Title: SUBSTITUTED BENZANILIDES AS MODULATORS OF THE CCR5 RECEPTOR

Abstract: This invention relates to substituted benzanilides which are modulators, agonists or antagonists, of the CCR5 receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5, including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, by the use of substituted benzanilides which are CCR5 receptor antagonists. Furthermore, since CD8+ T cells have been implicated in COPD, CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.
SUBSTITUTED BENZANILIDES AS MODULATORS OF THE CCR5 RECEPTOR

FIELD OF THE INVENTION

This invention relates to substituted benzanilides which are modulators, agonists or antagonists, of the CC chemokine receptor CC-CKR5 now designated as CCR5 (Nature Medicine 1996, 2, 1174-8). In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5.

BACKGROUND OF THE INVENTION


T cells, as well as other inflammatory cells, will migrate into tissues in response to the production of a variety of chemotactic factors. Among these factors are a superfamily of 8-12 kDa proteins known as the chemokines. These proteins share structural features such as the presence of 3-4 conserved cysteine residues. RANTES, which stands for Regulated upon Activation Normal T cell Expressed and Secreted, is an 8 kDa protein member of CC branch of the chemokine family. These proteins recruit and activate immune and inflammatory cells through an interaction with G-protein coupled receptors. The CC branch is defined by the absence of an intervening amino acid residue between the first two cysteine residues and members of this family predominately elicit the migration of mononuclear cells, eosinophils and basophils (M. Baggiozini, B. Dewald, and B. Moser, Adv. Immunol. 55: 97-179, 1994; and J.J. Oppenheim, C.O.C. Zachariae, N. Mukaida, and K. Matsushima, Annu. Rev. Immunol. 9: 617-648, 1991).

RANTES potently produces chemotaxis of T cells, basophils, eosinophils, monocytes and mast cells. RANTES was originally identified as gene product induced

Several receptors have been identified that bind RANTES. In particular, CCR5, when expressed in either HEK 293 cells or CHO cells, binds RANTES. This receptor is expressed in T-cells and in monocytes and macrophages, immune/inflammatory cells that are important in the maintenance of a chronic inflammatory reaction. Pharmacological characterization of CCR5 indicates similarities to the RANTES binding site observed on isolated T cells. Therefore, antagonism of RANTES’ action on CCR5, as well as antagonism of other natural modulators of CCR5, should inhibit the recruitment and activation of T cells and macrophages into inflammatory lesions and provide a novel therapeutic approach for the treatment of atopic and autoimmune disorders.
Since T cells express CCR5, selective receptor modulators of CCR5, particularly antagonists, are likely to provide beneficial effects in diseases including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis, or idiopathic pulmonary fibrosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, treating and/or preventing rejection of transplanted organs, and inflammatory bowel disease, all in mammals, preferably humans. Furthermore, since CD8+ T cells have been implicated in chronic obstructive pulmonary disease (COPD), CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

Surprisingly, it has now been discovered that this class of non-peptide compounds, in particular substituted benzanilides of formula (I), function as CCR5 receptor modulators, and therefore, have utility in the treatment and prevention of disease states mediated by CCR5 receptor mechanisms.

SUMMARY OF THE INVENTION

The present invention is to novel compounds of formula (I) and their use as CCR5 modulators for the treatment of certain disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis, or idiopathic pulmonary fibrosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, treating and/or preventing rejection of transplanted organs, inflammatory bowel disease, and HIV infection, all in mammals, preferably humans. The preferred compounds for use as CCR5 modulators are those compounds of Formula (I) as noted herein.

Further, the present invention is directed to methods for making and using the compounds of formula (I), as well as pharmaceutical compositions of formula (I) or a pharmaceutically acceptable salts or solvates thereof.

Yet further, the present invention is directed to the use of a CCR5 receptor ligand in the manufacture of a medicament for the prophylaxis or treatment of certain disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis, or idiopathic pulmonary fibrosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple
sclerosis, treating and/or preventing rejection of transplanted organs, inflammatory bowel disease, and HIV infection, for example in a mammal such as a human.

Still further, the present invention is directed to a CCR5 receptor ligand, or a pharmaceutically acceptable salt, or solvate thereof, for use in the prophylaxis or treatment of certain disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis, or idiopathic pulmonary fibrosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, treating and/or preventing rejection of transplanted organs, inflammatory bowel disease, and HIV infection, for example in a mammal such as a human.

The present invention is also directed to combined therapy to prevent and treat inflammatory and immunoregulatory disorders or diseases, including asthma and allergic diseases, as well as rheumatoid arthritis and atherosclerosis, and those pathologies noted above, and is illustrated by the combination of the compounds of this invention and other compounds which are known for such utilities.

The present invention is further directed to combinations of the present compounds of formula (I) 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 the skilled artisan.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that substituted benzanillides of formula (I) are CCR5 receptor modulators. It has also now been discovered that selective inhibition of CCR5 receptor mechanisms by treatment with the receptor modulators of formula (I), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of disease states, including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis, or idiopathic pulmonary fibrosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, treating and/or preventing rejection of transplanted organs, and inflammatory bowel disease, all in mammals, preferably humans. Furthermore, since CD8+ T cells have been implicated in COPD, CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD.
Also, since CCR5 is a co-receptor for entry into cells, selective receptor modulators may be useful in the treatment of HIV infection.

Preferred compounds for use as CCR5 modulators are those compounds of Formula (I) as noted herein.

A preferred group of compounds for use herein are those compounds of the Formula (I) or a pharmaceutically acceptable salt or solvate thereof:

![Chemical structure](image)

wherein \( Ar \) is a group selected from (i), (ii) or (iii);

wherein:

- the basic nitrogen in moiety \( E \) may be optionally quarternized with \( C_{1-6}\)-alkyl or
- is optionally present as the N-oxide;

\( R^1 \) and \( R^2 \) are each independently one or more of hydrogen, C\(_{1-6}\)-alkyl, C\(_{2-6}\)-alkenyl, C\(_{2-6}\)-alkynyl, C\(_{3-7}\)-cycloalkyl, C\(_{3-6}\)-cycloalkenyl, aryl, (CH\(_2\))\(_a\)NR\(_7\)R\(_8\), (CH\(_2\))\(_a\)NR\(_7\)COR\(_9\), (CH\(_2\))\(_a\)NR\(_7\)CO\(_2\)R\(_{10}\), (CH\(_2\))\(_a\)NR\(_7\)SO\(_2\)R\(_{11}\), (CH\(_2\))\(_a\)CONR\(_{12}\)R\(_{13}\), hydroxyC\(_{1-6}\)-alkyl, C\(_{1-4}\)-alkoxyalkyl (optionally substituted by a C\(_{1-4}\)-alkoxy or hydroxy group), (CH\(_2\))\(_a\)CO\(_2\)C\(_{1-6}\)-alkyl, (CH\(_2\))\(_b\)OC(O)R\(_{14}\), CR\(_{15}\)=NOR\(_{16}\), CNR\(_{15}\)=NOR\(_{16}\), COR\(_{17}\), CONR\(_{12}\)R\(_{13}\), CONR\(_{12}\)(CH\(_2\))\(_c\)OC\(_{1-4}\)-alkyl, CONR\(_{12}\)(CH\(_2\))\(_a\)CO\(_2\)R\(_{18}\), CONHNR\(_{19}\)R\(_{20}\), CONR\(_{12}\)SO\(_2\)R\(_{21}\), CO\(_2\)R\(_{22}\), cyano, trifluoromethyl, NR\(_7\)R\(_8\), NR\(_7\)COR\(_9\), NR\(_{23}\)CO(CH\(_2\))\(_a\)NR\(_{23}\)R\(_{24}\), NR\(_{23}\)CONR\(_{23}\)R\(_{24}\), NR\(_7\)CO\(_2\)R\(_{10}\), NR\(_7\)SO\(_2\)R\(_{11}\), N=CNR\(_{23}\)NR\(_{23}\)R\(_{24}\), nitro, hydroxy, C\(_{1-6}\)-alkoxy, hydroxyC\(_1\)-alkoxy, C\(_1\)-alkoxyC\(_1\)-alkoxy, OC(O)NR\(_{25}\)R\(_{26}\), SR\(_{27}\), SOR\(_{28}\), SO\(_2\)R\(_{28}\);

\( R^3 \) and \( R^4 \) are each independently one or more of hydrogen, C\(_{1-6}\)-alkyl, C\(_3\)-7cycloalkyl, C\(_3\)-cycloalkenyl, hydroxyC\(_1\)-alkyl, C\(_1\)-alkylOCC\(_1\)-alkyl, CONR\(_{29}\)R\(_{30}\), CO\(_2\)R\(_{31}\), cyano, aryl, trifluoromethyl, NR\(_{29}\)R\(_{30}\), nitro, hydroxy, C\(_1\)-alkoxy, acetoxy, or halogen;

when \( Ar \) is (i) or (ii) the phenyl ring substituted with \( R^2 \) may be substituted with \( R^2' \), wherein \( R^2' \) is hydrogen, (CH\(_2\))\(_a\)CN, (CH\(_2\))\(_a\)CO\(_2\)H,
CR^{15'}=CR^{16'}CO_2R^{18'}, COCR^{15'}R^{16'}OR^{18'}, Oaryl, Oaralkyl, O(CH_2)_dCO_2R^{18'}, and Saryl;

R^{5'} is one or more of hydrogen, C_1-6alkyl, C_1-6alkoxy or halogen;
R^{6'} is one or more of hydrogen, C_1-6alkyl, C_3-7cycloalkyl (optionally substituted by a hydroxy or an oxo group), hydroxyC_1-6alkyl, hydroxyC_3-6alkenyl, hydroxyC_3-6alkynyl, (CH_2)_dOR^{32'}, (CH_2)_dCOR^{33'}, (CH_2)_dCR^{34'}=NOR^{35'}, CONR^{36}R^{37'}, CO_2R^{38'}, hydroxy, O(CH_2)_eR^{39'}, NR^{36}R^{37'}, SR^{40'}, SO_2NR^{41}R^{42'} or halogen; or, R^{5'} and R^{6'} form a fused benzo ring optionally substituted with C_1-6alkyl, C_1-6alkoxy or halogen;

R^{7'} and R^{8'} are independently hydrogen or C_1-6alkyl, or together with the nitrogen to which they are attached, R^{7'} and R^{8'} form a 5- to 6-membered heterocyclic ring, which ring may optionally be substituted by an oxo group and, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

R^{9'} is hydrogen, C_1-6alkyl or C_1-4alkoxyalkyl;

R^{10'} is C_1-6alkyl;

R^{11'} is C_1-6alkyl or phenyl;

R^{12'} and R^{13'} are independently hydrogen or C_1-6alkyl, or together with the nitrogen to which they are attached, R^{12'} and R^{13'} form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

R^{14'} is C_1-4alkyl, optionally substituted by C_1-6alkoxy;

R^{15'} and R^{16'} are independently hydrogen or C_1-6alkyl;

R^{17'} is hydrogen or C_1-6alkyl;

R^{18'} is hydrogen or C_1-6alkyl;

R^{19'} and R^{20'} are independently hydrogen or C_1-6alkyl;

R^{21'} is hydrogen or C_1-6alkyl;

R^{22'} is hydrogen or C_1-6alkyl optionally substituted with one or two substituents selected from C_1-6alkyl, C_1-6alkoxy, hydroxy, or NR^{7'}R^{8'};

R^{23'} and R^{24'} are independently hydrogen or C_1-6alkyl;

R^{25'} and R^{26'} are independently hydrogen or C_1-6alkyl, or together with the nitrogen to which they are attached, R^{25'} and R^{26'} form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

R^{27'} is hydrogen or C_1-6alkyl;

R^{28'} is C_1-6alkyl;

R^{29'}, R^{30'} and R^{31'} are independently hydrogen or C_1-6alkyl;
R^{32}' is C_{1-6}alkyl, hydroxyC_{1-6}alkyl, or C_{1-4}alkanoyl;
R^{33}' is hydrogen or C_{1-6}alkyl;
R^{34}' is hydrogen or C_{1-6}alkyl;
R^{35}' is hydrogen or C_{1-6}alkyl;
R^{36}' and R^{37}' are independently hydrogen or C_{1-6}alkyl or together with the nitrogen to which they are attached, R^{36}' and R^{37}' form a 5- to 6-membered heterocyclic ring, which ring may be optionally substituted by an oxo group and, which, when the ring is 6-membered, may optionally contain one oxygen or sulfur atom or an NH group or a group NR^{43}', wherein R^{43}' is C_{1-6}alkyl, COR^{44'} or CO_{2}R^{45'};
wherein R^{44'} and R^{45'} are independently hydrogen or C_{1-6}alkyl;
R^{38}' is hydrogen or C_{1-6}alkyl;
R^{39}' is C_{1-6}alkoxy, CO_{2}H, CO_{2}C_{1-6}alkyl or CONR^{36}R^{37}';
R^{40}' is C_{1-6}alkyl;
R^{41}' and R^{42}' are independently hydrogen or C_{1-6}alkyl;
P is a 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;
a' is 1, 2, 3 or 4;
b' is 0, 1, 2 or 3;
c' is 1, 2 or 3;
d' is 0, 1, 2, 3, 4, 5, or 6; and
e' is 1, 2, 3, 4, 5 or 6;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONR^{46'}; NHCO, -NHCH_{2}, or CH_{2}NH, wherein R^{46}' is hydrogen or C_{1-6}alkyl,
E is a group (a):

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {B} ;
  \node (B) at (2,0) {(CR^1R^2)_a} ;
  \node (C) at (4,0) {NR^3R^4} ;
  \node (D) at (2,-1) {(R^9)_b} ;
  \draw (A) -- (B) -- (C) ;
  \draw (B) -- (D) ;
\end{tikzpicture}
\end{center}

(a);

wherein:
B is oxygen, C\equiv C, S(O)_{2}, CR^7=CR^8, or CR^7R^8, or B is NR^9;
R^1 and R^2 are independently hydrogen or C_{1-6}alkyl; alternatively B(CR^1R^2)\_a
is OCR^1R^2CR^1(OH)CR^1R^2 or OCR^1R^2CR^1(OCOCH_3)CR^1R^2;
R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, C_{5-7}cycloalkenyl, a C_{5-7}heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring
which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C₁₋₆alkyl, aryl, CONR¹⁰R¹¹, NR¹⁰R¹¹, hydroxy, OCOR¹², NHCOF₃, NSO₂R¹², NHCO₂R¹⁴, or NHCO₂C₁₋₆alkyl wherein the alkyl of NHCO₂C₁₋₆alkyl is optionally substituted by OH;

R⁵ is hydrogen, C₁₋₆alkyl, aryl, CN, CONR¹⁵R¹⁶, CO₂R¹⁷, trifluoromethyl, NHCO₂R¹⁸, hydroxy, C₁₋₆alkoxy, benzyloxy, OCH₂CO₂C₁₋₆alkyl, OCF₃, S(O)dR¹⁹, SO₂NR²⁰R²¹ or halogen;

R⁶ is hydrogen, C₁₋₆alkyl, aryl, trifluoromethyl, hydroxy, C₁₋₆alkoxy or halogen, or R⁶ taken together with R³⁰' forms a group D where D is (CR²²R²³)ₖ or D is (CR²²R²³)ₖ-G where G is oxygen, sulfur or CR²²=CR²³, CR²²=N, =CR²²O, =CR²²S, or =CR²²-NR²³;

R⁷, R⁸, R¹⁰, R¹¹, R¹², R¹⁵, R¹⁶, R¹⁷, R²⁰, R²¹, R²², and R²³ are independently hydrogen or C₁₋₆alkyl;

R⁹ is hydrogen, C₁₋₆alkyl, or phenylC₁₋₆alkyl;

R¹³, R¹⁴, R¹⁸, and R¹⁹ are independently C₁₋₆alkyl;

a is 1, 2, 3, or 4;

b is 1 or 2;

c and d are independently 0, 1 or 2;

e is 2, 3 or 4;

f is 0, 1, 2 or 3;

and further wherein, when Ar is (i), (ii) or (iii), and A is CONR⁴⁶, NHCO, or CH₂NH, wherein R⁴⁶' is hydrogen or C₁₋₆alkyl,

alternatively, E is a group (b):

![Diagram](image)

R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³¹, and R³² are independently hydrogen or C₁₋₆alkyl;

R³⁰ is hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₅₋₇cycloalkenyl, or a C₅₋₇heterocyclic ring;

R³³ is hydrogen, C₁₋₆alkyl, trifluoromethyl, hydroxy or halogen, or R³³ and R³⁰' together form a group -K- where K is (CR³⁴R³⁵)ₖ or K is (CR³⁴R³⁵)ₖ-M and M is oxygen, sulfur, CR³⁴=CR³⁵, CR³⁴=N, or N=N;

J is oxygen, CR³⁶R³⁷, or NR³⁸, or J is a group S(O)ₖ;

R³⁴, R³⁵, R³⁶, R³⁷, and R³⁸ are independently hydrogen or C₁₋₆alkyl;
g is 1, 2 or 3;
h is 1, 2 or 3;
i is 2, 3, or 4;
j is 0, 1, 2, or 3;
k is 0, 1 or 2;

and further wherein, when Ar is (i), (ii) or (iii), and A is CONR^{46'}, NHCO, -NHCH₂, or CH₂NH, wherein R^{46'} is hydrogen or C₁₋₆alkyl, alternatively, E is a group (c):

[Diagram]

wherein:
Q is oxygen, S(O)ₙ, CR^{44}=CR^{45}, CR^{44}R^{45}, or Q is NR^{46};
R^{39} and R^{40} are independently hydrogen or C₁₋₆alkyl;
R^{41} is a group of formula (d):

[Diagram]

or R^{41} is a group of formula (e):

[Diagram]

