone:hexanes = 1:3) to give methyl 8-benzyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylate.

**Step 4.** To the compound of Step 3 (0.13g, 0.45 mmol) in 4 mL of THF at -78 °C was added LHMD (0.53 mL as 1.0M solution). After 30 min, iodomethane (0.033 mL, 0.53 mmol) was added and the solution was allowed to warm to rt slowly for 14 h. Volatiles were removed by vacuum and the residue was purified by preparative TLC plate (EtOAc:Hexanes: 2N NH₃ in MeOH = 10:10:1) to give the title compound.

**INTERMEDIATE 10. methyl 2-(8-benzyl-1-oxa-8-azaspiro[4.5]dec-3-yl)pent-4-enolate**

**Step 1.** 3-Allyl-8-benzyl-1-oxa-8-azaspiro[4.5]decan-2-one was prepared from 8-benzyl-1-oxa-8-azaspiro[4.5]decan-2-one (Intermediate 9, step 1) by the same procedures as described for Intermediate 1.

**Step 2.** To the compound of Step 1 (0.32g, 1.14 mmol) in a mixture of THF and toluene (6 ml, 1:1) at -78 °C was added diisobutylaluminum hydride (2.73 ml as 1M solution in toluene). After 1 h, it was quenched with 3 drops of HCl (2M) and warm to rt. It was poured into ether. The ether solution was washed with saturated K₂CO₃ (1x), brine (1x), dried with Na₂SO₄, filtered and dried. The residue was dissolved in 5 mL of CH₂Cl₂ was added triethylsilane (0.55 mL, 3.42 mmol) and BF₃·Et₂O (0.36 mL, 2.85 mmol) at -78 °C. After 15 min, the solution was warmed to rt for 0.5 h and was poured into ether. The ether solution was washed with NaHCO₃ (1x) and brine (1x), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (acetone:hexanes = 1:5) to give 3-allyl-8-benzyl-1-oxa-8-azaspiro[4.5]decane.

**Step 3.** To the compound of Step 2 (50.1 mg, 0.18 mmol) in 4 mL of acetone was added OsO₄ (4.6 mg, 0.018 mmol), water (0.025 mL) and Jones’s reagent (0.23 mL as a 8M solution). After 5 h at rt, the solution was added NaHCO₃ and the resulting mixture was filtered through celite. Volatiles were removed and the residue was dissolved in methanol. To the solution was added thionyl chloride (0.039 mL, 0.36 mmol) and the solution was heated at reflux for 2h. Volatiles were removed and the residue was purified by preparative TLC plate (acetone:hexanes = 1:3) to give methyl (8-benzyl-1-oxa-8-azaspiro[4.5]dec-3-yl)acetate.

**Step 4.** The title compound was prepared from the compound of Step 3 as described for Intermediate 1.
INTERMEDIATE 11 tert-Butyl 3-(2-tert-butoxy-2-oxoethyl)-2-oxo-3-propyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

Step 1. tert-Butyl 3-(2-tert-butoxy-2-oxoethyl)-2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate was prepared from tert-butyl 2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate as described for Intermediate 1, Step 3.

Step 2. tert-Butyl 3-allyl-3-(2-tert-butoxy-2-oxoethyl)-2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate was prepared from the compound of Step 1 as described in Intermediate 1, Step 3.

Step 3. The title compound was prepared from the compound of Step 2 as described in Intermediate 4.

INTERMEDIATE 12 methyl 2-(1-oxa-8-azaspiro[4.5]dec-2-yl)pentanoate

Step 1. A solution of methyl 8-benzyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylate (0.447g, 1.54 mmol) in 15 ml of THF was added LAH (1.85 ml as 1M solution) at 0 °C. After 20 min, it was quenched with 3 drops of water and was dried with Na₂SO₄. The solution was filtered through celite and concentrated to give (8-benzyl-1-oxa-8-azaspiro[4.5]dec-2-yl)methanol.

Step 2. To the compound of Step 1 (0.41g, 1.56 mmol) in 6 mL of CH₂Cl₂ was added Et₃N (0.65 mL, 4.68 mmol) and MsCl (0.24 mL, 3.12 mmol). After 1h, it was poured into ether and the solution was washed with NaHCO₃ and brine, dried with Na₂SO₄ and concentrated. The residue was dissolved in 20 mL of DMF and the solution was added KCN (0.31g, 4.68 mmol). The solution was heated at 100 °C for 12 h and volatiles were removed by vacuum. The residue was dissolved in ether and was washed with NaHCO₃ and brine, dried with Na₂SO₄ and concentrated. The residue was purified by purified by flash chromatography (acetone:hexanes = 1:3) to give (8-benzyl-1-oxa-8-azaspiro[4.5]dec-2-yl)acetonitrile.

Step 3. To the compound of Step 2 (0.28 g, 1.05 mmol) in 4 ml of dioxane was added 2 mL of concentrated HCl and the resulting solution was heated at reflux for 4 h. It was then added 10 ml of methanol and the mixture was heated at reflux for 2h. Volatiles were removed and the residue was dissolved in ether. The ether solution was washed with NaHCO₃, dried with Na₂SO₄, filtered through celite and concentrated. The residue was purified by preparative TLC plate (acetone:Hexanes = 1 : 3) to give methyl (8-benzyl-1-oxa-8-azaspiro[4.5]dec-2-yl)acetate.
Step 4. To the compound of Step 3 (63 mg, 0.21 mmol) in 3 mL of THF at -78 °C was added LHMDS (0.42 mL as 1.0M solution). After 15 min, allyl iodide (0.038 mL, 0.42 mmol) was added and the solution was stirred at -78 °C for 25 min. It was quenched with 2 drops of water and was added 1 mL of Et3N. Volatiles were removed by vacuum and the residue was purified by preparative TLC plate (EtOAc:Hexanes = 2 : 1) to give methyl 2-(8-benzyl-1-oxa-8-azaspiro[4.5]dec-2-yl)pent-4-enoate.

Step 5. To the compound of Step 4 (57.5 mg, 0.17 mmol) in 5 mL of methanol was added ammonium formate (0.38 g, 6.1 mmol) and 96 mg of Pd(OH)2 on carbon (10%). The solution was heated at 70 °C for 40 min, filtered through celite and concentrated to give the title compound.

INTERMEDIATE 13 tert-butyl 2-oxo-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

Step 1. A solution of tert-butyl 2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (2.81g, 11 mmol) in 40 mL of THF at -78 °C was added LHMDS (30.8 mmol). After 20 min, allyl iodide (4.82 mL, 52.7 mmol) was added and the solution was stirred at -78 °C for 20 min and at rt for 40 min. It was poured into ether. The ether layer was washed with NaHCO3 and was dried with Na2SO4. Upon filtration through celite and removal of solvent, the residue was purified by flash chromatography (EtOAc:hexanes = 1:6) to give tert-butyl 3,3-diallyl-2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate.

Step 2. The title compound was prepared from tert-butyl 2-oxo-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate as described in Intermediate 4.

INTERMEDIATE 14 tert-butyl 15-oxo-3,14-dioxa-11-azadispiro[5.1.5.2]pentadecane-11-carboxylate

The title compound was prepared from tert-butyl 2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate and 1-bromo-2-(2-bromoethoxy)ethane as described in Intermediate 13, Step 1.
INTERMEDIATE 15 tert-butyl 3-methyl-2-oxo-3-propyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

The title compound was prepared from tert-butyl 3-allyl-3-methyl-2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate with same procedure as Intermediate 4.

INTERMEDIATE 16.

Thioacetamide (75 g, 1 mol) was suspended in CCl₄ (250 mL), and a solution of ethyl bromopyruvate (205 g, 1.05 mol) in CCl₄ (250 mL) was added by portions with intensive stirring. An exothermic reaction was observed, resulting in formation of a layer of heavy orangish-red oil, that was separated, washed with ether (3×250 mL) and heated in a boiling water bath for 1 hour. Then water was added (1 L), followed by solid sodium bicarbonate addition to alkaline pH. The ethyl ester was extracted with ether (5×250 mL), the extracts dried over anhydrous sodium sulfate, concentrated in vacuo and the residue was distilled under vacuum.