R^{42} is hydrogen, C₁₋₆alkyl, aryl, CN, CONR^{48}R^{49}, CO₂R^{50}, trifluoromethyl, NHCO₂R^{51}, hydroxy, C₁₋₆alkoxy, benzyloxy, OCH₂CO₂C₁₋₆alkyl, OCF₃,

S(O)ₙR^{52}, SO₂NR^{53}R^{54}, or halogen;
R^{43} is hydrogen or R^{43} together with R^{30'} forms a group R where R is CR^{55}=CR^{56}, CR^{55}=CR^{56}CR^{55}R^{56}, or (CR^{55}R^{56})t;
R^{44}, R^{45}, R^{46}, R^{48}, R^{49}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{56} are independently hydrogen or C₁₋₆alkyl;

R^{47} is hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₅₋₇cycloalkenyl, or a C₅₋₇heterocyclic ring;
R^{51} and R^{52} are independently C_{1-6}alkyl;
1 is 0, 1, 2, or 3;
m is 1 or 2;
n is 0, 1, or 2
o, p, and q are independently integers having the value 1, 2, or 3;
r is 0, 1, 2, or 3;
s is 0, 1, or 2;
t is 2 or 3;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONH, NHCO, or CH_{2}NH,
alternatively, E is a group (f):
\[
\begin{array}{c}
W \quad \text{(f)}; \\
\end{array}
\]
R^{57} and R^{58} are independently hydrogen or C_{1-6}alkyl;
R^{59} and R^{60} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, C_{5-7}cycloalkenyl, a C_{5-7}heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, CONR^{61}R^{62}, NR^{61}R^{62}, hydroxy, OCOR^{63}, NHCOCF_{3}, NHSO_{2}R^{64}, NHCO_{2}R^{65}, or NHOCOC_{0-6}alkyl wherein the alkyl of NHOCOC_{0-6}alkyl is optionally substituted by OH;
T is -(CR^{66}R^{67})_{v} or -O(CR^{66}R^{67})_{w};
W is oxygen, S(O)_{x}, NR^{68}, or W is CR^{69}=CR^{70} or CR^{69}R^{70};
R^{61}, R^{62}, R^{63}, R^{66}, R^{67}, R^{68}, R^{69}, and R^{70} are independently hydrogen or C_{1-6}alkyl;
R^{64} and R^{65} are independently C_{1-6}alkyl;
u is 1 to 4;
v is 2 or 3;
w is 1, 2, or 3;
x is 0, 1 or 2;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONR^{46}, NHCO, or CH_{2}NH, wherein R^{46} is hydrogen or C_{1-6}alkyl,
alternatively, E is a group (g):
$R^{71}$ is a 5- to 7-membered saturated or partially saturated heterocyclic ring containing a basic nitrogen atom and optionally a further 1 or 2 heteroatoms selected from nitrogen, oxygen or sulfur or $R^{71}$ is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur, which ring systems may be optionally substituted with one or more of $C_{1-6}$alkyl and optionally substituted on nitrogen with hydrogen, $C_{1-6}$alkyl or $C_{3-7}$cycloalkyl, $C_{5-7}$cycloalkenyl, or a $C_{5-7}$heterocyclic ring; $R^{71}$ is substituted with one or more of $R^{71}$, wherein $R^{71}$ is hydrogen, $CR^{1a}R^{2}NR^{3}R^{4}$, $CR^{1a}R^{2}OR^{3}$, $CONR^{6}R^{7}$, $CO_{2}R^{8}$, cyano, $NR^{3}R^{4}$, nitro, hydroxy, $C_{1-6}$alkoxy, $SR^{9}$, $SOR^{10}$, $SO_{2}R^{10}$, $SO_{2}NR^{6}R^{7}$ or $SO_{3}H$, wherein $R^{1a}$ and $R^{2}$ are independently hydrogen or $C_{1-6}$alkyl; $R^{3}$ and $R^{4}$ are independently hydrogen or $C_{1-6}$alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom; alternatively $R^{4}$ is $COR^{11}$, $CONR^{12}R^{13}$, $CO_{2}R^{14}$, $SO_{2}R^{15}$, $SO_{2}NR^{12}R^{13}$, or $SO_{2}OR^{16}$, wherein $R^{11}$ is hydrogen, $C_{1-6}$alkyl, aryl, or trifluoromethyl; $R^{12}$ and $R^{13}$ are independently hydrogen or $C_{1-6}$alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom; $R^{14}$ is $C_{1-6}$alkyl or aryl; $R^{15}$ is $C_{1-6}$alkyl, aryl, or trifluoromethyl; and $R^{16}$ is aryl; $R^{5}$ is $C_{1-6}$alkyl, aryl, or trifluoromethyl; $R^{6}$ and $R^{7}$ are independently hydrogen or $C_{1-6}$alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom; $R^{8}$ is hydrogen or $C_{1-6}$alkyl; $R^{9}$ is hydrogen, $C_{1-6}$alkyl, aryl, or trifluoromethyl; and $R^{10}$ is $C_{1-6}$alkyl, aryl, or trifluoromethyl;

$R^{72}$ is hydrogen, $C_{1-6}$alkyl, aryl, CN, $CONR^{74}R^{75}$, $CO_{2}R^{76}$, trifluoromethyl, NHCO$_{2}R^{77}$, hydroxy, $C_{1-6}$alkoxy, benzzyloxy, OCH$_{2}CO_{2}C_{1-6}$alkyl, OCF$_{3}$, S(O)$_{2}R^{78}$, $SO_{2}NR^{79}R^{80}$, or halogen;

$R^{73}$ is hydrogen, $C_{1-6}$alkyl, hydroxy, $C_{1-6}$alkoxy or halogen, or $R^{73}$ and $R^{30}$ taken together from a group $-X-\text{ where } X$ is $(CR^{81}R^{82})_{aa}$ or $X$ is $(CR^{81}R^{82})_{ab}$ and $Y$ is oxygen, sulfur or $CR^{81}=CR^{82};$

$R^{74}$, $R^{75}$, $R^{76}$, $R^{79}$, $R^{80}$, $R^{81}$, and $R^{82}$ are independently hydrogen or $C_{1-6}$alkyl;

$R^{77}$ and $R^{78}$ are independently $C_{1-6}$alkyl;

$y$ is 1 or 2;
$z$ is 0, 1, or 2;
$aa$ is 2, 3 or 4;
$ab$ is 0, 1, 2 or 3;
and further wherein, when $Ar$ is (i), (ii) or (iii), and $A$ is $\text{CONR}^{46}', \text{NHC}O$, or $\text{CH}_2\text{NH}$, wherein $R^{46'}$ is hydrogen or $C_1$-$6$alkyl;
alternatively, $E$ is a group (h):

$$\begin{align*}
\text{R}^{83} & \quad \text{(CR}^{84}\text{R}^{86})_{\text{ae}} \quad \text{NR}^{85}\text{R}^{86} \\
\text{R}^{87} & \quad \text{(h);}
\end{align*}$$

$R^{83}$ and $R^{84}$ are independently hydrogen or $C_1$-$6$alkyl;
$R^{85}$ and $R^{86}$ are independently hydrogen, $C_1$-$6$alkyl, $C_3$-$7$cycloalkyl, aralkyl,
$C_5$-$7$cycloalkenyl, a $C_5$-$7$heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include $C_1$-$6$alkyl, aryl, $\text{CONR}^{88}\text{R}^{89}$, $\text{NR}^{90}\text{R}^{91}$, hydroxy, $\text{OCOR}^{92}$, $\text{NHC}O\text{CF}_3$, $\text{NHSO}_2\text{R}^{93}$, $\text{NCO}_2\text{R}^{94}$, or $\text{NHC}O\text{C}_0$-$6$alkyl wherein the alky1 of $\text{NHC}O\text{C}_0$-$6$alkyl is optionally substituted by $\text{OH}$;
$R^{87}$ is hydrogen or $C_1$-$6$alkyl, $C_1$-$6$alkoxy, or halogen, or $R^{87}$ together with $R^{30'}$ forms a group -AA- where AA is $(\text{CR}^{95}\text{R}^{96})_{\text{ad}}$ or AA is $(\text{CR}^{95}=\text{CR}^{96})_{\text{ae}}$-$\text{AB}$ and AB is oxygen, sulfur, $\text{CR}^{95}=\text{CR}^{96}$, $\text{CR}^{95}=\text{N}$, $\text{CR}^{95}\text{NR}^{96}$ or $\text{N}=\text{N};$
$Z$ is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;
$R^{88}$, $R^{89}$, $R^{90}$, $R^{91}$, $R^{92}$, $R^{95}$, and $R^{96}$ are independently hydrogen or $C_1$-$6$alkyl;
$R^{93}$ and $R^{94}$ are independently $C_1$-$6$alkyl;
$ac$ is 0 to 4;
$ad$ is 1, 2 or 3;
$ae$ is 0, 1 or 2;
and further wherein, when $Ar$ is (i), (ii) or (iii), and $A$ is $\text{CONR}^{46}'$, $\text{NHC}O$, or $\text{CH}_2\text{NH}$, wherein $R^{46'}$ is hydrogen or $C_1$-$6$alkyl,
alternatively, $E$ is a group (i):
R⁹⁷ and R⁹⁸ are independently hydrogen, C₁-6alkyl, C₃-7cycloalkyl, aralkyl, C₅-7cycloalkenyl, a C₅-7heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C₁-6alkyl, aryl, CONR¹⁰²R¹⁰³, NR¹⁰⁴R¹⁰⁵, hydroxy, OCOR¹⁰⁶, NHCOCF₃, NHSO₂R¹⁰⁷, NHCO₂R¹⁰⁸, or NHOCOC₀-6alkyl wherein the alkyl of NHOCOC₀-6alkyl is optionally substituted by OH;
R⁹⁹ and R¹⁰⁰ are independently hydrogen or C₁-6alkyl;
R¹⁰¹ is hydrogen or C₁-6alkyl or R¹⁰¹ and R³⁰ together form a group AD where AD is (CR¹⁰⁹R¹¹⁰)ai or AD is (CR¹⁰⁹R¹¹⁰)aj-AE and AE is oxygen, sulfur or CR¹⁰⁹=CR¹¹⁰;
AC is oxygen, CR¹¹¹R¹¹² or NR¹¹³ or AC is a group S(O)ak;
R¹⁰², R¹⁰³, R¹⁰⁴, R¹⁰⁵, R¹⁰⁶, R¹⁰⁹, R¹¹⁰, R¹¹¹, R¹¹², and R¹¹³ are independently hydrogen or C₁-6alkyl;
R¹⁰⁷ and R¹⁰⁸ are independently C₁-6alkyl;
af is 0, 1, 2, 3, or 4;
ag is 1, 2, or 3;
ah is 1, 2, 3 or 4;
ai is 2, 3 or 4;
aj is 0, 1, 2, or 3; and
ak is 0, 1 or 2, provided that when R² is hydrogen and E is a group (a), (f) (h) or (i), then one or both of R³ or R⁴, R⁵⁹ or R⁶⁰, R⁸⁵ or R⁸⁶, or R⁹⁷ or R⁹⁸ is C₅-7cycloalkenyl, or a C₅-7heterocyclic ring; or when R² is hydrogen and E is a group (b) or (c), then R³⁰ and R⁴⁷ are C₅-7cycloalkenyl, or a C₅-7heterocyclic ring; or when R² is hydrogen and E is group (g), then either R⁷¹ is not hydrogen and/or R⁷¹ is substituted on nitrogen with C₅-7cycloalkenyl or a C₅-7heterocyclic ring.

For compounds of formula (l) various embodiments are as follows. It will be understood that the basic nitrogen in moiety E may be optionally quaternized with C₁-6alkyl or is optionally present as the N-oxide.

Suitably, Ar is (i), (ii), or (iii). Preferably, Ar is (i) or (ii).
Suitably, when Ar is (i) or (ii), the terminal phenyl group in (i) and (ii) can be attached to the phenyl group bearing group A in any position. Preferably, the terminal phenyl ring is attached to the phenyl bearing group A in a position meta or para to group A.

Suitably, R^1 and R^2 are each independently one or more of hydrogen, C_1-
6alkyl, C_2-6alkenyl, C_2-6alkynyl, C_3-7cycloalkyl, C_3-6cycloalkenyl, aryl,
(CH_2)_nNR^7R^8, (CH_2)_nNR^7COR^9, (CH_2)_nNR^7CO_2R^{10}, (CH_2)_nNR^7SO_2R^{11},
(CH_2)_nCONR^{12}R^{13}, hydroxyC_1-6alkyl, C_1-4alkoxyalkyl (optionally substituted by a
C_1-4alkoxy or hydroxy group), (CH_2)_nCO_2C_1-6alkyl, (CH_2)_nOC(O)R^{14},
CR^{15}=NOR^{16}, CNR^{15}=NOR^{16}, COR^{17}, CONR^{12}R^{13}, CONR^{12}(CH_2)_nOC(O)_1-
4alkyl, CONR^{12}(CH_2)_nCO_2R^{18}, CONHNR^{19}R^{20}, CONR^{12}SO_2R^{21}, CO_2R^{22},
cyano, trifluoromethyl, NR^7R^8, NR^7COR^9, NR^7CO(CH_2)_nNR^7R^{24},
NR^7CONR^{23}R^{24}, NR^7CO_2R^{10}, NR^7SO_2R^{11}, N=CR^23NR^23R^{24}, nitro,
hydroxy, C_1-galkoxy, hydroxyC_1-6alkoxy, C_1-galkoxyC_1-6alkoxy, OC(O)NR^25R^{26},
SR^{27}, SOR^{28}, SO_2R^{28}, SO_2NR^25R^{26} or halogen.

Suitably, R^3 and R^4 are each independently one or more of hydrogen, C_1-
6alkyl, C_3-7cycloalkyl, C_3-6cycloalkenyl, hydroxyC_1-6alkyl, C_1-galkylOC_1-6alkyl,
CONR^{29}R^{30}, CO_2R^{31}, cyano, aryl, trifluoromethyl, NR^29R^{30}, nitro, hydroxy, C_1-
galkoxy, acyloxy, or halogen.

Suitably, R^2 is also R^2 where R^2 is hydrogen, (CH_2)_nCN, (CH_2)_nCO_2H,
CR^{15}=CR^{16}CO_2R^{18}, COCR^{15}R^{16}OR^{18}, Oaryl, Oaralkyl, O(CH_2)_nCO_2R^{18}, and
Saryl. Preferably, R^2 is hydrogen, (CH_2)_nCN, (CH_2)_nCO_2H, COCR^{15}R^{16}OR^{18},
and O(CH_2)_nCO_2R^{18} attached to the 3'- or 4'-position.

Suitably, R^5 is one or more of hydrogen, C_1-6alkyl, C_1-6alkoxy or halogen.

Suitably, R^6 is one or more of hydrogen, C_1-6alkyl, C_3-7cycloalkyl (optionally
substituted by a hydroxy or an oxo group), hydroxyC_1-6alkyl, hydroxyC_3-6alkenyl,
hydroxyC_3-6alkynyl, (CH_2)_nOR^{32}, (CH_2)_nCOR^{33}, (CH_2)_nCR^{34}=NOR^{35},
CONR^{36}R^{37}, CO_2R^{38}, hydroxy, O(CH_2)_eR^{39}, NR^{36}R^{37}, SR^{40}, SO_2NR^{41}R^{42},
or halogen; or, R^5 and R^6 form a fused benzene ring optionally substituted with C_1-6
alkyl, C_1-galkoxy or halogen.

Suitably, R^7 and R^8 are each independently hydrogen or C_1-6alkyl, or together
with the nitrogen to which they are attached, R^7 and R^8 form a 5- to 6-membered
heterocyclic ring, which ring may optionally be substituted by an oxo group and,
when the ring is 6-membered, may optionally contain in the ring one oxygen or
sulfur atom.

Suitably, R^9 is hydrogen, C_1-6alkyl or C_1-4alkoxyalkyl.

Suitably, R^{10} is C_1-6alkyl.
Suitably, R₁¹' is C₁₋₆alkyl or phenyl.

Suitably, R₁²' and R₁³' are independently hydrogen or C₁₋₆alkyl, or together with the nitrogen to which they are attached, R₁²' and R₁³' form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom.

Suitably, R₁⁴' is C₁₋₆alkyl, optionally substituted by C₁₋₆alkoxy.

Suitably, R₁⁵' and R₁⁶' are independently hydrogen or C₁₋₆alkyl.

Suitably, R₁⁷' is hydrogen or C₁₋₆alkyl.

Suitably, R₁⁸' is hydrogen or C₁₋₆alkyl.

Suitably, R₁⁹' and R₂₀' are independently hydrogen or C₁₋₆alkyl.

Suitably, R₂¹' is hydrogen or C₁₋₆alkyl.

Suitably, R₂²' is hydrogen or C₁₋₆alkyl optionally substituted with one or two substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, or NR⁷'R⁸'.

Suitably, R₂³' and R₂⁴' are independently hydrogen or C₁₋₆alkyl.

Suitably, R₂⁵' and R₂⁶' are independently hydrogen or C₁₋₆alkyl, or together with the nitrogen to which they are attached, R₂⁵' and R₂⁶' form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom.

Suitably, R₂⁷' is hydrogen or C₁₋₆alkyl.

Suitably, R₂⁸' is C₁₋₆alkyl.

Suitably, R₂⁹', R₃₀' and R₃₁' are independently hydrogen or C₁₋₆alkyl.

Suitably, R₃₂' is C₁₋₆alkyl, hydroxyC₁₋₆alkyl, or C₁₋₄alkanoyl.

Suitably, R₃₃' is hydrogen or C₁₋₆alkyl.

Suitably, R₃₄' is hydrogen or C₁₋₆alkyl.

Suitably, R₃₅' is hydrogen or C₁₋₆alkyl.