Ethyl 2-methylthiazole-4-carboxylate (100 g, 0.58 mol) was dissolved in a minimum amount of cold methanol, and a solution of potassium hydroxide (36 g, 0.64 mol) in a minimum amount of cold methanol was added. The hydrolysis of the ester was rapid, and the potassium salt of the target acid precipitated from the mixture. Water was added to homogeneity, and the methanol was evaporated. The azeotropic was acidified carefully with concentrated hydrochloric acid, the precipitant acid filtered off, washed with cold water, and recrystallized with water to provide 55 g of 2-methylthiazole-4-carboxylic acid.

2-Methylthiazole-4-carboxylic acid (2 g, 13.9 mmol) was combined with N,N-(methoxy)methyamine HCl (1.78 g, 18.18 mmol), N-hydroxybenzotriazole (2.83 g, 20.98 mmol), diluted into methylene chloride (30 mL), treated with diisopropylethylamine (6.1 mL, 34.97 mmol) and then treated with solid BOP reagent (6.80 g, 15.38 mmol) at 0 °C. The reaction mixture was warmed to room temperature and maintained under TLC control (SiO₂, 20% acetone-hexanes). The reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and methylene chloride, the organic phase dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified (Biotage 40M SiO₂, 20-25% acetone-hexanes) to provide the N-methoxy-N-methyl amide as a pale yellow oil (2.04 g, 78%).

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2-Methylthiazole-4-N-methoxy-N-methyl amide (2.05 g, 11.02 mmol) was
diluted into dry toluene (30 mL), chilled to -78 °C, and treated with fresh DIBAL-H (8.4 mL, 1.5
M toluene) under nitrogen. The reaction mixture was maintained 10 minutes under TLC control
(SiO₂, 20% acetone-hexanes), quenched at -78 °C with saturated aqueous Rochelle salt, warmed
to room temperature, partitioned between water and chloroform, and the organic phase dried over
anhydrous sodium sulfate, filtered, concentrated in vacuo and dried under vacuum to provide the
aldehyde as a yellow oil which was used directly in the next reaction without purification.

2-Methylthiazole-4-carboxaldehyde (1.4 g, 11.02 mmol) was diluted into dry
toluene (30 mL), treated with the solid stabilized ylide (Ph₃P=CHC(O)N(CH₃)(OCH₃), 4.6 g,
12.67 mmol) at 23 °C, and the reaction mixture heated at 60 °C overnight under nitrogen. The
reaction mixture was concentrated in vacuo and purified (Biotage 40M SiO₂, 15-20% acetone-
hexanes) to provide the N-methoxy-N-methyl acrylamide as a white solid (1.43 g, 61%).

**INTERMEDIATE 17. 1-Methylpyrazole-5-carboxaldehyde**

n-BuLi (2.5 M hexanes, 300 mL, 0.075 mol) was added dropwise to a stirred
solution of 1-methylpyrazole (50 g, 0.609 mol) in dry ether (300 mL) at 0 °C. The reaction
mixture suspension was then heated at reflux for 1.5 h, cooled to 0 °C and a mixture of DMF (65
mL) and ether (80 mL) was added dropwise. The reaction mixture was heated again at reflux for
1 h and maintained at room temperature overnight. An aqueous 2 M HCl solution (300 mL) was
added slowly at 0 °C, and the aqueous phase was separated and extracted with ether, the organic
phase dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified (SiO₂,
diethyl ether) to provide the title compound as a yellow oil (28 g, 41%).

**INTERMEDIATE 18. 1-Methylpyrazole-4-carboxaldehyde**

Phosphorus oxychloride (181 g, 1.18 mol) was added dropwise to a stirred solution of 1-
methylpyrazole (97 g, 1.18 mol) in dry DMF (240 mL) at 100 °C. The reaction mixture was
maintained at this temperature for 2 h, cooled to room temperature, poured onto ice water (1 L),
and basified to pH 8 by the addition of 2 M aqueous sodium hydroxide solution. The mixture
was then extracted with chloroform (4X500 mL), the organic phase dried over anhydrous sodium
sulfate, filtered, concentrated in vacuo to a brown oil and the excess DMF distilled away. The
crude product was purified (SiO₂, diethyl ether) to provide the title compound as a pale yellow
oil (52 g, 40%).

**INTERMEDIATE 19. 1-Methylpyrazole-3-carboxaldehyde**
A stirred solution of 3-methylpyrazole (82.1 g, 1.0 mol) in water (3.5 L) was heated to 70 °C. Potassium permanganate (111 g, 0.70 mol) was added in one portion, keeping the temperature near 70 °C. The reaction mixture was stirred for 1 h at 70 °C, and then a second portion of potassium permanganate (111 g) was added at 70 °C. After 1 h, a final portion of potassium permanganate (111 g) was added at 70 °C. The reaction mixture was stirred a further 2 h at 70 °C, and any unreacted oxidant was reduced by the dropwise addition of isopropanol. The reaction mixture was cooled to room temperature, filtered, the solid was rinsed with water, and the filtrate evaporated to 500 mL. The aqueous was chilled to 0 °C, acidified with concentrated HCl, filtered, the solid product washed with water, and dried under vacuum to provide pyrazole-3-carboxylic acid as a white solid (64.4 g, 57%).

Dimethyl sulfate (236 g, 177 mL, 1.87 mol) was added dropwise over 45 min to a stirred solution of pyrazole-3-carboxylic acid (200 g, 1.78 mol) in 20% aqueous sodium hydroxide (850 mL) at 40 °C. The reaction mixture was heated at 80 °C for 2 h, cooled to room temperature, filtered, the filtrate acidified to pH 1 with concentrated HCl, the precipitate filtered, washed with water, and dried under vacuum to yield 1-methylpyrazole-5-carboxylic acid (85 g, 38%). The filtrate was concentrated in vacuo to 800 mL, extracted with chloroform (15X400 mL), the organic phase dried over anhydrous magnesium sulfate, concentrated in vacuo, and the residue recrystallized from isopropanol to yield 1-methylpyrazole-3-carboxylic acid (74 g) as a white crystalline solid.

A suspension of the acid (90 g, 0.71 mol) and DMF (1 drop) in thionyl chloride (250 mL) was stirred at reflux under nitrogen for 2 h. The solvent was evaporated from the reaction mixture, the residue azeotroped with toluene (3X200 mL), diluted into toluene (250 mL), added to a suspension of Pd-C (10 wt%, 9.3 g) in toluene (500 mL), and the mixture stirred at reflux for 8 h with a gentle flow of hydrogen gas through the suspension. After cooling to room temperature, the suspension was filtered through celite, washed with toluene, and concentrated in vacuo. The residue was fractionally distilled under vacuum to provide the title compound (50 g, 63%) as a low melting white solid (bp = 92 °C @ 8 mmHg).

INTERMEDIATE 20. Benzothiazole-2-carboxaldehyde

To a solution of benzothiazole (145 g, 1.07 mol) in dry THF (1 L) was added dropwise a solution of n-butyllithium in hexane (1.6 M, 700 mL, 1.12 mol) at -80 °C with stirring. The mixture was stirred for 30 min at -80 °C, and a solution of DMF (100 mL, 1.7 mol) in THF (100 mL) was added dropwise at -80 °C. The reaction mixture was warmed to room temperature, treated with concentrated HCl (120 mL), and the organic layer was separated, dried over potassium
carbonate, concentrated in vacuo, and the residue was recrystallized from ethanol to provide the title compound (70%).

INTERMEDIATE 21. Isoxazole-3-carboxaldehyde

A solution of ethyl nitroacetate (133 g, 1.0 mol) in dry dioxane (3 L) was treated with phenylisocyanate (130 g, 1.1 mol). Acetylene was bubbled through a solution, and triethylamine (111 g, 1.1 mol) was added dropwise for 5 h. The mixture was filtered, and the precipitate was washed with dioxane. The filtrate was evaporated, and the residue was distilled, providing the fraction with a boiling point of 110-112 °C at 12 mmHg as the product isoxazole ester (89 g, 63%). This material was diluted into toluene (1 L), and this solution then added dropwise to a solution of diisobutyl aluminum hydride (630 mL, 0.63 mol, 1M toluene) at -75 °C with stirring. The reaction mixture was stirred for 30 min, and 10% aqueous ammonium chloride (excess) was added. The organic partition was separated, washed with water (100 mL) and evaporated. The residue was distilled to provide the fraction with a boiling point of 85-90 °C at 12 mmHg as the title compound (42 g, 43%).