Suitably, R₃₆' and R₃₇' are independently hydrogen or C₁₋₆alkyl or together with the nitrogen to which they are attached, R₃₆' and R₃₇' form a 5- to 6-membered heterocyclic ring, which ring may be optionally substituted by an oxo group and, which, when the ring is 6-membered, may optionally contain one oxygen or sulfur atom or an NH group or a group NR₄₃', wherein R₄₃' is C₁₋₆alkyl, COR₄₄' or CO₂R₄₅', wherein R₄₄' and R₄₅' are independently hydrogen or C₁₋₆alkyl.

Suitably, R₃₈' is hydrogen or C₁₋₆alkyl.

Suitably, R₃₉' is C₁₋₆alkoxy, CO₂H, CO₂C₁₋₆alkyl or CONR₃₆'R₃₇'.

Suitably, R₄₀' is C₁₋₆alkyl.

Suitably, R₄₁' and R₄₂' are independently hydrogen or C₁₋₆alkyl.
Suitably, P is a 5- to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen, or sulfur, suitable heterocyclic rings include aromatic groups such as thiényl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiazolyl, pyridyl, pyrimidyl, pyrazinyl, and dioxanyl. Saturated and partially saturated rings are also within the scope of the invention, in particular rings including an oxo or thioxo moiety such as lactams and thiolactams. Suitably, the heterocyclic ring can be linked to the remainder of the molecule via a carbon atom, or, when present, a nitrogen atom.

Suitable substituents for these rings include one or more of R⁴⁺. Preferably, P is 1,2,4-oxadiazol-3-yl and R⁴⁺ is 5-methyl.

Suitably, a' is 1, 2, 3 or 4.
Suitably, b' is 0, 1, 2 or 3.
Suitably, c' is 1, 2 or 3.
Suitably, d' is 0, 1, 2, 3, 4, 5, or 6, and
Suitably, e' is 1, 2, 3, 4, 5 or 6.

Suitably, when Ar is (i), (ii), or (iii), substituent E is selected from the following groups:

![Diagram of chemical structures (a) to (h)]

(b); (c); (f); (h); and
Suitably, when Ar is (i), (ii) or (iii), and A is CONR^{46}, \text{NHCO}, \text{-NHCH}_2, \text{or CH}_2\text{NH}, wherein R^{46} is hydrogen or C_{1-galkyl}, E suitably is a group (a):

![Chemical Structure](image)

B is suitably oxygen, C\_7 C, S(O)\_7 C, CR^{7}=CR^{8}, or CR^{7}R^{8}, or B is NR^{9}. B is preferably CR^{7}R^{8}, or oxygen.

R^{1} and R^{2} are suitably independently hydrogen or C_{1-galkyl}. Preferably, R^{1} and R^{2} are hydrogen. Alternatively, B(CR^{1}R^{2})_{a} is OCR^{1}R^{2}CR^{1}(OH)CR^{1}R^{2} or OCR^{1}R^{2}CR^{1}(OCOCH\_3)CR^{1}R^{2}. Preferably, when B(CR^{1}R^{2})_{a} is OCR^{1}R^{2}CR^{1}(OH)CR^{1}R^{2} or OCR^{1}R^{2}CR^{1}(OCOCH\_3)CR^{1}R^{2}, R^{1} and R^{2} are hydrogen.

R^{3} and R^{4} are suitably independently hydrogen, C_{1-galkyl}, C_{3-cycloalkyl}, aralkyl, C_{5-cycloalkenyl}, a C_{5-7}heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-galkyl}, aryl, CONR^{10}R^{11}, NR^{10}R^{11}, hydroxy, OCOR^{12}, NHCOCF\_3, NSO\_2 R^{13}, NHCO\_2 R^{14}, or NHCO\_2 6alkyl wherein the alkyl of NHCO\_2 6alkyl is optionally substituted by OH.

Preferably R^{3} and R^{4} are both C_{1-galkyl}, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur.

Preferably, B-(CR^{1}R^{2})_{a}NR^{3}R^{4} is ortho to R^{5}, meta to A and para to R^{6}, and R^{5} is para to A.

R^{5} is suitably hydrogen, C_{1-6alkyl}, aryl, CN, CONR^{15}R^{16}, CO\_2 R^{17}, trifluoromethyl, NHCO\_2 R^{18}, hydroxy, C_{1-6alkoxy}, benzoyloxy, OCH\_2 CO\_2 C_{1-6alkyl}, OCF\_3, S(O)\_d R^{19}, SO\_2 NR^{20} R^{21}, or halogen. R^{5} is preferably C_{1-6alkoxy}, SC_{1-6alkyl} or halogen.
R^6 is suitably hydrogen, C_{1-6}alkyl, aryl, trifluoromethyl, hydroxy, C_{1-6}alkoxy, or halogen, or R^6 taken together with R^{46'} forms a group D where D is (CR^{22}R^{23})_e or D is (CR^{22}R^{23})_{G-G} where G is oxygen, sulfur, or CR^{22}=CR^{23}, CR^{22}=N, =CR^{22}O, =CR^{22}S, or =CR^{22}NR^{23}. Preferably, R^6 is hydrogen.

R^7, R^8, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{22}, and R^{23} are suitably independently hydrogen or C_{1-6}alkyl.

R^9 is suitably hydrogen, C_{1-6}alkyl, or phenylC_{1-6}alkyl.

R^{13}, R^{14}, R^{18}, and R^{19} are suitably independently C_{1-6}alkyl.

a is suitably 1, 2, 3, or 4. Preferably, a is 2 or 3.

b is suitably 1 or 2. Preferably, b is 1.

c and d are suitably independently 0, 1, or 2.

e is suitably 2, 3, or 4.

f is suitably 0, 1, 2, or 3.

Alternatively, when Ar is (i), (ii) or (iii), and A is CONR^{46'}, NHCO, or CH_{2}NH, wherein R^{46'} is hydrogen or C_{1-6}alkyl, E suitably is a group (b):

(b).

R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31}, and R^{32} are suitably independently hydrogen or C_{1-6}alkyl. R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31}, and R^{32} are preferably hydrogen.

R^{30} is suitably hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl or a C_{5-7}heterocyclic ring. Preferably, R^{30} is C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl or a C_{5-7}heterocyclic ring.

R^{33} is suitably hydrogen, C_{1-6}alkyl, trifluoromethyl, hydroxy or halogen, or R^{33} and R^{46'} together form a group -K- where K is (CR^{34}R^{35})_i or K is (CR^{34}R^{35})_{j=1-M} and M is oxygen, sulfur, CR^{34}=CR^{35}, CR^{34}=N, or N=N. Preferably, R^{33} is hydrogen.

J is suitably oxygen, CR^{36}R^{37}, or NR^{38}, or J is a group S(O)_k. Preferably, J is oxygen. Preferably, J is para to A.

R^{34}, R^{35}, R^{36}, R^{37}, R^{38} are suitably independently hydrogen or C_{1-6}alkyl.

g is suitably 1, 2, or 3. Preferably, g is 2 or 3.

h is suitably 1, 2, or 3. Preferably, h is 1.
i is suitably 2, 3, or 4.
j is suitably 0, 1, 2, or 3.
k is suitably 0, 1 or 2.

Alternatively, when Ar is (i), (ii) or (iii), and A is CONR^{46}, NHCO{-}, -NHCH_{2}, or CH_{2}NH, wherein R^{46} is hydrogen or C_{1}-alkyl, E suitably is a group (c):

Suitably, Q is oxygen, S(O)_{n}, CR^{44}+CR^{45}, C=C, or CR^{44}R^{45}, wherein n is 0, 1 or 2, and R^{44} and R^{45} are independently hydrogen or C_{1}-alkyl, or suitably, Q is NR^{46} wherein R^{46} is hydrogen or alkyl; suitably, R^{39} and R^{40} are independently hydrogen or C_{1}-alkyl; suitably, R^{42} is hydrogen, C_{1}-alkyl, aryl, CN, CONR^{48}R^{49}, CO_{2}R^{50}, trifluoromethyl, NHCO_{2}R^{51}, hydroxy, C_{1}-alkoxy, benzyloxy, OCH_{2}CO_{2}C_{1}-alkyl, OCF_{3}, S(O)_{3}R^{52}, SO_{2}NR^{53}R^{54}, or halogen, wherein R^{48}, R^{49}, R^{50}, R^{53}, and R^{54} are hydrogen or C_{1}-alkyl, and R^{51} and R^{52} are C_{1}-alkyl; suitably, R^{43} is hydrogen or R^{43} together with R^{46} forms a group R wherein R is CR^{55}+CR^{56}, CR^{55}+CR^{56}+CR^{55}R^{56}, or (CR^{55}R^{56})_{t} wherein R^{55} and R^{56} are independently hydrogen or C_{1}-alkyl and t is 2 or 3; suitably, R^{41} is selected from a group of formula (d) or (e); suitably R^{47} is hydrogen, C_{1}-alkyl, C_{3}-7 cycloalkyl, C_{5}-7cycloalkenyl, or a C_{5}-7heterocyclic ring; suitably, l is 0, 1, 2 or 3, m is 1 or 2, n and s are independently 0, 1 or 2, o, p and q are independently 1, 2 or 3, and r is 0, 1, 2 or 3.

Alternatively, when Ar is (i), (ii) or (iii), and A is CONH, NHCO, or CH_{2}NH, E suitably is a group (f):

R^{57} and R^{58} are independently hydrogen or C_{1}-alkyl; suitably R^{59} and R^{60} are independently hydrogen, C_{1}-alkyl, C_{3}-7cycloalkyl, aralkyl, C_{5}-7cycloalkenyl, a C_{5}-7heterocyclic ring or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1}-alkyl, aryl, CONR^{61}R^{62}, NR^{61}R^{62}, hydroxy, OCOR^{63}, NHCOCF_{3}, NHSO_{2}R^{64}, NHCO_{2}R^{65} or NHCO_{2}R^{65} or NHCO_{2}R^{65} wherein the alkyl of NHCO_{2}R^{65} is optionally substituted by OH, and wherein R^{61}, R^{62}, and R^{63} are independently hydrogen or C_{1}-alkyl, and R^{64} and R^{65} are independently C_{1}-alkyl; suitably, T is - (CR^{66}R^{67})_{v} or -O(OR^{66}R^{67})_{w}, wherein R^{66} and R^{67} are independently hydrogen or C_{1}-alkyl, wherein v is 2 or 3, and w is 1, 2 or 3; suitably,
W is oxygen, S(O)ₓ, wherein x is 0, 1 or 2, or W is NR⁶⁸, wherein R⁶⁸ is hydrogen or C₁₋₆-alkyl, or W is CR⁶⁹=CR⁷⁰, C=C, or CR⁶⁹R⁷⁰, wherein R⁶⁹ and R⁷⁰ are independently hydrogen or C₁₋₆-alkyl; and suitably, u is an integer from 1-4.

Alternatively, when Ar is (i), (ii) or (iii), and A is CONR⁴⁶', NHCO, or CH₂NH, wherein R⁴⁶' is hydrogen or C₁₋₆-alkyl, E suitably is a group (g):

\[
\begin{array}{c}
\text{R}^{71} \\
\text{R}^{73}
\end{array}
\]

Suitably, R⁷¹ is an optionally substituted 5- to 7-membered saturated or partially saturated heterocyclic ring containing a basic nitrogen atom and optionally a further one or two heteroatoms selected from nitrogen, oxygen or sulfur, or R⁷¹ is an optionally substituted 6,6 or 6,5-bicyclic ring system containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur, which ring systems may be optionally substituted with one or more of C₁₋₆-alkyl, and substituted on nitrogen with hydrogen, C₁₋₆-alkyl, C₃₋₇-cycloalkyl, C₅₋₇-cycloalkenyl, or a C₅₋₇-heterocyclic ring. Examples of such ring systems include, but are not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, pyrazolidine, 1,2,3,6-tetrahydropyridine, hexahydroazepine, tropane, isoquinuclidine and granatane rings. Preferably, R⁷¹ is an optionally substituted 5- or 6-membered saturated or partially saturated heterocyclic ring containing a nitrogen atom and is substituted on nitrogen with C₁₋₆-alkyl, C₃₋₇-cycloalkyl, C₅₋₇-cycloalkenyl, or a C₅₋₇-heterocyclic ring.

Suitably, R⁷¹ is substituted with one or more of R⁷¹ wherein R⁷¹ is hydrogen, CR¹aR²R²⁰NR³R⁴⁰, CR¹aR²OR³⁰, COR⁵⁰, CONR⁶⁰R⁷⁰, CO₂R⁸⁰, cyano, NR³⁰R⁴⁰, nitro, hydroxy, C₁₋₆-alkoxy, SR⁹⁰, SOR¹⁰⁰, SO₂R¹⁰⁰, SO₂NR⁶⁰R⁷⁰ or SO₃H wherein R¹⁰ and R²⁰ are independently hydrogen or C₁₋₆-alkyl, provided that R⁷¹ is not a substituent on the basic nitrogen of R⁷¹.

Suitably, R³⁰ and R⁴⁰ are independently hydrogen or C₁₋₆-alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom.

Alternatively, R⁴⁰ is COR¹¹⁰, CONR¹²⁰R¹³⁰, CO₂R¹⁴⁰, SO₂R¹⁵⁰, SO₂NR¹²⁰R¹³⁰, or SO₂OR¹⁶⁰ wherein R¹¹⁰ is hydrogen, C₁₋₆-alkyl, aryl, or trifluoromethyl; R¹²⁰ and R¹³⁰ are independently hydrogen or C₁₋₆-alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom; R¹⁴⁰ is C₁₋₆-alkyl or aryl; R¹⁵⁰ is C₁₋₆-alkyl, aryl, or
trifluoromethyl; and R\textsuperscript{16}\textsuperscript{16} is aryl; R\textsuperscript{5}\textsuperscript{5} is hydrogen, C\textsubscript{1}-alkyl, aryl, or trifluoromethyl; R\textsuperscript{6}\textsuperscript{6} and R\textsuperscript{7}\textsuperscript{7} are independently hydrogen or C\textsubscript{1}-alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom; R\textsuperscript{8}\textsuperscript{8} is hydrogen or C\textsubscript{1}-alkyl; R\textsuperscript{9}\textsuperscript{9} is hydrogen, C\textsubscript{1}-alkyl, aryl, or trifluoromethyl; and R\textsuperscript{10}\textsuperscript{10} is C\textsubscript{1}-alkyl, aryl, or trifluoromethyl. Preferably, R\textsuperscript{71}\textsuperscript{71} is hydrogen or cyan.

R\textsuperscript{71} is preferably located meta to A, ortho to R\textsuperscript{72} and para to R\textsuperscript{73}, and R\textsuperscript{72} is located para to A.

Suitably, R\textsuperscript{72} is hydrogen, C\textsubscript{1}-alkyl, aryl, CN, CONR\textsubscript{74}R\textsubscript{75}, CO\textsubscript{2}R\textsubscript{76}, trifluoromethyl, NHCO\textsubscript{2}R\textsubscript{77}, hydroxy, C\textsubscript{1}-alkoxy, benzylxy, OCH\textsubscript{2}CO\textsubscript{2}C\textsubscript{1}-alkyl, OCF\textsubscript{3}, S(O)\textsubscript{2}R\textsubscript{78}, SO\textsubscript{2}NR\textsubscript{79}R\textsubscript{80}, or halogen wherein R\textsuperscript{74}, R\textsuperscript{75}, R\textsuperscript{76}, R\textsuperscript{79} and R\textsuperscript{80} are independently hydrogen or C\textsubscript{1}-alkyl, R\textsuperscript{77} and R\textsuperscript{78} are C\textsubscript{1}-alkyl, and z is 0, 1, or 2. R\textsuperscript{72} is preferably C\textsubscript{1}-alkoxy, SC\textsubscript{1}-alkyl or halogen.

R\textsuperscript{73} is hydrogen, C\textsubscript{1}-alkyl, hydroxy, C\textsubscript{1}-alkoxy or halogen, or R\textsuperscript{73} and R\textsuperscript{46}' taken together from a group -X- where X is (CR\textsuperscript{81}R\textsuperscript{82})\textsubscript{aa}, wherein aa is 2, 3 or 4, and R\textsuperscript{81} and R\textsuperscript{82} are independently hydrogen or C\textsubscript{1}-alkyl, or X is (CR\textsuperscript{81}R\textsuperscript{82})\textsubscript{ab}-Y, wherein ab is 0, 1, 2 or 3, and Y is oxygen, sulfur or CR\textsuperscript{81}=CR\textsuperscript{82} wherein R\textsuperscript{81} and R\textsuperscript{82} are independently hydrogen or C\textsubscript{1}-alkyl. Preferably, R\textsuperscript{73} is hydrogen.

Suitably, y is an integer from 1-2. Preferably, y is 1.

Alternatively, when Ar is (i), (ii) or (iii), and A is CONR\textsubscript{46}', NHCO, or CH\textsubscript{2}NH, wherein R\textsuperscript{46}' is hydrogen or C\textsubscript{1}-alkyl, E suitably is a group (h):

\[
\begin{array}{c}
\text{R}^{87} \\
\text{Z} \\
\text{(CR}^{85}R^{86})_{ae} \\
\text{---NR}^{88}R^{89}
\end{array}
\]

Suitably, R\textsuperscript{87} is hydrogen, C\textsubscript{1}-alkyl, C\textsubscript{1}-alkoxy or halogen, or R\textsuperscript{87} together with R\textsuperscript{46}' form a group -AA-, wherein AA is (CR\textsuperscript{95}R\textsuperscript{88})\textsubscript{ad}, wherein ad is 1, 2 or 3, and R\textsuperscript{95} and R\textsuperscript{88} are independently hydrogen or C\textsubscript{1}-alkyl, or AA is (CR\textsuperscript{95}CR\textsuperscript{96})\textsubscript{ae}-AB, wherein ae is 0, 1 or 2, and AB is oxygen, sulfur, CR\textsuperscript{95}=CR\textsuperscript{96}, CR\textsuperscript{95}=N, CR\textsuperscript{95}NR\textsuperscript{96} or N=N, wherein R\textsuperscript{95} and R\textsuperscript{96} are independently hydrogen or C\textsubscript{1}-alkyl.

Suitably, R\textsuperscript{83} and R\textsuperscript{84} are independently hydrogen or C\textsubscript{1}-alkyl.

Suitably, R\textsuperscript{85} and R\textsuperscript{86} are independently hydrogen, C\textsubscript{1}-alkyl, C\textsubscript{3}-7cycloalkyl, aralkyl, C\textsubscript{5}-7cycloalkenyl, a C\textsubscript{5}-7heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C\textsubscript{1}-alkyl, aryl, CONR\textsubscript{88}R\textsubscript{89},
NR⁹⁰R⁹¹, hydroxy, OCOR⁹², NHCOCF₃, NHSO₂R⁹³, NHCO₂R⁹⁴, or NHCOC₀-6alkyl wherein the alkyl of the NHCOC₀-6alkyl is optionally substituted by OH, and wherein R⁸⁸, R⁸⁹, R⁹⁰, R⁹¹ and R⁹² are independently hydrogen or C₁₆alkyl, and R⁹³ and R⁹⁴ are independently C₁₆alkyl.

Suitably Z is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur; suitably ac is 0-4.

Alternatively, when Ar is (i), (ii) or (iii), and A is CONR⁴⁶', NHCO, or CH₂NH, wherein R⁴⁶' is hydrogen or C₁₆alkyl, E suitably is a group (i):

Suitably, R¹⁰¹ is hydrogen or C₁₆alkyl or R¹⁰¹ and R⁴⁶' together form a group -AD- wherein AD is (CR¹⁰⁹R¹¹⁰)ₐi wherein ai is 2, 3 or 4 or AD is (CR¹⁰⁹R¹¹⁰)ₐj-AE wherein aj is 0, 1, 2 or 3 and AE is oxygen, sulfur or CR¹⁰⁹=CR¹¹⁰, and R¹⁰⁹ and R¹¹⁰ are independently hydrogen or C₁₆alkyl.

Suitably, R⁹⁷ and R⁹⁸ are independently hydrogen, C₁₆alkyl, C₃₋₇cycloalkyl, aralkyl, C₅₋₇cycloalkenyl, a C₅₋₇heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C₁₆alkyl, aryl, CONR¹⁰²R¹⁰³, NR¹⁰⁴R¹⁰⁵, hydroxy, OCOR¹⁰⁶, NHCOCF₃, NHSO₂R¹⁰⁷, NHCO₂R¹⁰⁸, or NHCOC₀-6alkyl wherein the alkyl of NHCOC₀-6alkyl is optionally substituted by OH, and wherein R¹⁰², R¹⁰³, R¹⁰⁴, R¹⁰⁵ and R¹⁰⁶ are independently hydrogen or C₁₆alkyl, and R¹⁰⁷ and R¹⁰⁸ are independently C₁₆alkyl.

Suitably, R⁹⁹ and R¹⁰⁰ are independently hydrogen or C₁₆alkyl; suitably, AC is oxygen, CR¹¹¹R¹¹² or NR¹¹³ wherein R¹¹¹, R¹¹² and R¹¹³ are independently hydrogen or C₁₆alkyl or AC is a group S(O)ak wherein ak is 0, 1 or 2; suitably, ag is an integer from 1-3, ah is an integer from 1-4, and af is 0-4.

Preferably, A is CONR⁴⁶', NHCO, or CH₂NH, wherein R⁴⁶' is hydrogen.

More preferably, A is CONR⁴⁶' or NHCO, wherein R⁴⁶' is hydrogen.

Most preferably, A is CONR⁴⁶', wherein R⁴⁶' is hydrogen.

Preferably, when Ar is (i), (ii), or (iii), E is group (a), (b), or (g).
More preferably, when Ar is (i) or (ii), the terminal phenyl in (i) and (ii) is attached to the phenyl ring bearing group A in a position para to group A.

More preferably, when Ar is (i), (ii) or (iii), E is group (g).

Most preferably, when Ar is (i) or (ii), E is group (g).

More preferably, R²" is hydrogen, or (CH₂)ₐ-CN, (CH₂)ₐ-CO₂H, COCR¹⁵R¹⁶OR¹₈", and O(CH₂)ₐ-CO₂R¹₈" attached to the 3'-position.

Most preferably, R²" is hydrogen, cyanomethyl, or cyanoethyl attached to the 3'-position.

More preferably, when E is group (a), A is attached to group (a) meta to B-(CR¹R²)ₐ-NR³R⁴ and para to (R⁵)ₐ, wherein B is oxygen or CR⁷R⁸, R¹ and R² are hydrogen, R⁵ is methoxy, methylthio or iodo, R³ and R⁴ are independently C₃-₆alkyl, or R³ and R⁴ taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring optionally substituted with one or more of C₃-₆alkyl and acetamido or hydroxyl, R⁶ is hydrogen, a is 2 or 3 when B is oxygen and a is 2 when B is CH₂, and b is 1.

Most preferably, when E is group (a), A is attached to group (a) meta to B-(CR¹R²)ₐ-NR³R⁴ and para to (R⁵)ₐ, wherein B is oxygen or CH₂, R¹ and R² are hydrogen, R⁵ is methoxy, R³ and R⁴ are independently isopropyl or tert-butyl, or R³ and R⁴ taken together with the nitrogen to which they are attached are 1-(2,2,6,6-tetramethylpiperidinyl), 1-(4-acetamido-2,2,6,6-tetramethyl piperidinyl), 1-(4-hydroxy-2,2,6,6-tetramethyl piperidinyl) or 1-(4-hydroxy-2,2,4,6,6-(pentamethyl)piperidinyl), R⁶ is hydrogen, a is 2 when B is oxygen, and b is 1.

More preferably, when E is group (b), A is attached to group (b) para to J, J is oxygen, R³₃ is hydrogen, R²₄, R²₅, R²₆, R²⁷, R²₈, R²₉, R₃₁ and R₃₂ are hydrogen, R₃₀ is C₃-₆alkyl, g is 2 and h is 1.

Most preferably, when E is group (b), A is attached to group (b) para to J, J is oxygen, R³₃ is hydrogen, R²₄, R²₅, R²₆, R²⁷, R²₈, R²₉, R₃₁ and R₃₂ are hydrogen, R₃₀ is isopropyl, g is 2 and h is 1.

More preferably, when E is group (g), A is attached to group (g) meta to R⁷¹ and para to R⁷₂, R⁷¹ is an optionally substituted 5- or 6-membered saturated or partially saturated heterocyclic ring containing a nitrogen atom and substituted on nitrogen with C₃-₆alkyl, C₃-₇cycloalkyl, C₅-₇cycloalkenyl, or a C₅-₇heterocyclic ring, R⁷₂ is methoxy, methylthio or iodo, y is 1, R⁷₃ is hydrogen, and R⁷₁" is hydrogen or cyano, attached to the benzylic carbon of R⁷₁.

Most preferably, when E is group (g), A is attached to group (g) meta to R⁷¹ and para to R⁷₂ wherein R⁷₁ is piperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, or
pyrrolidin-3-yl substituted on nitrogen with isopropyl, 3-pentyl, cyclopropyl, 
cyclopentyl, tetrahydro-2H-pyran-4-yl, or cyclopent-3-enyl, R71" is hydrogen or 4-cyano, R72 is methoxy, y is 1, and R73 is hydrogen.

A preferred subgenus of compounds of formula (I) is wherein A is CONR46', 
NHCO, or CH2NH, wherein R46' is hydrogen; Ar is (i), (ii), or (iii); and E is group (a), (b), or (g).

A more preferred subgenus of compounds of formula (I) is wherein A is CONR46' or 
NHCO, wherein R46' is hydrogen; Ar is (i) or (ii), and the terminal phenyl in (i) and (ii) is 
attached to the phenyl ring bearing group A in a position para to group A; E is group (a), (b), or (g); and R2" is hydrogen, or (CH2)a-CN, (CH2)a-CO2H, COCR15'R16'OR18', and 
O(CH2)a-CO2R18' attached to the 3'-position. When E is group (a), A is attached to group (a) 
meta to B-(CR1R2)a-NR3R4 and para to (R5)b, wherein B is oxygen or CR7R8, R1 and R 2 are 
hydrogen, R5 is methoxy, methylthio or iodo, R3 and R4 are independently C3-galkyl, or 
R3 and R4 taken together with the nitrogen to which they are attached form a 5- or 6-membered 
heterocyclic ring optionally substituted with one or more of C1-galkyl and acetamido or 
hydroxyl, R6 is hydrogen, a is 2 or 3 when B is oxygen and a is 2 when B is CH2, and b is 1. 
When E is group (b), A is attached to group (b) para to J, J is oxygen, R33 is hydrogen, R24, 
R25, R26, R27, R28, R29, R31 and R32 are hydrogen, R30 is C3-galkyl, g is 2 and h is 1. 
When E is group (g), A is attached to group (g) meta to R71 and para to R72, R71 is an 
optionally substituted 5- or 6-membered saturated or partially saturated heterocyclic ring 
containing a nitrogen atom and substituted on nitrogen with C3-galkyl, C3-gcycloalkyl, or C5- 
gcycloalkenyl, R72 is methoxy, methylthio or iodo, y is 1, R73 is hydrogen, and R71" is 
attached to the benzylic carbon of R71, and is hydrogen or cyano.

Another preferred subgenus of compounds of formula (I) is wherein A is CONR46', 
wherein R46' is hydrogen; Ar is (i), (ii), or (iii); E is group (a), (b), or (g), wherein Ar is (i) or (ii), the terminal phenyl in (i) and (ii) is attached to the phenyl ring bearing group A in a 
position para to group A; and wherein when E is group (a), A is attached to group (a) meta to 
B-(CR1R2)a-NR3R4 and para to (R5)b, wherein B is oxygen or CH2, R1 and R 2 are 
hydrogen, R5 is methoxy, R3 and R4 are independently isopropyl or tert-butyl, or R3 and R4 taken 
together with the nitrogen to which they are attached are 1-(2,2,6,6- 
tetramethylpiperidinyl), 1-(4-acetamido-2,2,6,6-tetramethyl piperidinyl), 1-(4-hydroxy-2,2,6,6-tetramethyl piperidinyl) or 1-(4-hydroxy-2,2,4,6,6-(pentamethyl)piperidinyl), R6 is hydrogen, 
a is 2 when B is oxygen, and b is 1; and wherein when E is group (b), A is attached to group 
(b) para to J, J is oxygen, R33 is hydrogen, R24, R25, R26, R27, R28, R29, R31 and R32 are 
hydrogen, R30 is isopropyl, g is 2 and h is 1; and wherein when E is group (g), A is attached to 
group (g) meta to R71 and para to R72 wherein R71 is piperidin-4-yl, 1,2,3,6-

tetrahydropyridin-4-yl, or pyrrolidin-3-yl substituted on nitrogen with isopropyl, 3-pentyl, cyclopropyl, cyclopentyl, tetrahydro-2H-pyran-4-yl, or cyclopent-3-enyl, R71" is hydrogen or 4-cyano, R72 is methoxy, y is 1, and R73 is hydrogen.

A particularly preferred subgenus of compounds of formula (I) is wherein A is CONR46, wherein R46 is hydrogen; Ar is (i) or (ii), wherein the terminal phenyl in (i) and (ii) is attached to the phenyl ring bearing group A in a position para to group A; E is group (g); R2" is hydrogen, cyanomethyl, or cyanoethyl attached to the 3'-position; wherein A is attached to group (g) meta to R71 and para to R72, R71 is piperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, or pyrrolidin-3-yl substituted on nitrogen with isopropyl, 3-pentyl, cyclopropyl, cyclopentyl, tetrahydro-2H-pyran-4-yl, or cyclopent-3-enyl, R71" is hydrogen or 4-cyano, R72 is methoxy, y is 1, and R73 is hydrogen.

The term "acyloxy" is used herein at all occurrences to mean a moiety -O-C(O)-R, wherein R is hydrogen or C1-6-alkyl as defined below.

The term "C1-4-alkanoyl" is used herein at all occurrences to mean a -C(O)C1-4-alkyl group wherein the alkyl portion is as defined below.

The term "alkenyl" is used herein at all occurrences to mean a straight or branched chain radical of 2 to 6 carbon atoms, unless the length is limited thereto, wherein there is at least one double bond between two of the carbon atoms in the chain, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butene, 2-butene, and the like.

The term "alkoxy" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, and the like.

The term "C1-6-alkoxyC1-6-alkoxy" is used herein at all occurrences to mean an alkoxy group as defined above, substituted with an alkoxy group as defined above.

The term "C1-4-alkoxyalkyl" is used herein at all occurrences to mean a C1-4-alkoxy group as defined above bonded to an alkyl group as defined below, including, but not limited to, -CH2-CH2-O-CH2-CH2-CH3 and the like.

The term "C1-6-alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The term "alkynyl" is used herein at all occurrences to mean a straight or branched chain radical of 2 to 8 carbon atoms, unless the chain length is limited thereto,
wherein there is at least one triple bond between two of the carbon atoms in the chain, including, but not limited to, acetylene, 1-propylene, 2-propylene, and the like.

The term "aralkyl" is used herein at all occurrences to mean an aryl moiety as defined above, which is connected to an alkyl moiety as defined below, including, but not limited to, benzyl or phenethyl, and the like.

The term "aryl" is used herein at all occurrences to mean a 6-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, including, but not limited to, phenyl, naphthalenyl, biphenyl, phenanthryl, anthracenyl, and the like.

The term "6,6 or 6,5 bicyclic ring" is used herein at all occurrences to mean a 6,6 or 6,5-bicyclic ring system containing a nitrogen atom and optionally a further heteroatom selected from nitrogen, oxygen, or sulfur, which ring system may be optionally substituted with C1-6alkyl. Examples of such ring systems include, but are not limited to, tropane, isoquinuclidine and granatane rings.

The term "cycloalkenyl" is used herein at all occurrences to mean cyclic radicals, preferably of 5 to 8 carbons, which have at least one double bond between two of the carbon atoms in the ring, including but not limited to, cyclopentenyl, cyclohexenyl, and the like.

The terms "cycloalkyl" and "cyclic alkyl" are used herein at all occurrences to mean cyclic radicals, preferably comprising 3 to 7 carbon atoms which may be mono- or bicyclo- fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthalenyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "heteroaryl" is used herein at all occurrences to mean a 5-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, which ring or ring systems contain 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur, including, but not limited to, indolyl, benzofuranyl, thianaphthenyl, quinolyl, isoquinolyl, pyrrolyl, furanyl, thiencyl, pyridyl, and the like.

The term "hydroxyC1-6alkoxy" is used herein at all occurrences to mean an hydroxyl group bonded to an alkoxy group as defined above, including, but not limited to, -O-CH2-CH(OH)CH3 and the like.
The terms "hydroxyC\textsubscript{1-6}alkyl" and "hydroxyalkyl" are used herein interchangeably to mean an hydroxyl group bonded to a C\textsubscript{1-6}alkyl group as defined above, including, but not limited to, methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, tert-butanol, and the like.

The term "heterocyclic ring" is used herein at all occurrences to mean a saturated or partially saturated 5-10-membered ring system (unless the cyclic ring system is otherwise limited) in which the ring system contains one to 3 heteroatoms selected from oxygen, sulfur, or nitrogen, which ring system may be optionally substituted with C\textsubscript{1-6}alkyl. Examples of such rings include, but are not limited to, piperidine, tetrahydropyridine, and piperazine, pyrrolidine, piperidine, morpholine, imidazolidine, pyrazolidine, hexahydroazepine, tropane, isoquinuclidine, granatane, and the like. When the heterocyclic ring is fused to a phenyl group, as when E is the group (h), the term "heterocyclic ring", together with the phenyl ring to which it is fused, forms a ring which includes, but is not limited to, dihydro-1,4-benzoxazine and 1,2,3,4-tetrahydroquinoline, which may be optionally substituted by C\textsubscript{1-6}alkyl or oxo.

The term "heteroatom" is used herein at all occurrences to mean an oxygen atom, a sulfur atom or a nitrogen atom. It will be recognized that when the heteroatom is nitrogen, it may form an NR\textsubscript{a} or NR\textsubscript{a}R\textsubscript{b} moiety, wherein R\textsubscript{a} and R\textsubscript{b} are, independently, hydrogen or C\textsubscript{1} to C\textsubscript{6} alkyl, or together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6- or 7-membered ring, including, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, pyridine, and the like. It will be recognized that the saturated or unsaturated 5-, 6- or 7-membered ring may optionally have one or more additional heteroatoms in the ring.

The term "optionally substituted" is used herein at all occurrences to mean an optionally substituted 5- to 7-membered heterocyclic ring wherein the optional substituents are one or more of C\textsubscript{1-6}alkyl.

The term "oxo" is used herein at all occurrences to mean a double bonded oxygen atom attached to a chemical moiety as a substituent.

The term "CCR5 mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by CCR5.

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.
The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention.

Among the preferred compounds of the invention are the following compounds:

10 N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'- (ethoxyacetyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'- (hydroxyacetyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'- (methoxyacetyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-(2-methoxy-2-oxoethoxy)-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

15 3'-(2-Cyanoethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide;
3'-(2-Cyanomethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'-(cyanoethyl)-

20 1,1'-biphenyl-4-carboxamide;
N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'-(cyanomethyl)-
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-(cyanoethyl)-

25 1,1'-biphenyl-4-carboxamide;
N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'-(cyanomethyl)-
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-(cyanoethyl)-

30 1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'
(cyanomethyl)-1,1'-biphenyl-4-carboxamide;
3'-(2-Cyanoethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;

35 3'-(2-Cyanomethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
N-[3-[(tetrahydro-2H-pyranyl-4-yl)4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-[2-Carboxyethyl]-N-[3-[(1-methylethyl)4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[(Bis1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'.