INTERMEDIATE 22. 4-Bromothiophene-3-carboxaldehyde

A stirred and cooled solution of thiophene (185 mL, 2.3 mol) at 0 °C in chloroform was treated dropwise with bromine (500 mL, 1560 g, 9.75 mol) for 5 h. During the last hour bromine was added without cooling the reaction mixture. Then the mixture was stirred and heated at reflux for 5 h, cooled to room temperature, quenched with 3 M aqueous NaOH, and stirred vigorously to consume excess bromine. The aqueous layer was separated, the organic phase was washed with water, and then with acetone (150 mL) to remove remaining water. The organic residue was dried and then dissolved at reflux in chloroform (1 L). When cooling, the target tetrabromo-thiophene was precipitated as colorless crystals (693 g, 75%). A solution of this tetrabromothiophene (47 g, 0.12 mol) in dry diethyl ether (300 mL) was cooled to 0 °C and treated dropwise with butyllithium in hexane (150 mL, 0.24 mol, 1.6 M) for 80-90 min under argon. Then the mixture was stirred for an additional 20 min, and ice water (250 mL) was added carefully with stirring. The organic phase was separated, the aqueous phase extracted twice with ether, and the organic extracts all combined, dried over anhydrous calcium chloride, and concentrated in vacuo. The residue was distilled at 15 mmHg to give 22 g (77%) of 3,4-dibromothiophene. A solution of this 3,4-dibromothiophene (72 g, 33 mL, 0.3 mol) in dry ether (120 mL) was cooled to -78 °C, added to a solution of nBuLi (206 mL, 0.33 mol, 1.6 M) at -78 °C, and stirred for 5 min. A cold -78 °C solution of DMF (35 mL, 33 g, 0.45 mol) in dry ether (120 mL) was slowly added to the reaction mixture at -78 °C. After 10 min, the cold bath was removed and an aqueous HCl (150
mL, 6N) solution was added carefully, the mixture warmed to 23 °C and the aqueous phase separated and washed further with ether. The organic extracts were then combined, washed with saturated aqueous sodium bicarbonate, and the organic partition evaporated. The residue was distilled twice under vacuum to provide pure title compound (40 g, 69%).

INTERMEDIATE 23. 4-Methoxythiophene-3-carboxaldehyde
LAH (1.2 g, 31.6 mmol) was tared and diluted with dry THF (150 mL) under nitrogen. Solid neat 4-methoxythiophene-3-carboxylic acid (2.5 g, 15.8 mmol) was added over 10 portions. Upon completion of gas evolution, the mixture was maintained overnight, TLC monitored (50% EtOAc-hexane), and quenched at 23 °C carefully with the dropwise addition of saturated aqueous Rochelle salt (15 mL). The mixture was filtered through a pad of celite, washed with ethyl acetate and concentrated in vacuo. The crude product alcohol (2.35 g, 15.9 mmol) was dissolved in methylene chloride (80 mL), cooled to 0 °C, and DMSO (10 mL) was added followed by triethylamine (6.9 mL, 47.9 mmol). Solid sulfur trioxide pyridine complex (7.6 g, 47.9 mmol) was added, and the mixture then warmed to room temperature and maintained 4 h (TLC, 50% EtOAc-hexane). The mixture was quenched with saturated aqueous sodium bicarbonate and partitioned with chloroform. The organic phase was concentrated in vacuo to provide the pure title compound (2.6 g) in quantitative yield.

INTERMEDIATE 24. 1,2,5-thiadiazol-3-carboxaldehyde
To a mixture of benzene and acetic acid (2 L) were added benzothiazdiazole (136 g, 1 mol) and potassium permanganate (632 g, 4 mol). The mixture was stirred vigorously at 80 °C for 24 h, filtered and concentrated in vacuo. This diacid residue was distilled with thermal decarboxylation in vacuum at 180 °C to give the desired thiadiazole carboxylic acid (26 g, 20%), which was converted to the corresponding aldehyde as described for Intermediate 23.

INTERMEDIATE 25. 3-Methyl-4-furazanecarboxaldehyde
Succinic anhydride (100 g, 1 M) and dimethylglyoxime were thoroughly mixed, placed in a 1 L flask and heated to 160 °C with dimethylfurazane being distilled. The distillate was extracted several times with ether. Ether extracts were combined, washed with water and dried over calcium chloride. The solvent was evaporated, and the residue distilled at 154-159 °C yielding 3,4-dimethylfurazane (30 g, 30%). Finely ground potassium permanganate (50 g, 0.3 M) was added by small portions to a solution of 3,4-dimethylfurazane (6 g, 0.06M) in 150 mL of diluted (1:1) sulfuric acid at 10-15 °C. The mixture was maintained at 10 °C for 2 h, warmed to 23 °C overnight. The mixture was filtered, and the filtrate extracted profusely with ether. The solvent
was evaporated, the residue was washed with petroleum ether, and left to crystallize in a vacuum desiccator. The crystals were washed with hot benzene, concentrated in vacuo, the residue dissolved in methylene chloride, the solution filtered, and concentrated in vacuo to give 3-methyl-4-furazanecarboxylic acid (4 g, 80%), which was converted into the corresponding aldehyde as described for Intermediate 23.

INTERMEDIATE 26. N-methylimidazole-2-carboxaldehyde
Dry acetonitrile (600 mL) was added to N-methylimidazole (150 g, 1.8 mol), followed by triethylamine (503 mL, 3.6 mol) in one portion, and the mixture cooled to -30 °C. Neat ethyl chloroformate (350 mL, 3.6 mol) was added slowly over 15 min. The turbid mixture was then warmed to room temperature and maintained overnight. The solid triethyl ammonium chloride was filtered off, washed with EtOAc, and the filtrate concentrated in vacuo. Dichloromethane (500 mL) was added and the solution was extracted with water (300 mL), the organic phase dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, EtOAc) and recrystallization from ether/heptane (2:1) to provide 188 g (66%) of N-methylimidazole-2-carboxy ethyl ester. This N-methylimidazole-2-carboxy ethyl ester (120 g, 0.77 mol) was treated with a solution of sodium hydroxide (37 g, 0.9 mol) in water (60 mL), and the mixture heated at reflux for 1 h. The mixture cooled to 50 °C, acidified to pH 2 with concentrated HCl, cooled further to 5 °C and the precipitate filtered. The solid was washed with ether, diluted into water (70 mL), heated gently under 60 °C, and upon cooling the product crystallizes to give 75 g (77%) of N-methylimidazole-2-carboxylic acid, which was converted into the corresponding aldehyde as described for Intermediate 23.

EXAMPLE 1
3-Benzyl-8-\{[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-ylmethyl]-1-oxa-8-azaspiro[4.5]decan-2-one

- 43 -
A solution of tert-butyl 3-benzyl-2-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (0.32g, 0.93 mmol) in 2 mL of CH₂Cl₂ was added 2 mL of 4 N HCl in dioxane and the solution was stirred at rt for 16 h. Volatiles were removed and the residue was dissolved in 10 mL of 1,2-dichloroethane. To the solution was added (3R,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidine-3-carbaldehyde (0.35g, 1.02 mmol), Et₃N (0.52 mL, 3.72 mmol) and NaB(OAc)₃H (0.39 g, 1.96 mmol). After 3 h, the mixture was poured into CH₂Cl₂ and the resulting solution was washed with NaHCO₃, dried with Na₂SO₄ and concentrated. The residue was purified by flash chromatography (acetone: hexanes = 1:3) to give the title compound. Mass Spectrum (CI) m/e 569 (M+1).