3'-Chloro-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'.

ethoxycarbonyl-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'.

sulfamoyl-1,1'-biphenyl-4-carboxamide;

3'-[(2-Cyanoethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'.

ureido-1,1'-biphenyl-4-carboxamide;

3'-[(Cyanomethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'.

isoproxy-1,1'-biphenyl-4-carboxamide;

3'-Cyano-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'.

3'-Dimethyl-1,1'-biphenyl-4-carboxamide;

3'-Acetamido-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetyl-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-[2-Carboxyethyl]-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'.

(1H-tetrazol-5-yl)-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'.

(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'.

(methanesulfonamido)-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-
dichloro-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'
bis(methoxycarbonyl)-1,1'-biphenyl-4-carboxamide; and
3'-Carboxamido-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-
methoxyphenyl]-1,1'-biphenyl-4-carboxamide.

Among the more preferred compounds of the invention is the following compound:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'
(ethoxyacetyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'
(hydroxyacetyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'
(methoxycetyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'(2-ethoxy-2-
oxoethoxy)-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'
biphenyl-4-carboxamide;

3'-(2-Cyanoethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-
piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide;
3'-(2-Cyanomethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-
piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'-
(3'-methyl-1,1'-biphenyl-4-carboxamide;
N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'
(3'-cyanomethyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'
(3'-cyanomethyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'
(3'-cyanoethyl)-1,1'-biphenyl-4-carboxamide;
3'-(2-Cyanoethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
3'-(2-Cyanomethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
N-[3-[1-(tetrahydro-2H-pyran-4-yl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-[2-Carboxyethyl]-N-[3-[1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[2-Bis(1-methylthyl)amino]ethoxy]-4-methoxyphenyl]-3'-carboxamido-1,1'-biphenyl-4-carboxamide;

3'-Chloro-N-[3-[4-cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-3'-ethoxycarbonyl-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-3'-sulfamoyl-1,1'-biphenyl-4-carboxamide;

3'-[2-Cyanoethyl]-N-[3-[4-cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-3'-ureido-1,1'-biphenyl-4-carboxamide;

3'-(Cyanomethyl)-N-[3-[4-cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-3'-isoproxy-1,1'-biphenyl-4-carboxamide;

3'-Cyan-N-[3-[4-cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-dimethyl-1,1'-biphenyl-4-carboxamide;

3'-Acetamido-N-[3-[4-cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-Acetyl-N-[3-[4-cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

3'-[2-Carboxyethyl]-N-[3-[4-cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide;

N-[3-[4-Cyano-1-(1-methylthyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(methanesulfonamido)-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-dichloro-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-bis(methoxy carbonyl)-1,1'-biphenyl-4-carboxamide; and

3'-Carboxamido-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide.

Among the most preferred compounds of the invention is the following compound:

3'-(2-Cyanomethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[1-(tetrahydro-2H-pyran-4-yl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
3'-(2-Cyanoethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
3'-(2-Cyanomethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
3'-Chloro-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-ethoxycarbonyl-1,1'-biphenyl-4-carboxamide;
3'-(2-Cyanoethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-ureido-1,1'-biphenyl-4-carboxamide;
3'-(Cyanoethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-isopropoxy-1,1'-biphenyl-4-carboxamide;
3'-Cyano-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-dimethyl-1,1'-biphenyl-4-carboxamide;
3'-Acetamido-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
3'-Acetyl-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(methanesulfonamido)-1,1'-biphenyl-4-carboxamide; and
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-bis(methoxycarbonyl)-1,1'-biphenyl-4-carboxamide.

10 **Formulation of Pharmaceutical Compositions**

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") in an amount sufficient to treat COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis, or idiopathic pulmonary fibrosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, treating and/or preventing rejection of transplanted organs, inflammatory bowel disease, and HIV infection, ("CCR5-mediated disease states") with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of CCR5 mediated disease states. The amount of active
ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the bloodstream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride.
chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis, or idiopathic pulmonary fibrosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, treating and/or preventing rejection of transplanted organs, inflammatory bowel disease, and HIV infection, all in mammals, preferably humans, which comprises administering to such mammal an effective amount of a CCR5 receptor modulator, in particular, a compound as depicted in formula (I).

By the term "treating" is meant either prophylactic or therapeutic therapy. Such formula (I) compound can be administered to such mammal in a conventional dosage
form prepared by combining the formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The formula (I) compound is administered to a mammal in need of treatment for COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis, or idiopathic pulmonary fibrosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, treating and/or preventing rejection of transplanted organs, inflammatory bowel disease, and HIV infection, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

In another aspect, the invention relates to a method for modulating factors which exacerbate the symptoms of the CCR5-mediated diseases described herein.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Methods of Preparation

The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.
For example, as shown in Scheme 1, compounds of formula (I) wherein A is NR⁴⁶⁺ are synthesized from an appropriately substituted benzoic acid, for example 1-1, and an appropriately substituted aniline 1-2 by treatment with a suitable coupling reagent, for example benzotriazol-1-ylxytris(dimethylamino)phosphonium hexafluorophosphate, and a suitable base, for example diisopropylethylamine, in a suitable solvent, for example acetonitrile, to afford the title compound 1-3. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience).

Alternatively, compounds of formula (I) may be obtained as shown in Scheme 2 by treatment of a suitably substituted aniline 1-2 with a suitably substituted boronobenzoic acid, for example 2-1, with a suitable coupling reagent, for example 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxy-7-azabenzotriazole, in a suitable solvent, for example acetonitrile, to give 2-2. Treatment of 2-2 with a suitably substituted aryl bromide, aryl iodide or aryl triflate, in the presence of a suitable catalyst, for example [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), and a suitable base, for example 2M sodium carbonate, in a suitable solvent, for example dimethylformamide, at a suitable temperature, for example 80°C, for a suitable time, for example overnight, affords compounds of formula (I) 1-3.

Scheme 1

```
R¹⁺ R²⁺ R³⁺          R¹⁺ R²⁺ R³⁺ R⁴⁶⁺
|___|___|___          |___|___|___|___|
|___|___|___            |___|___|___|___|
OH  +  H-N=E  →  BOP reagent, DIEA, MeCN

1-1          1-2          1-3
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Specifically, compounds of formula (I) wherein Ar is represented by group (i) or (ii), A is CONH and E is represented by group (a), were prepared according to the methods of international application publication number WO 95/26328, published 5 October 1995 and international application publication number WO 95/15954, published 15 June 1995.

Compounds of formula (I) wherein Ar is represented by group (ii), A is CONH and E is represented by group (f), were prepared according to the methods of international application publication number WO 95/17401, published 29 June 1995.

Compounds of formula (I) wherein Ar is represented by group (i), A is CONH and E is represented by group (g), were prepared according to the methods of international application publication number WO 96/31508 published 10 October 1996.

Anilines used in the preparation of compounds of formula (I) wherein E is represented by group (g), R^{72} is, for example, C_{1}-alkoxy, R^{71} is piperidinyl, and R^{71}'' is attached to the piperidinyl ring at the 4-position and is, for example, COR^{5}''', CONR^{6}''R^{7}'', CO_{2}R^{8}''', cyano, SO_{2}R^{10}''', or SO_{2}NR^{6}''R^{7}'' can be prepared following the general procedures of Cammack and Reeves, J. Heterocyclic Chem., 1986, 23, 73-5; Iorio, et. al., Farmaco, Ed. Sci., 1977, 32, 212-19; Buchi, et. al., Helv. Chim. Acta, 1952, 35, 1527-1536; and DE 735866, and the general procedure shown in Scheme 3.
Alternatively, 3-5 may be obtained from 3-4 by reductive amination using an appropriately substituted aldehyde or ketone, an appropriate reducing agent, for example sodiumcyanoborohydride, in an appropriate solvent, for example methanol containing acetic acid.


Anilines wherein $R^{71}$" is $CR^{1a}R^{2"}NR^{3}R^{4}"$ or $CR^{1a}R^{2"}OR^{3}"$ can be prepared following the general procedures of Ong, et. al., J. Med. Chem., 1983, 26, 981-986 and Iorio, et. al., Farmaco, Ed. Sci., 1977, 32, 212-19; by reduction of 3-5 or 3-6 wherein $R^{71}$" is $COR^{5}"$, $CONR^{6"}R^{7}"$, $CO_{2}R^{8}"$, or cyano, with a suitable reducing agent, for example lithium aluminum hydride, in a suitable solvent, for example ether, or, wherein $R^{71}$" is cyano, by catalytic hydrogenation.
Scheme 3

3-1 \[\rightarrow\] 3-2 \[\rightarrow\] 3-3

3-4 \[\rightarrow\] 3-5

3-6

(a) CH₃N(CH₂CH₂Cl)₂, NaH, DMF, 50-90°C; (b) HNO₃, Ac₂O; (c) ClCO₂CHClCH₃, DIPEA, 1,2-dichloroethane; MeOH, *; (d) iPrI, K₂CO₃, acetone; 70°C, 24 h; (e) H₂, Pd/C, ethanol.
Compounds of formula (I) wherein Ar is represented by group (i), A is CONH and E is represented by group (c), were prepared according the methods of international application publication number WO 95/30675, published 16 November 1995.

Compounds of formula (I) wherein Ar is represented by group (i), A is CONH and E is represented by group (b), were prepared according the methods of international application publication number WO 96/11934, published 25 April 1996.

Compounds of formula (I) wherein Ar is represented by group (i) or (ii) and A is represented by CONR⁴⁶' and E is represented by group (a), where R⁴⁶' and R⁶ are represented by group D, where D is (CR²²R²³)ₑ, where e is 2, 3 or 4 and R²² and R²³ are independently hydrogen or C₁₋₆alkyl or D is (CR²²R²³)ᵢ-G where i is 0, 1, 2 or 3 and G is oxygen, sulfur or CR²²=CR²³, were prepared according the methods of international application publication number WO 96/06079, published 29 February 1996 and international application publication number WO 95/17398, published 29 June 1995.

Compounds of formula (I) wherein Ar is represented by group (i) or (ii), and A is represented by CONR⁴⁶' and E is represented by group (h), were prepared according the methods of international application publication number WO 97/07120, published 27 February 1997.

Compounds of formula (I) wherein Ar is represented by group (i) and A is represented by CONR⁴⁶' and E is represented by group (b), where R⁴⁶' and R³ are represented by the group K, where K is (CR³⁴R³⁵)ᵢ, where i is 2, 3, or 4 and R³⁴ and R³⁵ are independently hydrogen or C₁₋₆alkyl or K is (CR³⁴R³⁵)ᵢ-M where j is 0, 1, 2, or 3 and M is oxygen, sulfur or CR³⁴=CR³⁵, were prepared according the methods of international application publication number WO 96/19477, published 27 June 1996.
Compounds of formula (I) wherein Ar is represented by group (i) and A is represented by CONR\textsuperscript{46'} and E is represented by group (i), were prepared according the methods of international application publication number WO 97/19070, published 29 May 1997.

Specifically, compounds of formula (I) wherein Ar is represented by group (i), (ii) or (iii), A is CONR\textsuperscript{46'}, NHCO or CH\textsubscript{2}NH, and E is represented by group (a), were prepared according to the methods of international application publication number WO 95/15954, published 15 June 1995, international application publication number WO 95/17398, published 29 June 1995, international application publication number WO 95/26328, published 5 October 1995, international application publication number WO 96/06079, published 29 February 1996, GB 2276161 published 21 September 1994, and GB 2276165 published 21 September 1994.

Compounds of formula (I) wherein Ar is (i) or (ii), and A is CONR\textsuperscript{46'} or NHCO, and E is represented by group (b), were prepared according to the methods of international application publication number WO 96/11934, published 25 April 1996, and WO 96/19477, published 27 June 1996. Other applications cover the spiro compounds WO 97/17350, published 15 May 1997; WO 97/34900, published 25 September 1997; WO 97/34901, published 25 September 1997; WO 97/35861, published 2 October 1997; WO 97/35862, published 2 October 1997.

Compounds of formula (I) wherein Ar is (i), (ii) or (iii), A is CONR\textsuperscript{46'}, NHCO or CH\textsubscript{2}NH, and E is (c), were prepared according the methods of international application publication number WO 95/30675, published 16 November 1995, and GB 2276165, published 21 September 1994.

Compounds of formula (I) wherein Ar is (i) or (ii), A is CONR\textsuperscript{46'}, and E is a group (g), were prepared according the methods of international application publication number WO 96/31508, published 10 October 1996.

Compounds of formula (I) when Ar is (i) or (ii), A is CONR\textsuperscript{46'}, and E is group (h), were prepared according the methods of international application publication number WO 95/32967, published 7 December 1995 and WO 97/07120, published 27 February 1997.

Compounds of formula (I) Ar is (i) or (ii), and A is CONR\textsuperscript{46'} or CH\textsubscript{2}NH, and E is group (i), were prepared according the methods of international application publication number WO 97/19070, published 29 May 1997.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of
the present invention. In the Examples, mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated.

**EXAMPLES**

**Preparation 1**

**Preparation of 3′-(2-Ethoxy-2-oxoethoxy)-1,1′-biphenyl-4-carboxylic acid**

a) tributyl(ethoxymethyl)stannane

Following the general procedure of Kaufman, Synlett 1997, (12), 1377-1378, a solution of butyllithium in hexane (2.5M, 3 mL, 7.5 mmol) was added dropwise to a stirred solution of diisopropylamine (1.15 mL, 8.2 mL) in anhydrous tetrahydrofuran (15 mL) at 0°C, stirred for 5 min, and treated with tributyltin hydride (2 mL, 7.4 mmol) added over 3 min. The resulting yellow-green solution was stirred for 15 min, cooled to -78°C, and treated with chloromethyl ethyl ether (0.5 mL, 7.5 mmol). The mixture was stirred for 10 min, warmed to RT, stirred for 2 h, quenched with water, and extracted with ether. The combined organic phase was washed with brine and with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane followed by dichloromethane) to give the title compound (1.28 g).

b) 2-ethoxy-1-(3-iodophenyl)ethanone

Following the general procedure of Labadie, et. al., J. Org. Chem. 1983, 48, 4634-42, a solution of 3-iodobenzoyl chloride (0.53 g, 2 mmol) and benzylchlorobis(triphenylphosphine)palladium (15 mg) in chloroform (1 mL) was treated with a solution of the compound of Preparation 1(a) (0.7 g, 2 mmol) in chloroform (4 mL). The resulting yellow solution was placed in a sealed vial, heated to 65°C, and shaken for 16 h. The mixture was cooled, poured into ether (30 mL), and the resulting mixture was extracted with water and then with aqueous potassium fluoride with vigorous shaking. The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was purified by chromatography (silica gel, 4:1 hexane/ethyl acetate) to give the title compound (50 mg).
c) 3'- (2-ethoxy-2-oxoethoxy)-1,1'-biphenyl-4-carboxylic acid

A mixture of the compound of Preparation 1(b) (70 mg, 0.24 mmol), 4-boronobenzoic acid (40 mg, 0.24 mmol), tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.012 mmol), and sodium carbonate (68 mg, 0.64 mmol) dissolved in water (3 mL) and dimethylformamide (3 mL) was heated to reflux for 16 h. The mixture was concentrated in vacuo and the residue was partitioned between ether and 5% sodium carbonate. The aqueous phase was acidified with 3M hydrochloric acid and the resulting precipitate was isolated by filtration, washed with water, and dried to give the title compound.

Preparation 2
Preparation of 3'- (2-Methoxy-2-oxoethoxy)-1,1'-biphenyl-4-carboxylic acid

Following the procedure of Preparation 1(a)-1(c), except substituting chloromethyl methyl ether for chloromethyl ethyl ether, gave the title compound.

Preparation 3
Preparation of 3'- (2-Ethoxy-2-oxoethoxy)-1,1'-biphenyl-4-carboxylic acid

A mixture of methyl (3-bromophenoxy)acetate (1.29 g, 5 mmol), prepared from 3-bromophenol, methyl bromoacetate, and potassium carbonate in acetone, 4-boronobenzoic acid (1.25 g, 7.5 mmol), triethylamine (2.1 mL, 15 mmol), palladium acetate (33.5 mg), and tri-o-tolylphosphine (95 mg) in dry dimethylformamide (20 mL) was heated to 100°C for 3.5 h, cooled, and concentrated in vacuo. The residue was taken up in water, extracted with ethyl acetate and then with dichloromethane. The combined dichloromethane extract was concentrated in vacuo to give the title compound.

Preparation 4
Preparation of 3- [4- Cyano-1- (1-methylethyl)-4- piperidinyl]- 4- methoxy- benzeneamine

a) 4- [2- (methoxy) phenyl]-1- methyl-4- piperidinocarbonitrile

Following the general procedure of Ong, et. al., J. Heterocycl. Chem. 1981, 18, 815-20 and of Patane, et. al., Bioorg. Med. Chem. Lett. 2000, 10, 1621-1624, a solution of (2-methoxyphenyl)acetonitrile (7.4 g, 50 mmol) in anhydrous dimethylformamide (120 mL) was added over 5 min to sodium hydride (4.8 g, 200 mmol) with good stirring. The mixture was stirred for 1 h and treated with a solution of N- methyl bis(2-chloroethyl)amine (7.19 g, 50 mmol) in dimethylformamide (100 mL) at a rate such that the internal temperature remained below 50°C. The resulting mixture was
gradually heated to 90°C and stirred at 90°C for 16 h. The mixture was carefully quenched with ice water and extracted with ether three times. The combined organic phase was extracted with 2N hydrochloric acid and the acidic aqueous extract was carefully basified with 10% aqueous sodium hydroxide. The resulting mixture was extracted with ether, dried (MgSO₄), and concentrated *in vacuo* to give the title compound (9.65 g, 84%). MS(ES) m/z 231.2 [M+H]+.

b) 4-[2-methoxy-5-(nitro)phenyl]-1-methyl-4-piperidinecarbonitrile

70% Nitric acid (4.9 mL, 76 mmol) was added dropwise to a solution of the compound of Preparation 4(a) (8.7 g, 38 mmol) stirred in acetic anhydride (50 mL) at 0°C and the mixture was stirred for 1 h. The reaction was carefully quenched with ice water, and the resulting mixture was basified with 10% aqueous sodium hydroxide, and extracted with dichloromethane three times. The combined organic phase was dried (MgSO₄) and concentrated *in vacuo* to give a mixture of the title compound, accompanied by a small amount of 4-[2-methoxy-3-(nitro)phenyl]-1-methyl-4-piperidinecarbonitrile, as a yellow oil that solidified on standing (9.2 g).

c) 4-[2-methoxy-5-(nitro)phenyl]-4-piperidinecarbonitrile

A solution of the compound of Preparation 4(b) (9.2 g, 33 mmol) and diisopropylethylamine (6.5 g, 50 mmol) in 1,2-dichloroethane (250 mL) was treated with 1-chloroethyl chloroformate (6.5 g, 43 mmol) at RT, stirred for 1 h, heated to reflux for 20 min, cooled, and concentrated *in vacuo*. The residue was dissolved in methanol, heated to reflux for 2 h, and the mixture was concentrated *in vacuo*. The residue was partitioned between 5% sodium bicarbonate and dichloromethane, the aqueous phase was extracted with dichloromethane, and the combined organic phase was dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a tan solid (7.88 g).

d) 4-[2-methoxy-5-(nitro)phenyl]-1-(1-methylethyl)-4-piperidinecarbonitrile

The compound of Preparation 4(c) (7.9 g, 30 mmol) was dissolved in acetonitrile (150 mL) and acetone (50 mL) and treated with potassium carbonate (16.7 g, 120 mmol) followed by isopropyl iodide (15.3 g, 90 mmol). The resulting mixture was heated to 70°C for 24 h, cooled, filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in dichloromethane and washed with water three times, dried (MgSO₄), concentrated *in vacuo*, and the resulting tan oil was purified by flash chromatography (silica gel, 3:1 hexane/ethyl acetate followed by 1:1 hexane/ethyl acetate) to give the title compound as a yellow oil that solidified on standing (2.35 g).

MS(ES) m/z 304.2 [M+H]+.

e) 3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxybenzenamine
A mixture of the compound of Preparation 4(d) (2.1 g, 7 mmol) in and 10% palladium-on-carbon (1 g) in ethanol (70 mL) was shaken in a hydrogen atmosphere (50 psi) for 2 h. The resulting mixture was filtered through Celite®, and the filtrate was concentrated in vacuo to give the title compound as a tan oil (2 g). MS(ES) m/e 274.2 [M+H]⁺.

Preparation 5
Preparation of 4-Methoxy-3-[(1-(1-methylethyl)-4-piperidinyl)benzenamine

a) 4-(2-methoxyphenyl)-1-(trifluoroacetyl)piperidine

Trifluoroacetic anhydride (8.1 g, 39 mmol) was added portionwise over 10 min to a solution of commercially available 4-(2-methoxyphenyl)piperidine (6.7 g, 35 mmol), triethylamine (7.8 g, 77 mmol), and dichloromethane (100 mL) at RT. The reaction was maintained at RT for 16 h. The resultant mixture was washed with saturated sodium bicarbonate, saturated ammonium chloride, and with brine, dried (MgSO₄), and concentrated in vacuo to afford 10 g (99%) of the title compound as an amber oil. MS(ES) m/e 288.1 [M+H]⁺.

b) 4-(2-methoxy-5-nitrophenyl)-1-(trifluoroacetyl)piperidine

Nitric acid (70%, 3.1 mL) was added portionwise to a solution of the compound of Preparation 5(a) (5.0 g, 17 mmol) in acetic anhydride (17 mL) at 0°C. The mixture was maintained at 0°C for an additional 30 min, combined with an identical concurrently run reaction, and poured into water (600 mL). The pH of the resultant mixture was adjusted to >9 by the addition of aqueous sodium carbonate followed by 10% sodium hydroxide. The resulting mixture was extracted with dichloromethane (2 × 400 mL) and the combined organic layers were washed with brine, dried (MgSO₄), and concentrated in vacuo to give 12 g (>100%) of a 2.2:1 mixture of the title compound and its 3-nitro isomer. The crude product was recrystallized from methanol (30 mL) to give 5.9 g (54%) of the title compound as off-white crystals. MS(ES) m/e 333.1 [M+H]⁺.
c) 4-(2-methoxy-5-nitrophenyl)piperidine

Potassium carbonate (10 g, 74 mmol) was added to a solution of the compound of Preparation 5(b) (4.9 g, 15 mmol), methanol (100 mL) and water (7.5 mL). The resultant mixture was stirred at RT for 40 h, concentrated in vacuo, and the residue partitioned between water and dichloromethane. The layers were separated and aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated in vacuo to give 3.7 g (>100%) of the title compound as an off-white solid. MS(ES) m/z 237.2 [M+H]⁺.

d) 4-(2-methoxy-5-nitrophenyl)-1-(1-methylethyl)piperidine

Potassium carbonate (8.6 g, 62 mmol) and isopropyl iodide (8.0 g, 47 mmol) were added to a solution of the compound of Preparation 5(c) (3.7 g, 16 mmol), dimethylformamide (10 mL) and acetonitrile (50 mL). The resultant mixture was heated at 70°C for 20 h, concentrated in vacuo, and the residue partitioned between water and dichloromethane. The aqueous phase was extracted with dichloromethane and the combined organic layers were washed with water (3 x 100 mL) and with brine, dried (MgSO₄), and concentrated in vacuo to provide 4.0 g (90%) of the title compound as a yellow solid. MS(ES) m/z 279.2 [M+H]⁺.

e) 4-methoxy-3-[1-(1-methylethyl)-4-piperidinyl]benzenamine

Palladium hydroxide on carbon (1.2 g, 20% dry weight) was added to a solution of the compound of Preparation 5(d) (4.0 g, 14 mmol) in ethanol (100 mL). The mixture was hydrogenated at 50 psi for 4 h, filtered through Celite®, and concentrated in vacuo. The residue was dissolved in ether (200 mL) and washed with 10% sodium carbonate and with water (2 x 100 mL). The ether solution was dried (MgSO₄) and concentrated in vacuo to provide 3.0 g (84%) of the title compound as a tan solid. MS(ES) m/z 249.2 [M+H]⁺.

Preparation 6

Preparation of N-[4-methoxy-3-[1-(1-methylethyl)-4-piperidinyl]phenyl]4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide  A mixture of the compound of Preparation 5(e) (2.48 g, 10 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (2.48 g, 10 mmol), and 1-hydroxy-7-azabenzotriazole (1.39 g, 10 mmol) dissolved in acetonitrile (75 mL) was treated with 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.31 g, 12 mmol) and stirred at RT for 16 h. The mixture was concentrated in vacuo and the residue was partitioned between dichloromethane and aqueous 5% sodium carbonate. The organic phase was dried
(MgSO₄) and concentrated in vacuo to afford the title compound. MS(ES) m/e 478.4 [M+H]+.

Preparation 7-9

Following the procedure of Preparation 6, except substituting 3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxylaniline (WO 9515954), 4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]benzenamine, (WO 9901127), or 3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxy]-benzenamine (WO 9901127) for the compound of Preparation 5(e), gave the following compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide: MS(ES) m/e 496.4 [M+H]+;

N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl)ethoxy]phenyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide: MS(ES) m/e 536.4 [M+H]+; and

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide: MS(ES) m/e 510.6 [M+H]+.

Preparation 10

Preparation of N-[3-(4-Piperidinyl)-4-methoxyphenyl]-1,1′-biphenyl-4-carboxamide