The following compounds were prepared following the procedures described in Example 1 and using the appropriate azaspiro[4.5]decane derivatives, which are either described in the Reference Example section or may be prepared using the procedure described therein:

<table>
<thead>
<tr>
<th>Ex.</th>
<th>R¹</th>
<th>R⁵/R⁶</th>
<th>MS (CI) m/e M+1</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>4-fluorobenzyl</td>
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<td>587</td>
</tr>
<tr>
<td>3</td>
<td>-CH₂CH₃</td>
<td>=O</td>
<td>507</td>
</tr>
<tr>
<td>4.</td>
<td>-CH₂CH=CH₂</td>
<td>=O</td>
<td>519</td>
</tr>
<tr>
<td>5</td>
<td>-CH₂CH₂CH₃</td>
<td>=O</td>
<td>521</td>
</tr>
<tr>
<td>6</td>
<td>-CH₂C(=CH₂)CH₃</td>
<td>=O</td>
<td>533</td>
</tr>
<tr>
<td>7</td>
<td>-CH₂CH(CH₃)₂</td>
<td>=O</td>
<td>535</td>
</tr>
<tr>
<td>8</td>
<td>-CH₂CH=C(CH₃)₂</td>
<td>=O</td>
<td>547</td>
</tr>
<tr>
<td>9</td>
<td>-CH₂CH₂CH(CH₃)₂</td>
<td>=O</td>
<td>549</td>
</tr>
<tr>
<td>10</td>
<td>-CH₂-cHex</td>
<td>=O</td>
<td>575</td>
</tr>
<tr>
<td>11</td>
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<td>H/H</td>
<td>555</td>
</tr>
<tr>
<td>12</td>
<td>4-fluorobenzyl</td>
<td>H/H</td>
<td>573</td>
</tr>
<tr>
<td>13</td>
<td>CH₂CH₃</td>
<td>H/H</td>
<td>493</td>
</tr>
<tr>
<td>14.</td>
<td>CH₂CH=CH₂</td>
<td>H/H</td>
<td>505</td>
</tr>
</tbody>
</table>
3-Benzyl-8-\{[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-1-oxa-8-azaspiro[4.5]decan-2-carbonitrile

| 15 | CH₂CH₂CH₃ | H/H | 507 |
| 16 | CH₂C(=CH₂)CH₃ | H/H | 519 |
| 17 | CH₂CH(CH₃)₂ | H/H | 521 |
| 18 | CH₂CH=C(CH₃)₂ | H/H | 533 |
| 19 | CH₂CH₂CH₂CH(CH₃)₂ | H/H | 535 |
| 20 | CH₂-cHex | H/H | 561 |

**EXAMPLE 21**

3-Benzyl-8-\{[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-1-oxa-8-azaspiro[4.5]decan-2-carbonitrile

Step 1. Compound of Example 1 (0.49g, 0.86 mmol) in a solution of 4 mL of THF and 4 mL of toluene at -78 °C was added DIBAL-H (2.06 mL as 1.0 M solution in toluene). After 1h, it was quenched with 4 drops of water and the mixture was poured into ether. The ether solution was washed with saturated K₂CO₃ (1x), brine (1x), dried with Na₂SO₄, filtered and dried to give 3-benzyl-8-\{[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-1-oxa-8-azaspiro[4.5]decan-2-ol as a pale solid.

Step 2. To a solution of the product of Step 1 (0.10g, 0.18 mmol) in 3 mL of CH₂Cl₂ was added TMSCN (0.2 mL, 1.5 mmol) and BF₃·Et₂O (0.091 mL, 0.72 mmol) at -78 °C. The solution was allowed to stirred at rt for 1h and was poured into ether. The ether solution was washed with NaHCO₃ (1x) and brine (1x), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (acetone:hexanes = 1:3) to give the title compound. Mass Spectrum (CI) m/e = 580 (M+1).

**EXAMPLE 22**

3-Benzyl-8-\{[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-1-oxa-8-azaspiro[4.5]decan-2-carboxylic acid
A solution of the compound of Example 21 (30 mg, 0.052 mmol) in 2 mL of
dioxane was added 1 mL of concentrated HCl and the solution was heated at reflux for 3h.
Volatile were removed by vacuum and the residue was purified by preparative TLC (CH$_2$Cl$_2$:
MeOH:NH$_3$.H$_2$O = 100:10:4) to give the title compound. Mass Spectrum (Cl) m/e = 599 (M+1).

The following compounds were prepared following the procedures described in
Example 1 and using the appropriate azaspiro[4.5]decane derivatives, which are either described
in the Reference Example section or may be prepared using the procedure described therein:

<table>
<thead>
<tr>
<th>Ex.</th>
<th>R$_1$/R$_2$</th>
<th>R$_5$/R$_6$</th>
<th>MS (Cl) m/e M+1</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>H/H</td>
<td>-CH$_2$CH=CH$_2$/H</td>
<td>505</td>
</tr>
<tr>
<td>24</td>
<td>H/H</td>
<td>-CH$_2$CH$_2$CH$_3$/H</td>
<td>507</td>
</tr>
<tr>
<td>25</td>
<td>-CH$_2$CH$_2$CH$_3$/H</td>
<td>H/H</td>
<td>521</td>
</tr>
<tr>
<td>26</td>
<td>-CH$_2$CH=CH$_2$/CH$_3$</td>
<td>=O</td>
<td>533</td>
</tr>
<tr>
<td>27</td>
<td>-CH$_2$CH=CH$_2$/CH$_3$</td>
<td>H/H</td>
<td>519</td>
</tr>
<tr>
<td>28</td>
<td>-CH$_2$-(4-F-Ph)/CH$_3$</td>
<td>=O</td>
<td>601</td>
</tr>
<tr>
<td>29</td>
<td>-CH$_2$-(4-F-Ph)/CH$_3$</td>
<td>H/H</td>
<td>587</td>
</tr>
</tbody>
</table>

The following compounds were prepared following the procedures described in
Example 1 using Intermediates 6, 7, 8 and other appropriate 2-oxa-8-azaspiro[4.5]decane
intermediates prepared according to the procedures described therein.
The following compounds were prepared following the procedures of Examples 21 and 22.
EXAMPLE 47

8-\{[(3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-2-methyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylic acid

A solution of Intermediate 9 (23.6 mg, 0.078 mmol), ammonium formate (98.3 mg, 1.6 mmol) and Pd(OH)$_2$ (30 mg, 10%) on carbon in 10 mL of methanol was heated at reflux for 30 min. The mixture was filtered through celite and volatiles were removed by vacuum. The residue was dissolved in CH$_2$Cl$_2$ and the solution was added (3R,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidine-3-carbaldehyde (22.6 mg, 0.067 mmol), NaB(OAc)$_3$H (28.4 mg, 0.13 mmol) and Et$_3$N (0.037 mL, 0.27 mmol). After 3h, volatiles were removed and the residue was purified by preparative TLC plate (acetone:hexanes = 1:3) to give the methyl ester of the title compound.

A solution of the above methyl ester (15 mg, 0.028 mmol), LiOH·H$_2$O (11.7 mg, 0.28 mmol), water (0.5 mL) in 1.5 mL of methanol was stirred at rt for 16h. Upon removal of volatiles, the residue purified by preparative TLC plate (CH$_2$Cl$_2$:MeOH: NH$_3$·H$_2$O = 100:20:8) to give the title compound. Mass Spectrum (Cl) m/e = 523 (M+1).

EXAMPLE 48

Methyl 8-\{[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-2-propyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylate
The title compound was prepared with same procedure as the Example 47 using an intermediate prepared analogously to Intermediate 9. Mass Spectrum (Cl) m/e = 565 (M+1).

**EXAMPLE 49**

\[ \text{8-}[[\text{3S,4S}-1-(2,4-	ext{Dichlorobenzyl})-4-	ext{thien-3-ylpyrroloidin-3-ylmethyl}]-2-	ext{propyl-1-oxa-8-azaspiro[4.5]dec-2-yl}]\text{methanol} \]

To the product of Example 48 (47 mg, 0.083 mmol) in 3 mL of THF was added LAH (0.16 mL as 1.0 M solution in THF) at 0°C. After 30 min, the reaction was quenched with 5N NaOH and the mixture was poured into ether. The ether layer was washed with NaOH (2N) and brine, dried with Na₂SO₄ and dried to give the title compound. Mass Spectrum (Cl) m/e = 537 (M+1).