a) 3-[1-(trifluoroacetyl)-4-piperidinyl]-4-methoxyaniline

Following the general procedure of Preparation 5(h), except substituting the compound of Preparation 5(e) for the compound of Preparation 5(g), gave the title compound.

b) 3-(4-piperidinyl)-4-methoxyaniline

Following the general procedure of Preparation 5(f), except substituting the compound of Preparation 10(a) for the compound of Preparation 5(e), gave the title compound.

c) 3-[1-(tert-butoxycarbonyl)-4-piperidinyl]-4-methoxyaniline

The compound of Preparation 10(b) (1.7 g, 8.5 mmol) was treated with di-tert-butyl dicarbonate (1.9 g, 8.6 mmol) in dichloromethane, stirred for 2 h, and concentrated in vacuo to give the title compound which was used without further purification. MS(ES) m/e 307.2 [M+H]+.

d) N-[3-[1-(tert-butoxycarbonyl)-4-piperidinyl]-4-methoxyphenyl]-1,1′-biphenyl-4-carboxamide

The compound of Preparation 10(c) (0.21 g, 0.7 mmol) was added to a mixture of 1,1′-biphenyl-4-carboxylic acid (0.14 g, 0.7 mmol), benzotriazol-1-
yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.31 g, 0.7 mmol) and triethylamine (0.14 g, 1.4 mmol) in dichloromethane (4 mL), and stirred at RT for 16 h. The resulting mixture was diluted with water and extracted with dichloromethane. The organic extracts were combined and dried (MgSO₄), concentrated in vacuo, and the residue was purified by chromatography (silica gel, 3:1 hexane/ethyl acetate) to afford the title compound MS(ES) m/z 487.4 [M+H]⁺.

e) N-[3-(4-piperidinyl)-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide

The compound of Preparation 10(d) (285 mg) dissolved in dichloromethane was treated with trifluoroacetic acid and stirred at RT. The resulting mixture was concentrated in vacuo to give the title compound, which was used without purification.

**Preparation 11**

**Preparation of N-[4-methoxy-3-[4-cyano-1-(1-methyl[ethyl]-4-piperidinyl)]phenyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide** Following the procedure of Preparation 6, except substituting the compound of Preparation 4(e) for the compound of Preparation 5(e), gave the title compound: MS(ES) m/z 503.2 [M+H]⁺.

**Example 1**

**Preparation of N-[3-[2-[Bis(1-methylethyl)aminoethoxy]-4-methoxyphenyl]-3'- (ethoxyacetyl)-1,1'-biphenyl-4-carboxamide** A solution of the compound of Preparation 1(c) (48 mg, 0.17 mmol), 3-[2-bis(1-methylethyl)aminoethoxy]-4-methoxyaniline (WO 9515954) (45 mg, 0.17 mmol), and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (75 mg, 0.17 mmol) in acetonitrile (5 mL) was treated with triethylamine (40 mg, 0.4 mmol) and the mixture was stirred at RT for 16 h. The mixture was concentrated in vacuo and the residue was purified by HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A:0.1% trifluoroacetic acid in acetonitrile B:0.1% aqueous trifluoroacetic acid, A:10 to 90% during 10 min, UV detection at 254 nm) to give the title compound. MS(ES) m/z 533.1 [M+H]⁺.

**Example 2**

**Preparation of N-[3-[2-[Bis(1-methylethyl)aminoethoxy]-4-methoxyphenyl]-3'- (hydroxyacetyl)-1,1'-biphenyl-4-carboxamide** Following the general procedure ofKatritzky, A. R. and Sengupta, S, Tetrahedron Lett. 1987, 28, 1847-50, 2.5M butyllithium in hexane (2 mL, 5 mmol) was added at to a solution of 1-trimethylsilylmethanol (0.5 g, 2.5 mmol) in tetrahydrofuran (25 mL) at -78°C and the
mixture was warmed to RT for 5 min after which a stream of dry carbon dioxide was bubbled through the solution for 10 min. The volatile components of the mixture were removed in vacuo, the vessel was purged with argon, and the residue was dissolved in tetrahydrofuran (25 mL). The solution was cooled to −78°C, treated slowly with 1.3M sec-butyllithium in cyclohexane (4.2 mL, 5.5 mmol), maintained at −25°C for 2 h, cooled to −78°C and treated with a solution of N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-ethoxycarbonyl-1,1'-biphenyl-4-carboxamide (WO 0040239) (0.38 g, 0.7 mmol) in tetrahydrofuran (10 mL). The mixture was stirred at RT for 30 min, quenched with saturated aqueous ammonium chloride, and extracted with ether. The combined organic phase was dried (MgSO4), taken up in dimethyl sulfoxide, and the mixture was concentrated in vacuo. The upper oily layer was removed and the residue was purified by HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A:0.1% trifluoroacetic acid in acetonitrile B:0.1% aqueous trifluoroacetic acid, A:10 to 90% during 10 min, UV detection at 254 nm) to give the title compound. MS(ES) m/e 505.1 [M+H]+.

**Example 3**

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-(methoxyacetyl)-1,1'-biphenyl-4-carboxamide

Following the procedure of Example 1, except substituting the compound of Preparation 2 for the compound of Preparation 1(c), gave the title compound. MS(ES) m/e 519.1 [M+H]+;

**Example 4**

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-(2-ethoxy-2-oxoethoxy)-1,1'-biphenyl-4-carboxamide

A solution of the compound of Preparation 3 (240 mg, 0.8 mmol), triethylamine (0.8 mL), and 3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyaniline (WO 9515954) (213 mg, 0.8 mmol) was treated with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (400 mg) and stirred at RT for 16 h. The mixture was concentrated in vacuo and the residue was purified by flash chromatography (silica gel, 0.25% methanol/dichloromethane). Fractions containing the title compound were pooled, concentrated in vacuo, the residue was triturated with ether, and the resulting white solid that was dried to afford the title compound (60 mg). MS(ES) m/e 549.0 [M+H]+.
Example 5
Preparation of N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide
The compound of Preparation 4(e) (41 mg, 0.15 mmol) and [1,1'-biphenyl]-4-carbonyl chloride (32.5 mg, 0.15 mmol) were dissolved in dichloromethane (1.5 mL), diisopropylethylamine (39 mg, 0.30 mmol) was added, and the resulting mixture was stirred at RT of 16 h. The mixture was concentrated in vacuo and the residue was purified by HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A:0.1% trifluoroacetic acid in acetonitrile B:0.1% aqueous trifluoroacetic acid, A:10 to 90% during 10 min, UV detection at 254 nm) to give the title compound. MS(ES) m/e 454.2 [M+H]^+.

Example 6
Preparation of 3'-(2-Carboxyethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide
A mixture of a solution of the compound of Preparation 6 in dimethylformamide (0.188M, 0.8 mL, 0.15 mmol), a solution of 3-bromobenzene propanoic acid in dimethylformamide (1M, 0.3 mL, 0.3 mmol), a solution of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) in dimethylformamide (0.0245M, 0.2 mL), and aqueous 2M sodium carbonate (0.3 mL, 0.6 mmol) was heated to 80°C for 16 h, concentrated in vacuo, and the residue was purified by HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A:0.1% trifluoroacetic acid in acetonitrile B:0.1% aqueous trifluoroacetic acid, A:10 to 90% during 10 min, UV detection at 254 nm) to give the title compound. MS(ES) m/e 501.2 [M+H]^+.

Examples 7-8
Following the procedure of Example 6, except substituting 3-(3-bromophenyl)propionitrile or 3-bromophenylacetonitrile for 3-(3-bromophenyl)propanoic acid, gave the following compounds:
3'-(2-cyanoethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 482.3 [M+H]^+; and
3'-(2-cyanomethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 468.3 [M+H]^+.

Example 9
Preparation of N-[3-[2-[(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-
(carboxyethyl)-1,1'-biphenyl-4-carboxamide

Following the procedure of Example 6, except substituting the compound of
Preparation 7 for the compound of Preparation 6, gave the title compound: MS(ES)
m/e 519.2 [M+H]+.

Examples 10-11

Following the procedures of Examples 7-8, except substituting the compound of
Preparation 7 for the compound of Preparation 6, gave the following compounds:
N-[3-[2-[(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-[cyanoethyl]-
1,1'-biphenyl-4-carboxamide: MS(ES) m/e 500.1 [M+H]+; and
N-[3-[2-[(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-[cyanomethyl]-
1,1'-biphenyl-4-carboxamide: MS(ES) m/e 486.3 [M+H]+.

Examples 12-13

Following the procedures of Examples 7-8, except substituting the compound of
Preparation 8 for the compound of Preparation 6, gave the following compounds:
3'-[2-(cyanoethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-
piperidiny1)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 540.4 [M+H]+;
and
3'-[2-(cyanomethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-
piperidiny1)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 526.4 [M+H]+.

Examples 14-15

Following the procedures of Examples 7-8, except substituting the compound of
Preparation 9 for the compound of Preparation 6, gave the following compounds:
N-[3-[3-[[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'-[cyanoethyl]-
1,1'-biphenyl-4-carboxamide: MS(ES) m/e 514.4 [M+H]+; and
N-[3-[3-[[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'-
cyanomethyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 500.2 [M+H]+.

Example 16

Preparation of N-[3-[1-(tetrahydro-2H-pyran-4-yl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide

A solution of the compound of Preparation 10(e) (46 mg, 0.12 mmol) and
tetrahydro-4H-pyran-4-one (59 mg, 0.6 mmol) in methanol (1 mL) was treated with
acetic acid (72 mg, 1.2 mmol), and sodium cyanoborohydride (30 mg, 0.48 mmol). The resulting mixture was heated to reflux for 16 h, cooled, filtered and concentrated _in vacuo_. The residue was dissolved in dimethyl sulfoxide and purified by HPLC to give the title compound: MS(ES) m/e 471.4 [M+H]+

**Example 17**

**Preparation of 3'-chloro-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide**  The compound of Preparation 11 (76 mg, 0.15 mmol) in dimethylformamide (0.8 mL) and 3-chlorobromobenzene (57 mg, 0.3 mmol) in dimethylformamide (0.3 mL) were mixed with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (4 mg, 0.005 mmol) followed by 2M sodium carbonate (0.3 mL, 0.6 mmol). The mixture was heated to 80°C for 16 h, filtered and purified by HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A:0.1% trifluoroacetic acid in acetonitrile B:0.1% aqueous trifluoroacetic acid, A:10 to 90% during 10 min, UV detection at 254 nm) to give the title compound: MS(ES) m/e 488.2 [M+H]+.

**Example 18**

**Preparation of 3'-[(2-carboxyethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide**

Following the general procedure of Example 6, except substituting the compound of Preparation 11 for the compound of Preparation 6 gave the title compound: MS(ES) m/e 526.2 [M+H]+.

**Examples 19-33**

Following the general procedure of Example 18, except substituting ethyl 3-bromobenzoate, 3-bromobenzenesulfonamide, 3-(3-bromophenyl)propionitrile, 3-bromophenylurea, (3-bromophenyl)acetonitrile, 1-bromo-3-isopropoxybenzene, 3-bromobenzenitrile, 1-bromo-3,5-dimethylbenzene, N-(3-bromophenyl)acetamide, 1-(3-bromophenyl)ethanone, 5-(3-bromophenyl)-1H-tetrazole, 3-(3-bromophenyl)-5-methyl-oxa[1,2,4]oxadiazole, N-(3-bromophenyl)methanesulfonamide, 1-bromo-3,5-dichlorobenzene, and dimethyl 5-bromo-isophthalate for 3-bromobenzenepropanoic acid, gave the following compounds:

N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-ethoxycarbonyl-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 526.2 [M+H]+;
N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-sulfamoyl-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 533.2 [M+H]^+;
3'-[2-cyanoethyl]-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 507.2 [M+H]^+;
N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-ureido-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 512.4 [M+H]^+;
3'-(cyanomethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 493.2 [M+H]^+;
N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-isopropoxy-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 512.4 [M+H]^+;
3'-cyano-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 479.2 [M+H]^+;
N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-dimethyl-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 482.4 [M+H]^+;
3'-acetamido-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 511.4 [M+H]^+;
3'-acetyl-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 496.4 [M+H]^+;
N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 522.2 [M+H]^+;
N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(5-methyl-1,2,4-oxadiazo1-3-yl)-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 536.2 [M+H]^+;
N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-methanesulfonamido)-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 547.2 [M+H]^+;
N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-dichloro-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 522.2 [M+H]^+; and
N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-bis(methoxycarbonyl)-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 570.2 [M+H]^+.

**Example 34**

Preparation of 3'-carboxamido-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide Following the general procedure of Example 18, except substituting 3-bromobenzencarboxamide for 3-bromobenzene propanoic acid, gave the title compound: MS(ES) m/e 497.4 [M+H]^+. 54
Biological Data:

**CCR5 Receptor Binding Assay**

CHO cell membranes (0.25 x10⁶ cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 ¹²⁵I-RANTES in a 96 well plate for 45 min. at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % NaN₃. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

**CCR5 Receptor Functional Assay**

The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced Ca²⁺ mobilization in RBL 2H3 cells stably expressing the hCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by Ca²⁺ mobilization in the same cells which is inhabitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min. at room temperature and diluting to 2 X 10⁶ cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM NaHCO₃, 1 mM KH₂PO₄ and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM CaCl₂, 1 mM MgCl₂ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X 10⁶ cells/mL in the same buffer with 2 μM Fura-2AM, and incubated for 35 min. at 37° C. Cells were centrifuged at 200 x g for 3 min. and resuspended in the same buffer without Fura-2AM, then incubated for 15 min. at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (10⁶ cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM CaCl₂, 1 mM MgCl₂ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min. in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal Ca²⁺ attained after 33 nM RANTES stimulation was calculated as described by Grynkwiewicz et al., (1985). The percent of maximal RANTES-induced Ca²⁺ was determined for each concentration of antagonist and the IC₅₀, defined as the concentration of test...
compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from
the concentration-response curves (5-7 concentrations of antagonists).

The compounds of this invention show CCR5 receptor modulator activity
having IC50 values in the range of 0.0001 to 100 μM. The full structure/activity
relationship has not yet been established for the compounds of this invention.
However, given the disclosure herein, one of ordinary skill in the art can utilize the
present assays in order to determine which compounds of formula (I) are modulators of
the CCR5 receptor and which bind thereto with an IC50 value in the range of 0.0001 to
100 μM.

All publications, including, but not limited to, patents and patent applications
cited in this specification, are herein incorporated by reference as if each individual
publication were specifically and individually indicated to be incorporated by reference
herein as though fully set forth.

The above description fully discloses the invention including preferred
embodiments thereof. Modifications and improvements of the embodiments
specifically disclosed herein are within the scope of the following claims. Without
further elaboration it is believed that one skilled in the art can, given the preceding
description, utilize the present invention to its fullest extent. Therefore any examples
are to be construed as merely illustrative and not a limitation on the scope of the present
invention in any way. The embodiments of the invention in which an exclusive
property or privilege is claimed are defined as follows.
What is claimed is:

1. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:

   \[
   \text{Ar} \rightarrow \text{A} \rightarrow \text{E}
   \]
   
   Formula (I)

   wherein Ar is a group selected from (i), (ii) or (iii);

   \[
   \begin{array}{c}
   \text{(i)} \\
   \text{(ii)} \\
   \text{(iii)}
   \end{array}
   \]

   wherein:

   the basic nitrogen in moiety E may be optionally quaternized with C\textsubscript{1-6}alkyl or is optionally present as the N-oxide;

   \( \text{R}^1 \) and \( \text{R}^2 \) are each independently one or more of hydrogen, C\textsubscript{1-6}alkyl, C\textsubscript{2-6}alkenyl, C\textsubscript{2-6}alkynyl, C\textsubscript{3-7}cycloalkyl, C\textsubscript{3-6}cycloalkenyl, aryl, (CH\textsubscript{2})\textsubscript{a}NR\textsuperscript{7}\textsubscript{R}\textsuperscript{8}, (CH\textsubscript{2})\textsubscript{a}NR\textsuperscript{7}COR\textsuperscript{9}, (CH\textsubscript{2})\textsubscript{a}NR\textsuperscript{7}CO\textsubscript{2}R\textsuperscript{10}, (CH\textsubscript{2})\textsubscript{a}NR\textsuperscript{7}SO\textsubscript{2}R\textsuperscript{11}, (CH\textsubscript{2})\textsubscript{a}CONR\textsuperscript{12}R\textsuperscript{13}, hydroxyC\textsubscript{1-6}alkyl, C\textsubscript{1-4}alkoxyalkyl (optionally substituted by a C\textsubscript{1-4}alkoxy or hydroxy group), (CH\textsubscript{2})\textsubscript{a}CO\textsubscript{2}C\textsubscript{1-6}alkyl, (CH\textsubscript{2})\textsubscript{b}OC(O)R\textsuperscript{14}, CR\textsuperscript{15}=NOR\textsuperscript{16}, CNR\textsuperscript{15}=NOR\textsuperscript{16}, COR\textsuperscript{17}, CONR\textsuperscript{12}R\textsuperscript{13}, CONR\textsuperscript{12}(CH\textsubscript{2})\textsubscript{c}OC(O)R\textsuperscript{18}, CONHNR\textsuperscript{19}R\textsuperscript{20}, CONC\textsubscript{12}SO\textsubscript{2}R\textsuperscript{21}, CO\textsubscript{2}R\textsuperscript{22}, cyano, trifluoromethyl, NR\textsuperscript{7}R\textsuperscript{8}, NR\textsuperscript{7}COR\textsuperscript{9}, NR\textsuperscript{23}CO(CH\textsubscript{2})\textsubscript{a}NR\textsuperscript{23}R\textsuperscript{24}, NR\textsuperscript{23}CONR\textsuperscript{23}R\textsuperscript{24}, NR\textsuperscript{7}CO\textsubscript{2}R\textsuperscript{10}, NR\textsuperscript{7}SO\textsubscript{2}R\textsuperscript{11}, N=CNR\textsuperscript{23}NR\textsuperscript{23}R\textsuperscript{24}, nitro, hydroxy, C\textsubscript{1-6}alkoxy, hydroxyC\textsubscript{1-6}alkoxy, C\textsubscript{1-6}alkoxyC\textsubscript{1-6}alkoxy, OC(O)NR\textsuperscript{25}R\textsuperscript{26}, SR\textsuperscript{27}, SOR\textsuperscript{28}, SO\textsubscript{2}R\textsuperscript{28}SO\textsubscript{2}NR\textsuperscript{25}R\textsuperscript{26} or halogen;