**EXAMPLE 50**

\[ \text{8-}[[\text{3S,4S}-1-(2,4-	ext{Dichlorobenzyl})-4-	ext{thien-3-ylpyrroloidin-3-ylmethyl}]-2-	ext{propyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylic acid} \]

The title compound was prepared from the compound of Example 48 with same hydrolysis procedure described in Example 47. Mass Spectrum (Cl) m/e = 551 (M+1).

The procedure described in Example 47 and that for preparing Intermediate 9 were followed in the synthesis of the following compounds:
<table>
<thead>
<tr>
<th>Example</th>
<th>R5/R6</th>
<th>MS (Cl) m/e (M+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>-CH₂CH=CH₂/CO₂CH₃</td>
<td>563</td>
</tr>
<tr>
<td>52</td>
<td>-CH₂CH=CH₂/CO₂H</td>
<td>549</td>
</tr>
<tr>
<td>53</td>
<td>-CH₂CH(CH₃)₂/CO₂H</td>
<td>565</td>
</tr>
<tr>
<td>54</td>
<td>-CH₂(CH₂)₂CH₃/CO₂H</td>
<td>565</td>
</tr>
</tbody>
</table>

**EXAMPLE 55**

2-((3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl)methyl]-1-oxa-8-azaspiro[4.5]dec-3-yl)pentanoic acid

The title compound was prepared from Intermediate 10 following the procedures described in Example 47. Mass Spectrum (Cl) m/e = 565 (M+1).

**EXAMPLE 56**

(8-((3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl)methyl]-2-oxo-3-propyl-1-oxa-8-azaspiro[4.5]dec-3-yl)acetic acid
The methyl ester of the title compound was prepared from Intermediate 11 as described in Example 1 except that methanol was solvent in first step. Mass Spectrum (CI) m/e = 593 (M+1).

The above methyl ester was hydrolyzed as described in Example 47 to provide the title compound. Mass Spectrum (CI) m/e = 579 (M+1).

**EXAMPLE 57**

2-(8-(((3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl)methyl)-1-oxa-8-azaspiro[4.5]dec-2-yl)pentanoic acid

![Chemical structure](image)

To Intermediate 12 (0.034 g, 0.133 mmol), (3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidine-3-carbaldehyde (0.051 g, 0.15 mmol) and Et3N (0.074 ml, 0.53 mmol) in CH2Cl2 (4 ml) was added NaB(OAc)3H (0.057 g, 0.27 mmol). After 2 h, it was poured into CH2Cl2. The organic layer was washed with NaHCO3, dried with MgSO4, filtered and concentrated. The residue was purified by prep TLC with acetone/hexane = 1:3 to give the methyl ester of the title compound. Mass Spectrum (CI) m/e = 581 (M+1).

A solution of the above methyl ester (32 mg, 0.055 mmol), LiOH·H2O (23.2 mg, 0.55 mmol), water (1 mL) in 3 mL of methanol was stirred at 60 °C for 5 h. Upon removal of volatiles, the residue was purified by preparative TLC plate (CH2Cl2:MeOH: NH3·H2O = 100:15:3) to give the title compound. Mass Spectrum (CI) m/e = 567 (M+1).

**EXAMPLE 58**

8-(((3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl)methyl)-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylic acid
Step 1. 8-\{[(3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-2-one was prepared from Intermediate 13 and (3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidine-3-carbaldehyde as described in Example 1. Mass Spectrum (CI) m/e = 563.

Step 2. 8-\{[(3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-2-carbonitrile was prepared from the compound of Step 1 as described in Example 21. Mass Spectrum (CI) m/e = 574.

Step 3. The title compound was prepared from the compound of Step 2 as described in Example 22. Mass Spectrum (CI) m/e = 593.

EXAMPLE 59

Isomers of 8-\{[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylic acid

Step 1. 4-methoxybenzyl 8-\{[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl\}-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylate

A solution of compound of Example 58 (0.078g, 0.13 mmol), p-methoxy benzyl chloride (0.020 mL, 0.14 mmol) and Cs2CO3 (0.047 g, 0.14 mmol) in 4 mL of DMF was stirred at rt for 16 h and was poured into ether. The ether layer was washed with brine and was dried with Na2SO4. Upon filtration through celite and removal of solvent, the residue was purified by flash chromatography (acetone:hexanes = 1:3) to give the title compound.
Step 2. The pair of diasteriomers of 4-methoxybenzyl 8-[[[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl]-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylate were separated by HPLC on ChiralPak AD column (5% EtOH in heptane).

Step 3. The fast isomer of 4-methoxybenzyl 8-[[[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl]-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylate (32.6 mg, 0.046 mmol) was dissolved in formic acid and was stirred at rt for 2h. Upon removal of volatiles, the residue was purified by reverse phase HPLC to give isomer 1. Mass Spectrum (ESI) m/e =593. Isomer 2 was obtained from slow isomer in same way. Mass Spectrum (CI) m/e =593.

EXAMPLE 60
3,3-Diallyl-8-[[[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl]-1-oxa-8-azaspiro[4.5]decan-2-one

The title compound was prepared as described in Example 58. Mass Spectrum (CI) m/e = 559.

EXAMPLE 61
3,3-Diallyl-8-[[[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl]-1-oxa-8-azaspiro[4.5]decan-2-carbonitrile

The title compound was prepared as described in Example 21. Mass Spectrum (CI) m/e = 570.
EXAMPLE 62

3,3-Diallyl-8-[(3S,4S)-1-(2,4-dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl]-1-oxa-8-azaspiro[4.5]decan-2-carboxylic acid

The title compound was prepared as described in Example 22. Mass Spectrum (CI) m/e =589.

EXAMPLE 63

8-[(3S,4S)-1-(2-Chloro-4-fluorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl]-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decan-2-carbonitrile

A solution of the compound of Example 58, Step 2 (0.24g, 0.42 mmol) in CH₂Cl₂ (4mL) and methanol (4mL) was added 2-chloroethyl chloroformate (0.18 mL, 1.66 mmol). After 1h, volatiles were removed and the residue was dissolved in 4 mL of CH₂Cl₂. To the solution was added 2-chloro-4-fluorobenzaldehyde (0.040g, 0.25 mmol), NaB(OAc)₃.H (0.088g, 0.42 mmol) and triethylamine (0.12 mL, 0.83 mmol). After 6h, the solution was poured into CH₂Cl₂ and was washed with sodium bicarbonate. It was dried with sodium sulfate. Upon filtration through celite and removal of solvent, the residue was purified by HPLC (ChiralPak AD column) to give the title compounds. Mass Spectrum (CI) m/e = 558 for both isomers.
EXAMPLE 64

8-{[(3S,4S)-1-(2-Chloro-4-fluorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl}-3,3-dipropyl-1-oxa-8-azaspiro[4.5]decane-2-carboxylic acid

The title compound was prepared as described in Example 22. Mass Spectrum (Cl) m/e = 577.

EXAMPLE 65

11-{[(3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl}-3,14-dioxa-11-azadispiro[5.1.5.2]pentadecan-15-one

The title compound was prepared from Intermediate 14 as described in Example 1. Mass Spectrum (Cl) m/e = 549.

EXAMPLE 66

11-{[(3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl]methyl}-3,14-dioxa-11-azadispiro[5.1.5.2]pentadecane-15-carbonitrile
The title compound was prepared from compound of Example 65 as described in Example 21. Mass Spectrum (Cl) m/e = 560 (M+1).

EXAMPLE 67
11-\{[(3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-ylmethyl]-3,14-dioxa-11-azadispiro[5.1.5.2]pentadecane-15-carboxylic acid

The title compound was prepared from the compound of Example 66 as described in Example 22. Mass Spectrum (Cl) m/e = 579 (M).

EXAMPLE 68
Isomers of 11-\{[(3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-ylmethyl]-3,14-dioxa-11-azadispiro[5.1.5.2]pentadecane-15-carboxylic acid.

The two diastereomers of the compound of Example 67 were separated by the same method as Example 59 except that ChiralPak OJ column was used. Mass Spectrum (Cl) m/e = 579 (M) for both isomers.
EXAMPLE 69
8-{{3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl}methyl}-1-oxa-8-azaspiro[4.5]decan-2-one

The title compound was prepared from tert-butyl 2-oxo-1-oxa-8-azaspiro[4.5]-decane-8-carboxylate with same procedure as Example 1. Mass Spectrum (Cl) m/e = 479 (M+1).

EXAMPLE 70
8-{{3S,4S)-1-(2,4-Dichlorobenzyl)-4-thien-3-ylpyrrolidin-3-yl}methyl}-3-methyl-3-propyl-1-oxa-8-azaspiro[4.5]decan-2-one

The title compound was prepared from Intermediate 15 with same procedure as Example 1. Mass Spectrum (Cl) m/e = 535 (M+1).

EXAMPLE 71
The title compound was prepared by following similar procedures in US Patent 6,489,354 and Example 11 utilizing tert-butyl 3-benzyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate. Mass Spectrum m/e = 570 (M+1).

The following compounds were prepared by using the appropriate aldehyde intermediate and following the procedures described for Intermediate 16 and Example 71:

<table>
<thead>
<tr>
<th>Example</th>
<th>R</th>
<th>MS (Cl) m/e (M+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>1-methyl-5-pyrazolyl</td>
<td>553</td>
</tr>
<tr>
<td>73</td>
<td>1-methyl-4-pyrazolyl</td>
<td>553</td>
</tr>
<tr>
<td>74</td>
<td>1-methyl-3-pyrazolyl</td>
<td>553</td>
</tr>
<tr>
<td>75</td>
<td>Benzothiazol-2-yl</td>
<td>606</td>
</tr>
<tr>
<td>76</td>
<td>3-isoxazolyl</td>
<td>540</td>
</tr>
<tr>
<td>77</td>
<td>4-bromo-3-thienyl</td>
<td>633</td>
</tr>
<tr>
<td>78</td>
<td>4-methoxy-3-thienyl</td>
<td>585</td>
</tr>
<tr>
<td>79</td>
<td>1,2,5-thiadiazol-3-yl</td>
<td>557</td>
</tr>
<tr>
<td>80</td>
<td>4-methyl-1,2,5-oxadiazol-3-yl</td>
<td>555</td>
</tr>
<tr>
<td>81</td>
<td>1-methyl-2-imidazolyl</td>
<td>553</td>
</tr>
</tbody>
</table>

EXAMPLE 82

To a solution of mercury sulfate (18 g) and sulfuric acid (5%, 600 mL), was gradually added dimethylvinylethynylcarbinol (230 g) with vigorous stirring for 1 h and the temperature was raised slowly to 85 °C. Mercury sulfate (18 g) was added in portions over 4 h at 85 °C. The upper layer was separated, and the lower layer was neutralized with potassium...
carbonate and extracted with ether twice. The separated upper layer was added to the ethereal extracts, washed with potassium carbonate, water and dried over magnesium sulfate. The ether was evaporated, and the residue distilled under vacuum, then distilled at 1 atm (168-175 °C) to provide the product pyrone (140 g, 53%).

A suspension of sodium (11 g) in dry toluene (150 mL) was heated to reflux, stirred vigorously, cooled to room temperature, and a first part of solution (5-6 mL) of chloroacetic acid ethyl ester (63 g, 0.5 mol) and the above 2,2-dimethyltetrahydropyran-4-one (64 g, 0.5 mol) was added. The remaining part of the solution was added dropwise at 23 °C. After 3-4 h and full consumption of sodium, dry methanol (8 mL) was added. The mixture was carefully quenched into ice water (100 mL), ether was added, the upper layer separated, the aqueous extracted with ether, the ethereal extracts combined, washed with water, and dried over magnesium sulfate. The solvent was evaporated, and the residue was distilled in vacuo (101 °C, 2 mmHg) to provide the product (74 g, 70%).

This product 5,5-dimethyl-1,6-dioxaspyro-2,5-octane-2-carboxylic acid ethyl ester (214 g, 1 mol) was added to a solution of sodium hydroxide (40 g, 1 mol) in water (100 mL) with stirring over 30 min at 30 °C. The reaction mixture was stirred for 2 h, water (200 mL) was added to dissolve precipitates, and the aqueous solution of the sodium salt of 5,5-dimethyl-1,6-dioxaspyro-2,5-octane-2-carboxylic acid was heated to 90 °C. Hydrochloric acid (1 mol, 15-20%) was added dropwise for 4 h, the forming aldehyde was simultaneously distilled, saturated with NaCl, extracted with ether (3X200 mL), the organic extracts dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was distilled in vacuo (61 °C at 7 mmHg) to provide the aldehyde intermediate (80 g, 55%).

To a cold 2,2-dimethyl-4-formyltetrahydropyran (17 g, 0.5 mol) was added a solution of potassium permanganate (79 g, 0.5 mol) in water (1 L), keeping the temperature at 25 °C. The mixture was maintained for 6 h, filtered from MnO₂, washed with water, the combined filtrate evaporated to the volume of 175 mL, acidified with HCl, extracted with diethyl ether, and the organic extracts dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was distilled under vacuum at 123 °C (5 mmHg) to yield 71 g (90%) of the desired acid. This carboxylic acid was incorporated into Example 82 by following the procedures of Examples 78 and 71, US Patent 6,489,354 and Example 11 from tert-butyl 3-benzyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate. Mass Spectrum m/e = 585 (M+1).
EXEMPLARY 83

The intermediate aldehyde (31 mg, 0.06 mmol) described as compound 98 in Scheme 19, was added to a solution of Ph₃PCBr₂ (54 mg, 0.12 mmol) and t-BuOK (0.12 mL, 0.12 mmol, 1 M THF) in dry THF (0.6 mL) at 23 °C. After formation of the dibromoalkene (TLC control, 5-10 min), the mixture was then cooled to -78 °C and 5 equivalents t-BuOK (0.31 mL, 1M THF) was added with vigorous stirring for 10 min. The temperature was raised slowly to -10 °C and the mixture was quenched with brine, extracted with ethyl acetate twice, concentrated in vacuo and purified by preparative thin layer chromatography (SiO₂, 50% acetone-hexane) to provide the desired acetylenic product [Mass Spectrum m/e = 497 (M+1)] along with minor amounts of intermediate dibromoalkene and monobromo alkene.

EXEMPLARY 84

The intermediate aldehyde (80 mg, 0.16 mmol) described as compound 98 in Scheme 19, was dissolved in dry methylene chloride (4 mL), treated with anhydrous sodium sulfate (160 mg), N,N-dimethylhydrazine (20 uL, 0.24 mmol), and stirred overnight at 40 °C (TLC control: 50% acetone-hexane). The mixture was filtered, washed with methylene chloride and purified by preparative thin layer chromatography (SiO₂, 50% acetone-hexane) to provide the desired hydrazone intermediate. This hydrazone (65 mg, 0.12 mmol) was diluted into dry diethyl ether (0.75 mL), treated with ethyl chloroformate (17 uL, 0.18 mmol) and the mixture was stirred for 1 h at room temperature. The mixture was then quenched with water, stirred for 30 min, the layers separated, and the aqueous partition washed thrice with ether. The combined organic phase was dried over anhydrous magnesium sulfate, concentrated in vacuo, and purified.
by preparative thin layer chromatography (SiO₂, 50% acetone-hexane) to provide the desired nitrile product. Mass Spectrum m/e = 498 (M+1).

**EXAMPLE 85**

The intermediate alcohol (40 mg, 0.079 mmol) described as compound 101 in Scheme 19, was dissolved in dry toluene (2.5 mL), treated with acetone cyanohydrin (11 uL, 0.12 mmol), TBP (30 uL, 0.12 mmol), TMAD (21 mg, 0.12 mmol), and the mixture maintained overnight at room temperature. The mixture was quenched with saturated aqueous sodium bicarbonate, extracted with EtOAc, the organic phase dried over anhydrous magnesium sulfate, concentrated in vacuo, and purified by preparative thin layer chromatography (SiO₂, 50% acetone-hexane) to provide the desired nitrile product (32 mg, 80%). Mass Spectrum m/e = 512 (M+1).

**EXAMPLES 86-138**

The following compounds were prepared under conditions similar to those described in the examples above. Other commercially available acrylate, carboxaldehyde or carboxylic acid starting materials known to those skilled in the art were used to generate the examples shown in the table below.

<table>
<thead>
<tr>
<th>EX.</th>
<th>R Group</th>
<th>MS (m/z) (M⁺+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>3-furanyl</td>
<td>540</td>
</tr>
</tbody>
</table>

- 61 -
<table>
<thead>
<tr>
<th>EX.</th>
<th>R Group</th>
<th>MS (m/z) (M⁺+1)</th>
</tr>
</thead>
<tbody>
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<td><img src="image" alt="R Group" /></td>
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<tr>
<td>88</td>
<td>phenyl</td>
<td>550</td>
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<tr>
<td>89</td>
<td>2-pyrazinyl</td>
<td>552</td>
</tr>
<tr>
<td>90</td>
<td>2-thienyl</td>
<td>555</td>
</tr>
<tr>
<td>91</td>
<td>2-furanyl</td>
<td>540</td>
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<tr>
<td>92</td>
<td>5-methyl-4-thiazolyl</td>
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</tr>
<tr>
<td>93</td>
<td>c-Bu</td>
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</tr>
<tr>
<td>94</td>
<td>2-pyrimidinyl</td>
<td>552</td>
</tr>
<tr>
<td>95</td>
<td>5-thiazolyl</td>
<td>557</td>
</tr>
<tr>
<td>96</td>
<td>4-fluorophenyl</td>
<td>568</td>
</tr>
<tr>
<td>97</td>
<td>2,5-difluorophenyl</td>
<td>586</td>
</tr>
<tr>
<td>98</td>
<td>3-OCH₃-phenyl</td>
<td>580</td>
</tr>
<tr>
<td>99</td>
<td>2-thiazolyl</td>
<td>557</td>
</tr>
<tr>
<td>100</td>
<td>4-thiazolyl</td>
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</tr>
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<td>101</td>
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<td>-C(O)NH₂</td>
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<td>103</td>
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<td>104</td>
<td>3-acyloxyphenyl</td>
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<td>105</td>
<td>1-OCH₃-cPr</td>
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</tr>
<tr>
<td>106</td>
<td>-CH₂OH</td>
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</tr>
<tr>
<td>107</td>
<td>-CH₂OCH₃</td>
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</tr>
<tr>
<td>108</td>
<td>-CH₂OCH₂CH=CH₂</td>
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<tr>
<td>109</td>
<td><img src="image" alt="R Group" /> 570</td>
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<tr>
<td>110</td>
<td>5-hydroxymethyl2-furanyl</td>
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<tr>
<td>111</td>
<td>3-pyridyl</td>
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<td>112</td>
<td>4-pyridyl</td>
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<tr>
<td>113</td>
<td>2-OCH₃-phenyl</td>
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<tr>
<td>114</td>
<td>1-propionyl-3-azetidinyl</td>
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<tr>
<td>115</td>
<td>Carboxy</td>
<td>518</td>
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<tr>
<td>EX.</td>
<td>R Group</td>
<td>MS (m/z) (M^+1)</td>
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<tr>
<td>-----</td>
<td>---------</td>
<td>----------------</td>
</tr>
<tr>
<td>116</td>
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</tr>
<tr>
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</tr>
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<td>118</td>
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<td>119</td>
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<td>120</td>
<td>1-methoxycarbonylmethyl-3-azetidinyl</td>
<td>601</td>
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<tr>
<td>121</td>
<td>2,4-dimethyl-5-thiazolyl</td>
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</tr>
<tr>
<td>122</td>
<td>5-indolyl</td>
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<tr>
<td>123</td>
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<td>640</td>
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<tr>
<td>124</td>
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<tr>
<td>125</td>
<td></td>
<td>586</td>
</tr>
<tr>
<td>126</td>
<td>1-(ethylaminocarbonyloxy)-cPr</td>
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<tr>
<td>127</td>
<td>1-acetylxy-cPr</td>
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<tr>
<td>128</td>
<td>1-OH-cPr</td>
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<tr>
<td>129</td>
<td>1-Ph-cPr</td>
<td>590</td>
</tr>
<tr>
<td>130</td>
<td>-CH(OH)CH₃</td>
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</tr>
<tr>
<td>131</td>
<td>3-(ethylaminocarbonyloxy)-Ph</td>
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</tr>
<tr>
<td>132</td>
<td>3-(methoxycarbonyloxy)-Ph</td>
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</tr>
<tr>
<td>133</td>
<td>3-CF₃-Ph</td>
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</tr>
<tr>
<td>134</td>
<td>3,5-di(OCH₃)-Ph</td>
<td>610</td>
</tr>
<tr>
<td>135</td>
<td>2,6-di(OCH₃)-Ph</td>
<td>610 H</td>
</tr>
<tr>
<td>136</td>
<td>2-fluorophenyl</td>
<td>568</td>
</tr>
<tr>
<td>137</td>
<td>3,5-difluorophenyl</td>
<td>586</td>
</tr>
<tr>
<td>138</td>
<td>-CH=CH₂</td>
<td>500</td>
</tr>
</tbody>
</table>

**EXAMPLES 139-141**

The following compounds were prepared under conditions similar to those described in the examples above. In the case of Example 141, the commercially available chloroindanone was used in the reductive amination of the pyrrolidine.
EX.

R Group.

MS (m/z) (M⁺+1)

139 2,4-dichlorobenzyl 609

140 2-chloro-4-fluorobenzyl 593

141 C

601

EX.

Structure

MS (m/z) (M⁺+1)

142

625

143

587

EXAMPLES 142-144

The following compounds were prepared under conditions similar to those described in the examples above.
<table>
<thead>
<tr>
<th>EX.</th>
<th>Structure</th>
<th>MS (m/z) (M+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>144</td>
<td><img src="" alt="Structure Image" /></td>
<td>629</td>
</tr>
</tbody>
</table>

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.
WHAT IS CLAIMED IS:

1. A compound of the formula I:

   \[
   \text{I}
   \]

   wherein

   X is selected from (1) \(-(\text{CH}_2)_m\)-, wherein m is 1, 2 or 3, (2) -CO-, and (3) -CH(C\(_{1-6}\) alkyl)-,
   one of Y\(_1\) and Y\(_2\) is O and the other is C(R\(_5\)R\(_6\));
   R\(_1\) is selected from (1) hydrogen, (2) C\(_{1-10}\) alkyl, (3) C\(_{2-10}\) alkenyl, (4) CH(R\(_a\))-Ar, (5) C(O)-
   Ar, (6) Ar, and (7) CO\(_2\)R\(_4\)c; wherein alkyl and alkenyl are each unsubstituted or substituted with
   OR\(_4\)c, CN, CO\(_2\)R\(_4\)c, OC(O)(C\(_{1-6}\) alkyl), OC(O)(halo substituted C\(_{1-6}\) alkyl), C\(_3\)-7 cycloalkyl;
   Ar is phenyl, pyridyl or imidazolyl wherein each is unsubstituted or substituted with halogen,
   OH, C\(_{1-6}\) alkyl optionally substituted with halogen, or OC\(_{1-6}\) alkyl optionally substituted with
   halogen;
   R\(_a\) is H or OR\(_9\),
   R\(_2\) is selected from (1) hydrogen, (2) C\(_{1-6}\) alkyl, (3) C\(_2\)-6 alkenyl, and (4) benzyl; or
   R\(_1\) and R\(_2\) taken together represent (1) \(\text{R}_3\)-CR\(_{4c}\)R\(_{4d}\), (2) -CH\(_2\)CH\(_2\)OCH\(_2\)CH\(_2\)-, or (3)
   -CH\(_2\)CH(CH\(_3\))OCH\(_3\)CH\(_3\)CH\(_2\)-;
   R\(_3\) is selected from (1) phenyl, (2) heterocyclyl, (3) C\(_{1-6}\)alkyl, (4) C\(_{2-6}\)alkenyl, (5) C\(_{2-6}\)alkynyl,
   (6) C\(_3\)-6cycloalkyl, (7) CO\(_2\)R\(_9\), (8) CONR\(_9\)R\(_9\), (9) CH(R\(_a\))-heterocyclyl, (10) CN, (11)
   C(O)R\(_9\), (12) OCOR\(_9\), (13) OCO\(_2\)R\(_9\) and (14) OCONR\(_9\)R\(_10\), wherein phenyl, heterocyclyl,
   alkyl, alkenyl, alkynyl and cycloalkyl are unsubstituted or substituted, and the substituent(s) are
   selected from halogen, CN, C\(_{1-6}\)alkyl, (CH\(_2\))\(_0\)-1OR\(_{4c}\), OC\(_3\)-6alkenyl, (CH\(_2\))\(_0\)-1C(O)\(_2\)R\(_4c\),
   OC(O)R\(_4\)c, OC(O)R\(_4\)c, OC(O)NR\(_4c\)R\(_4\)d, C(O)R\(_4\)c, SO\(_2\)C\(_1-6\)alkyl, phenyl, heterocyclyl,
   trifluoromethyl and trifluoromethoxy;
   R\(_{4c}\), R\(_{4d}\), and R\(_{4f}\) are independently selected from hydrogen and C\(_{1-6}\) alkyl;

   - 66 -
R⁵ is selected from (1) hydrogen, (2) C₁₋₆ alkyl, (3) C₂₋₆ alkenyl, (4) CN, (5) CO₂R⁴c, and (6) OH; wherein alkyl and alkenyl are unsubstituted or substituted with OR⁴c, CO₂R⁴c or CN;
R⁶ is selected from (1) hydrogen, (2) C₁₋₆ alkyl, and (3) C₂₋₆ alkenyl; or
R⁵ and R⁶ together represent oxo;
R⁷ is selected from phenyl, naphthyl, biphenyl, fluorenyl, indenyl, indanyl, dihydronaphthyl, tetrahydronaphthyl, octahydronaphthyl, adamantyl, and heterocycle, each of which is unsubstituted or substituted, where the substituents are independently selected from:
(a) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, O-C₁₋₆ alkyl, O-C₂₋₆ alkenyl, O-C₂₋₆ alkynyl wherein the alkyl, alkenyl, and alkynyl moieties are each unsubstituted or substituted, wherein the substituents are independently selected from
(i) hydroxy,
(ii) halogen,
(iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, wherein the alkyl, alkenyl, and alkynyl are each unsubstituted or substituted, wherein the substituents are independently selected from (A) phenyl, naphthyl and heterocycle each of which is unsubstituted or substituted, and wherein the substituents are independently selected from halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, -CO₂(C₁₋₆ alkyl), -NR⁴cR⁴d, and trifluoromethyl, (B) -OR⁴c, (C) -CO₂(C₁₋₆ alkyl), (D) -S(O)ₙ-(C₁₋₆ alkyl), wherein n is an integer selected from 0, 1 and 2, (E) halogen, and (I) -NR⁴cR⁴d,
(iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -NR⁹CO-NR⁹R¹⁰,
(vii) -NR⁹S(O)₂-R¹⁰,
(viii) -NR⁹S(O)₂-NR⁹R¹⁰,
(ix) -O-R⁹,
(x) -O(C₁₋₆ alkyl)-O-R⁹,
(xi) -OCO-R⁹,
(xii) -OCO₂-R⁹, and
(xiii) -OCO-NR⁹R¹⁰,
(xiv) -S(O)₂-NR⁹R¹⁰, wherein n is an integer selected from 0, 1 and 2,
(xv) -S(O)_n-R\textsuperscript{9},
(xvi) methyl substituted with 1 to 3 fluorine atoms,
(xvii) R\textsuperscript{11} wherein R\textsuperscript{11} is phenyl, naphthyl, indenyl, indanyl, or heterocycle,
(xviii) -CO-R\textsuperscript{11},
(xix) -CO-R\textsuperscript{9}, and
(vx) -CO-NR\textsuperscript{9}R\textsuperscript{10},
(c) -NO\textsubscript{2},
(d) halogen,
(e) methyl substituted with 1 to 3 fluorine atoms,
(f) -NR\textsuperscript{9}R\textsuperscript{10},
(g) -NR\textsuperscript{9}.COR\textsuperscript{10},
(h) -NR\textsuperscript{9}.CO\textsubscript{2}R\textsuperscript{10},
(i) -NR\textsuperscript{9}CO-NR\textsuperscript{9}R\textsuperscript{10},
(j) -NR\textsuperscript{9}S(O)\textsubscript{2}-R\textsuperscript{10},
(k) -NR\textsuperscript{9}S(O)\textsubscript{2}-NR\textsuperscript{9}R\textsuperscript{10},
(l) -CO-NR\textsuperscript{9}R\textsuperscript{10},
(m) -CO-R\textsuperscript{9},
(n) OH,
(o) -OCO-NR\textsuperscript{9}R\textsuperscript{10},
(p) -OCO-R\textsuperscript{9},
(q) -OCO\textsubscript{2}-R\textsuperscript{9},
(r) -S(O)\textsubscript{2}-NR\textsuperscript{9}R\textsuperscript{10}, and
(s) -S(O)_n-R\textsuperscript{9}; or

X- R\textsuperscript{7} is optionally substituted indanyl, wherein the substituents are as above for R\textsuperscript{7}; and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

2. A compound of Claim 1 wherein R\textsuperscript{3} is thienyl, thiazolyl, thiadiazolyl, pyrazolyl, isoxazolyl or furanyl.

3. A compound of Claim 1 wherein R\textsuperscript{3} is thienyl.

4. A compound of Claim 1 wherein X-R\textsuperscript{7} is CH\textsubscript{2}-phenyl wherein said phenyl is optionally substituted with one to three substituents selected from the list in Claim 1.
5. A compound of Claim 1 wherein X-R⁷ is CH₂-phenyl substituted with one to three halogen atoms.

6. A compound of Claim 1 wherein X-R⁷ is CH₂-(2,4-dichlorophenyl).

7. A compound of Claim 1 wherein Y¹ is O, and Y² is C(R⁵R⁶).

8. A compound of Claim 7 wherein R⁵ and R⁶ together represent oxo.

9. A compound of Claim 7 wherein R⁵ is CO₂R⁴c, and R⁶ is as defined in Claim 1.

10. A compound of Claim 1 having the formula Ia:

   \[ \text{Ia} \]

   wherein R³, R⁵, R⁶, R⁷ and X are as defined in Claim 1.

11. A compound of Claim 10 wherein R⁷ is phenyl substituted with one to three halogen atoms.

12. A compound of Claim 10 wherein X-R⁷ is CH₂-(2,4-dichlorophenyl).

13. A compound of Claim 10 wherein R³ is 3-thienyl.

14. A compound of Claim 10 wherein R⁵ is CO₂R⁴c.

15. A compound of Claim 1 having the formula Ib:
wherein R₁, R₂, R₅ and R₆ are as defined in Claim 1.

16. A compound of Claim 15 wherein R₅ is CO₂R⁴c.

17. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

18. A method for modulation of chemokine receptor activity in a mammal which comprises the administration of an effective amount of the compound of Claim 1.

19. A method for preventing infection by HIV, treating infection by HIV, delaying of the onset of AIDS, or treating AIDS comprising the administration to a patient of an effective amount of the compound of Claim 1.

20. A method for the prevention or treatment of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of the compound of Claim 1.

21. A method for the prevention or treatment of asthma, allergic rhinitis, dermatitis, conjunctivitis, atherosclerosis or rheumatoid arthritis which comprises the administration to a patient of an effective amount of the compound of Claim 1.
INTERNATIONAL SEARCH REPORT

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 471/10; A61K 31/4355, 31/438
US CL. : 546/18; 514/278

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 546/18; 514/278

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN STRUCTURE; File REGISTRY, File CAPPLUS, File USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Rita J. Deed
Telephone No. 571-272-1600

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