   \( \text{R}^3 \) and \( \text{R}^4 \) are each independently one or more of hydrogen, C\textsubscript{1-6}alkyl, C\textsubscript{3-7}cycloalkyl, C\textsubscript{3-6}cycloalkenyl, hydroxyC\textsubscript{1-6}alkyl, C\textsubscript{1-6}alkylOC\textsubscript{1-6}alkyl, CONC\textsubscript{29}R\textsuperscript{30}, CO\textsubscript{2}R\textsuperscript{31}, cyano, aryl, trifluoromethyl, NR\textsuperscript{29}R\textsuperscript{30}, nitro, hydroxy, C\textsubscript{1-6}alkoxy, acyloxy, or halogen;

   \( \text{R}^2 \) is also \( \text{R}^2'' \) wherein \( \text{R}^2'' \) is hydrogen, (CH\textsubscript{2})\textsubscript{a}CN, (CH\textsubscript{2})\textsubscript{a}CO\textsubscript{2}H, CR\textsuperscript{15}=CR\textsuperscript{16}CO\textsubscript{2}R\textsuperscript{18}, COCR\textsuperscript{15}R\textsuperscript{16}OR\textsuperscript{18}, Oaryl, Oaralkyl, O(CH\textsubscript{2})\textsubscript{a}CO\textsubscript{2}R\textsuperscript{18}, and Saryl;

   \( \text{R}^5 \) is one or more of hydrogen, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}alkoxy or halogen;

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R is one or more of hydrogen, C₆-alkyl, C₃-cycloalkyl (optionally substituted by a hydroxy or an oxo group), hydroxyC₆-alkyl, hydroxyC₆-alkenylnyl, hydroxyC₆-alkynyl, (CH₂)₂OR, (CH₂)₂COR, (CH₂)₄CR=NO₂R, CONR²⁻R⁷⁻, CO₂R³⁻, hydroxy, O(CH₂)₆R, NR³⁻R⁷⁻, SR⁴⁻, SO₂NR⁴⁻R⁴⁻⁻ or halogen; or, R' and R" form a fused benzo ring optionally substituted with C₆-alkyl, C₆-alkoxy or halogen;

R⁷⁻ and R⁸⁻ are independently hydrogen or C₆-alkyl, or together with the nitrogen to which they are attached, R⁷⁻ and R⁸⁻ form a 5- to 6-membered heterocyclic ring, which ring may optionally be substituted by an oxo group and, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

R⁹⁻ is hydrogen, C₆-alkyl or C₄-alkoxyalkyl;

R¹⁰⁻ is C₆-alkyl;

R¹¹⁻ is C₆-alkyl or phenyl;

R¹²⁻ and R¹³⁻ are independently hydrogen or C₆-alkyl, or together with the nitrogen to which they are attached, R¹²⁻ and R¹³⁻ form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

R¹⁴⁻ is C₄-alkyl, optionally substituted by C₆-alkoxy;

R¹⁵⁻ and R¹⁶⁻ are independently hydrogen or C₆-alkyl;

R¹⁷⁻ is hydrogen or C₆-alkyl;

R¹⁸⁻ is hydrogen or C₆-alkyl;

R¹⁹⁻ and R²⁰⁻ are independently hydrogen or C₆-alkyl;

R²¹⁻ is hydrogen or C₆-alkyl;

R²²⁻ is hydrogen or C₆-alkyl optionally substituted with one or two substituents selected from C₆-alkyl, C₆-alkoxy, hydroxy, or NR²⁻R⁸⁻;

R²³⁻ and R²⁴⁻ are independently hydrogen or C₆-alkyl;

R²⁵⁻ and R²⁶⁻ are independently hydrogen or C₆-alkyl, or together with the nitrogen to which they are attached, R²⁵⁻ and R²⁶⁻ form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

R²⁷⁻ is hydrogen or C₆-alkyl;

R²⁸⁻ is C₆-alkyl;

R²⁹⁻, R³⁰⁻ and R³¹⁻ are independently hydrogen or C₆-alkyl;

R³²⁻ is C₆-alkyl, hydroxyC₆-alkyl, or C₄-alkanoyl;

R³³⁻ is hydrogen or C₆-alkyl;

R³⁴⁻ is hydrogen or C₆-alkyl;
R^{35} is hydrogen or C_{1-6}alkyl;
R^{36'} and R^{37'} are independently hydrogen or C_{1-6}alkyl or together with the
nitrogen to which they are attached, R^{36'} and R^{37'} form a 5- to 6-membered
heterocyclic ring, which ring may be optionally substituted by an oxo group and,
which, when the ring is 6-membered, may optionally contain one oxygen or sulfur atom
or an NH group or a group NR^{43'}, wherein R^{43'} is C_{1-6}alkyl, COR^{44'} or CO_{2}R^{45'},
wherein R^{44'} and R^{45'} are independently hydrogen or C_{1-6}alkyl;
R^{38'} is hydrogen or C_{1-6}alkyl;
R^{39'} is C_{1-6}alkoxy, CO_{2}H, CO_{2}C_{1-6}alkyl or CONR^{36'}R^{37'};
R^{40'} is C_{1-6}alkyl;
R^{41'} and R^{42'} are independently hydrogen or C_{1-6}alkyl;
P is a 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected
from oxygen, nitrogen or sulfur;
a' is 1, 2, 3 or 4;
b' is 0, 1, 2 or 3;
c' is 1, 2 or 3;
d' is 0, 1, 2, 3, 4, 5, or 6; and
e' is 1, 2, 3, 4, 5 or 6;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONR^{46'}, NHCO, -
NHCH_{2}, or CH_{2}NH, wherein R^{46'} is hydrogen or C_{1-6}alkyl,
E is a group (a):

![Diagram](image)

(a);

wherein:
B is oxygen, C\equiv C, S(O)_{2}, CR^{7}=CR^{8}, or CR^{7}R^{8}, or B is NR^{9};
R^{1} and R^{2} are independently hydrogen or C_{1-6}alkyl; alternatively B(CR^{1}R^{2})_{a}
is OCR^{1}R^{2}CR^{1}(OH)CR^{1}R^{2} or OCR^{1}R^{2}CR^{1}(OCOCH_{3})CR^{1}R^{2};
R^{3} and R^{4} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, C_{5-}
cycloalkenyl, a C_{5-7}heterocyclic ring, or together with the nitrogen atom to which
they are attached form an optionally substituted 5- to 7-membered heterocyclic ring
which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur,
where optional substituents include C_{1-6}alkyl, aryl, CONR^{10}R^{11}, NR^{10}R^{11}, hydroxy,
OCOR^{12}, NHCOCF_{3}, NHSO_{2}R^{13}, NHCO_{2}R^{14}, or NHCCOC_{0}-alkyl wherein the alkyl of NHCCOC_{0}-alkyl is optionally substituted by OH;
R^{5} is hydrogen, C_{1}-alkyl, aryl, CN, CONR^{15}R^{16}, CO_{2}R^{17}, trifluoromethyl, NHCO_{2}R^{18}, hydroxy, C_{1}-alkoxy, benzyloxy, OCH_{2}CO_{2}C_{1}-alkyl, OCF_{3},
S(O)_{2}R^{19}, SO_{2}NR^{20}R^{21} or halogen;
R^{6} is hydrogen, C_{1}-alkyl, aryl, trifluoromethyl, hydroxy, C_{1}-alkoxy or halogen, or R^{6} taken together with R^{30'} forms a group D where D is (CR^{22}R^{23})_{e} or D is (CR^{22}R^{23})_{f}-G where G is oxygen, sulfur or CR^{22}=CR^{23}, CR^{22}=N, =CR^{22}O,
=CR^{22}S, or =CR^{22}NR^{23};
R^{7}, R^{8}, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{22}, and R^{23} are independently hydrogen or C_{1}-alkyl;
R^{9} is hydrogen, C_{1}-alkyl, or phenylC_{1}-alkyl;
R^{13}, R^{14}, R^{18}, and R^{19} are independently C_{1}-alkyl;
a is 1, 2, 3, or 4;
b is 1 or 2;
c and d are independently 0, 1 or 2;
e is 2, 3 or 4;
f is 0, 1, 2 or 3;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONR^{46'}, NHCO, or CH_{2}NH, wherein R^{46'} is hydrogen or C_{1}-alkyl,
alternatively, E is a group (b):
\[
\begin{align*}
\text{R}^{24}, \text{R}^{25}, \text{R}^{26}, \text{R}^{27}, \text{R}^{28}, \text{R}^{29}, \text{R}^{31}, \text{and R}^{32} & \text{ are independently hydrogen or C}_{1}-\text{alkyl;} \\
\text{R}^{30} & \text{ is hydrogen, C}_{1}-\text{alkyl, or C}_{3,-7}\text{cycloalkyl, C}_{5,-7}\text{cycloalkenyl, or a C}_{5,-7}\text{heterocyclic ring;} \\
\text{R}^{33} & \text{ is hydrogen, C}_{1}-\text{alkyl, trifluoromethyl, hydroxy or halogen, or R}^{33} \text{ and R}^{30'} \text{ together form a group -K- where K is (CR}^{34}\text{R}^{35})_{j} \text{ or K is (CR}^{34}\text{R}^{35})_{j} \text{-M and M is oxygen, sulfur, CR}^{34}=\text{CR}^{35}, \text{CR}^{34}=\text{N, or N=N;} \\
\text{J} & \text{ is oxygen, CR}^{36}\text{R}^{37}, \text{or NR}^{38}, \text{or J is a group S(O)}_{k}; \\
\text{R}^{34}, \text{R}^{35}, \text{R}^{36}, \text{R}^{37}, \text{and R}^{38} & \text{ are independently hydrogen or C}_{1}-\text{alkyl;} \\
g & \text{ is 1, 2 or 3;} \\
h & \text{ is 1, 2 or 3;} \\
\end{align*}
\]
i is 2, 3, or 4;
j is 0, 1, 2, or 3;
k is 0, 1 or 2;

and further wherein, when Ar is (i), (ii) or (iii), and A is CONR\(^{46}\), NHCO, -NHCH\(_2\), or CH\(_2\)NH, wherein R\(^{46}\) is hydrogen or C\(_{1-6}\)alkyl,
alternatively, E is a group (c):
\[
\begin{array}{c}
\text{Q} \quad \text{(CR}^{39} \text{R}^{40})_n \quad \text{R}^{41} \\
\text{R}^{42} \\
\text{R}^{43}
\end{array}
\]

wherein:
Q is oxygen, S(O)\(_n\), CR\(^{44}\)=CR\(^{45}\), CR\(^{44}\)R\(^{45}\), or Q is NR\(^{46}\);
R\(^{39}\) and R\(^{40}\) are independently hydrogen or C\(_{1-6}\)alkyl;
R\(^{41}\) is a group of formula (d):
\[
\begin{array}{c}
(\text{CH}_2)_o \\
(\text{CH}_2)_p \\
(\text{CH}_2)_q \\
\text{N}
\end{array}
\]

or R\(^{41}\) is a group of formula (e):
\[
\begin{array}{c}
\text{N} \\
(\text{CH}_2)_l \\
\text{R}^{47}
\end{array}
\]

R\(^{42}\) is hydrogen, C\(_{1-6}\)alkyl, aryl, CN, CONR\(^{48}\)R\(^{49}\), CO\(_2\)R\(^{50}\), trifluoromethyl, NHCO\(_2\)R\(^{51}\), hydroxy, C\(_{1-6}\)alkoxy, benzyloxy, OCH\(_2\)CO\(_2\)C\(_{1-6}\)alkyl, OCF\(_3\),
S(O)\(_3\)R\(^{52}\), SO\(_2\)NR\(^{53}\)R\(^{54}\), or halogen;
R\(^{43}\) is hydrogen or R\(^{43}\) together with R\(^{30}'\) forms a group R where R is
CR\(^{55}\)=CR\(^{56}\), CR\(^{55}\)=CR\(^{56}\)CR\(^{55}\)R\(^{56}\), or (CR\(^{55}\)R\(^{56}\));
R\(^{44}\), R\(^{45}\), R\(^{46}\), R\(^{48}\), R\(^{49}\), R\(^{50}\), R\(^{53}\), R\(^{54}\), R\(^{55}\), and R\(^{56}\) are independently hydrogen or C\(_{1-6}\)alkyl;
R\(^{47}\) is hydrogen, C\(_{1-6}\)alkyl, or C\(_{3-7}\) cycloalkyl, C\(_{3-7}\) cycloalkyl, C\(_{5-7}\)cycloalkenyl, or a C\(_{5-7}\)heterocyclic ring;
R\(^{51}\) and R\(^{52}\) are independently C\(_{1-6}\)alkyl;
1 is 0, 1, 2, or 3;
m is 1 or 2;
n is 0, 1, or 2
o, p, and q are independently integers having the value 1, 2, or 3;
r is 0, 1, 2, or 3;
s is 0, 1, or 2;
t is 2 or 3;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONH, NHCO, or CH₂NH,
alternatively, E is a group (f):

\[
\begin{array}{c}
\text{W} \quad \text{(f)}
\end{array}
\]

R¹⁷ and R¹⁸ are independently hydrogen or C₁-6-alkyl;
R¹⁹ and R²⁰ are independently hydrogen, C₁-6-alkyl, C₃-7-cycloalkyl, aralkyl,
C₅-7-cycloalkenyl, a C₅-7-heterocyclic ring, or together with the nitrogen atom to which
they are attached form an optionally substituted 5- to 7-membered heterocyclic ring
which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur,
where optional substituents include C₁-6-alkyl, aryl, CONR¹¹R¹², NR¹¹R¹², hydroxy,
OCOR¹³, NHOCF₃, NHSO₂R¹⁴, NHCO₂R¹⁵, or NHCOC₀-6-alkyl wherein the
alkyl of NHCOC₀-6-alkyl is optionally substituted by OH;

T is -(CR¹⁶R¹⁷)ᵥ- or -O(CR¹⁶R¹⁷)ᵥ-;
W is oxygen, S(O)ₓ, NR¹⁸, or W is CR¹⁹=CR²⁰ or CR¹⁹R²⁰;
R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are independently hydrogen or
C₁-6-alkyl;
R¹⁴ and R¹⁵ are independently C₁-6-alkyl;
u is 1 to 4;
v is 2 or 3;
w is 1, 2, or 3;
x is 0, 1 or 2;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONR⁴⁶, NHCO, or
CH₂NH, wherein R⁴⁶ is hydrogen or C₁-6-alkyl,
alternatively, E is a group (g):
R³⁷¹ is a 5- to 7-membered saturated or partially saturated heterocyclic ring containing a basic nitrogen atom and optionally a further 1 or 2 heteroatoms selected from nitrogen, oxygen or sulfur or R³⁷¹ is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur, which ring systems may be optionally substituted with one or more of C₁₋₆alkyl and optionally substituted on nitrogen with hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl, C₃₋₇cycloalkyl, C₅₋₇cycloalkenyl, or a C₅₋₇heterocyclic ring;

R³⁷¹ is substituted with one or more of R³⁷¹”, provided that R³⁷¹” is not present on the basic nitrogen of R³⁷¹, wherein R³⁷¹” is hydrogen, CR¹ᵃR²"NR³"R⁴”, CR¹ᵃR²"OR³”, COR⁵”, CONR⁶"R⁷”, CO₂R⁸”, cyano, NR³"R⁴”, nitro, hydroxy, C₁₋₆alkoxy, SR⁹”, SOR¹⁰”, SO₂R¹⁰”, SO₂NR⁶"R⁷” or SO₃H,

wherein:

R¹ᵃ and R²” are independently hydrogen or C₁₋₆alkyl;
R³” and R⁴” are independently hydrogen or C₁₋₆alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom; alternatively R⁴” is COR¹¹”, CONR¹²"R¹³", CO₂R¹⁴”, SO₂R¹⁵”, SO₂NR¹²"R¹³”, or SO₂OR¹⁶”, wherein R¹¹” is hydrogen, C₁₋₆alkyl, aryl, or trifluoromethyl; R¹²” and R¹³” are independently hydrogen or C₁₋₆alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom; R¹⁴” is hydrogen or C₁₋₆alkyl; R¹⁵” is hydrogen, C₁₋₆alkyl, aryl, or trifluoromethyl; and R¹⁶” is hydrogen or aryl;
R⁵” is C₁₋₆alkyl, aryl, or trifluoromethyl;
R⁶” and R⁷” are independently hydrogen or C₁₋₆alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom;
R⁸” is hydrogen or C₁₋₆alkyl;
R⁹” is hydrogen, C₁₋₆alkyl, aryl, or trifluoromethyl; and
R¹⁰” is C₁₋₆alkyl, aryl, or trifluoromethyl;
R³⁷² is hydrogen, C₁₋₆alkyl, aryl, CN, CONR⁷⁴R⁷⁵”, CO₂R⁷⁶”, trifluoromethyl, NHCO₂R⁷⁷”, hydroxy, C₁₋₆alkoxy, benzzyloxy, OCH₂CO₂C₁₋₆alkyl, OCF₃, S(O)₂R⁷⁸”, SO₂NR³⁷⁹R⁸⁰, or halogen;
R\textsuperscript{73} is hydrogen, \(\text{C}_{1-6}\text{-alkyl}\), hydroxy, \(\text{C}_{1-6}\text{-alkoxy}\) or halogen, or \(R\textsuperscript{73} \text{and } R\textsuperscript{30}'\) taken together from a group -X- where X is \((\text{CR}^{81}\text{R}^{82})_{(aa)}\) or X is \((\text{CR}^{81}\text{R}^{82})_{ab-Y}\) and Y is oxygen, sulfur or \(\text{CR}^{81}==\text{CR}^{82}\); \(R\textsuperscript{74}, R\textsuperscript{75}, R\textsuperscript{76}, R\textsuperscript{79}, R\textsuperscript{80}, R\textsuperscript{81}, \) and \(R\textsuperscript{82}\) are independently hydrogen or \(\text{C}_{1-6}\text{-alkyl}\);

\(R\textsuperscript{77}\) and \(R\textsuperscript{78}\) are independently \(\text{C}_{1-6}\text{-alkyl}\);

\(y\) is 1 or 2;

\(z\) is 0, 1, or 2;

\(aa\) is 2, 3 or 4;

\(ab\) is 0, 1, 2 or 3;

and further wherein, when \(Ar\) is (i), (ii) or (iii), and \(A\) is \(\text{CONR}^{46}, \text{NHCO}, \) or \(\text{CH}_{2}\text{NH}\), wherein \(R\textsuperscript{46}\) is hydrogen or \(\text{C}_{1-6}\text{-alkyl}\);

alternatively, \(E\) is a group (h):

\[
\begin{tikzpicture}
  \coordinate (Z) at (0,0);
  \coordinate (R87) at (-0.5,0.5);
  \coordinate (CR83R84ac) at (0,1);
  \coordinate (NR85R86) at (0.5,0.5);
  \draw (Z) -- (R87) -- (CR83R84ac) -- (NR85R86);
\end{tikzpicture}
\]

(h);

\(R\textsuperscript{83}\) and \(R\textsuperscript{84}\) are independently hydrogen or \(\text{C}_{1-6}\text{-alkyl}\);

\(R\textsuperscript{85}\) and \(R\textsuperscript{86}\) are independently hydrogen, \(\text{C}_{1-6}\text{-alkyl}\), \(\text{C}_{3-7}\text{-cycloalkyl}\), aralkyl, \(\text{C}_{5-7}\text{-cycloalkenyl}\), a \(\text{C}_{5-7}\text{-heterocyclic}\) ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include \(\text{C}_{1-6}\text{-alkyl}\), aryl, \(\text{CONR}^{88}\text{R}^{89}, \text{NR}^{90}\text{R}^{91}\), hydroxy, \(\text{OCOR}^{92}, \text{NHCOF}_{3}, \text{NHSO}_{2}^{93}, \text{NHCO}_{2}^{94}, \) or \(\text{NHCOC}_{0-6}\text{-alkyl}\) wherein the alkyl of \(\text{NHCOC}_{0-6}\text{-alkyl}\) is optionally substituted by OH;

\(R\textsuperscript{87}\) is hydrogen or \(\text{C}_{1-6}\text{-alkyl}\), \(\text{C}_{1-6}\text{-alkoxy}\), or halogen, or \(R\textsuperscript{87}\) together with \(R\textsuperscript{30}'\) forms a group -AA- where AA is \((\text{CR}^{95}\text{R}^{96})_{ad}\) or AA is \((\text{CR}^{95}==\text{CR}^{96})_{ae}\)-AB and AB is oxygen, sulfur, \(\text{CR}^{95}==\text{CR}^{96}, \text{CR}^{95}=\text{N}, \text{CR}^{95}\text{NR}^{96}\) or \(\text{N}=\text{N}\);

\(Z\) is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

\(R\textsuperscript{88}, R\textsuperscript{89}, R\textsuperscript{90}, R\textsuperscript{91}, R\textsuperscript{92}, R\textsuperscript{95}, \) and \(R\textsuperscript{96}\) are independently hydrogen or \(\text{C}_{1-6}\text{-alkyl}\);

\(R\textsuperscript{93}\) and \(R\textsuperscript{94}\) are independently \(\text{C}_{1-6}\text{-alkyl}\);

\(ac\) is 0 to 4;

\(ad\) is 1, 2 or 3;

\(ae\) is 0, 1 or 2;

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and further wherein, when Ar is (i), (ii) or (iii), and A is CONR^{46}', NHCO, or CH$_2$NH, wherein R^{46'} is hydrogen or C$_1$-alkyl, alternatively, E is a group (i):

(i):

5 R$^{97}$ and R$^{98}$ are independently hydrogen, C$_1$-alkyl, C$_3$-cycloalkyl, aralkyl, C$_5$-cycloalkenyl, a C$_5$-7-heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C$_1$-alkyl, aryl, CONR$_{102}$R$_{103}$, NR$_{104}$R$_{105}$, hydroxy, OCOR$^{106}$, NHCOCF$_3$, NHSO$_2$ R$^{107}$, NHCO$_2$R$^{108}$, or NHCO$_{0.6}$alkyl wherein the alkyl of NHCO$_{0.6}$alkyl is optionally substituted by OH;

R$^{99}$ and R$^{100}$ are independently hydrogen or C$_1$-alkyl;

R$^{101}$ is hydrogen or C$_1$-alkyl or R$^{101}$ and R$^{30'}$ together form a group -AD- wherein AD is (CR$^{109}$R$^{110}$)$_{ai}$ or AD is (CR$^{109}$R$^{110}$)$_{aj}$-AE and AE is oxygen, sulfur or CR$^{109}$-CR$^{110}$;

AC is oxygen, CR$_{111}$R$_{112}$ or NR$_{113}$ or AC is a group S(O)$_{ak}$;

R$_{102}$, R$_{103}$, R$_{104}$, R$_{105}$, R$_{106}$, R$_{109}$, R$_{110}$, R$_{111}$, R$_{112}$, and R$_{113}$ are independently hydrogen or C$_1$-alkyl;

R$^{107}$ and R$^{108}$ are independently C$_1$-alkyl;

af is 0, 1, 2, 3, or 4;

ag is 1, 2, or 3;

ah is 1, 2, 3 or 4;

ai is 2, 3 or 4;

aj is 0, 1, 2, or 3; and

ak is 0, 1 or 2, provided that when R$^{2''}$ is hydrogen and E is a group (a), (f) (h) or (i), then one or both of R$^3$ or R$^4$, R$^{59}$ or R$^{60}$, R$^{85}$ or R$^{86}$, or R$^{97}$ or R$^{98}$ is C$_5$-7-cycloalkenyl, or a C$_5$-7-heterocyclic ring; or when R$^{2''}$ is hydrogen and E is a group (b) or (c), then R$^{30}$ and R$^{47}$ are C$_5$-7-cycloalkenyl, or a C$_5$-7-heterocyclic ring; or when R$^{2''}$ is hydrogen and E is group (g), then either R$^{71''}$ is not hydrogen and/or R$^{71}$ is substituted on nitrogen with C$_5$-7-cycloalkenyl or a C$_5$-7-heterocyclic ring.
2. The compound of formula (I) according to claim 1, wherein A is CONR\(^{46}\), NHCO, or CH\(_2\)NH, wherein R\(^{46}\) is hydrogen; Ar is (i), (ii), or (iii); and E is group (a), (b), or (g).

3. The compound of formula (I) according to claim 1, wherein A is CONR\(^{46}\) or NHCO, wherein R\(^{46}\) is hydrogen; Ar is (i) or (ii), and the terminal phenyl in (i) and (ii) is attached to the phenyl ring bearing group A in a position para to group A; E is group (a), (b), or (g); and R\(^{2}\) is hydrogen, or (CH\(_2\))\(_a\)CN, (CH\(_2\))\(_a\)CO\(_2\)H, COCR\(^{15}\)R\(^{16}\)OR\(^{18}\), and O(CH\(_2\))\(_a\)CO\(_2\)R\(^{18}\) attached to the 3'-position.

4. The compound according to claim 3, wherein when E is group (a), A is attached to group (a) meta to B-(CR\(^1\)R\(^{2}\))\(_a\)-NR\(^3\)R\(^4\) and para to (R\(^5\))\(_b\), wherein B is oxygen or CR\(^7\)R\(^8\), R\(^1\) and R\(^2\) are hydrogen, R\(^5\) is methoxy, methylthio or iodo, R\(^3\) and R\(^4\) are independently C\(_3\)-alkyl, or R\(^3\) and R\(^4\) taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring optionally substituted with one or more of C\(_1\)-alkyl and acetamido or hydroxyl, R\(^6\) is hydrogen, a is 2 or 3 when B is oxygen and a is 2 when B is CH\(_2\), and b is 1.

5. The compound according to claim 3, wherein when E is group (b), A is attached to group (b) para to J, J is oxygen, R\(^{33}\) is hydrogen, R\(^{24}\), R\(^{25}\), R\(^{26}\), R\(^{27}\), R\(^{28}\), R\(^{29}\), R\(^{31}\) and R\(^{32}\) are hydrogen, R\(^{30}\) is C\(_3\)-alkyl, g is 2 and h is 1.

6. The compound according to claim 3, wherein when E is group (g), A is attached to group (g) meta to R\(^{71}\) and para to R\(^{72}\). R\(^{71}\) is an optionally substituted 5- or 6-membered saturated or partially saturated heterocyclic ring containing a nitrogen atom and substituted on nitrogen with C\(_3\)-alkyl or C\(_3\)-cycloalkyl, C\(_5\)-cycloalkenyl, or a C\(_5\)-heterocyclic ring; R\(^{72}\) is methoxy, methylthio or iodo, y is 1, R\(^{73}\) is hydrogen, and R\(^{71}\) is hydrogen or cyano.

7. The compound of formula (I) according to claim 1, wherein A is CONR\(^{46}\), wherein R\(^{46}\) is hydrogen; Ar is (i), (ii), or (iii); E is group (a), (b), or (g), wherein when Ar is (i) or (ii), the terminal phenyl in (i) and (ii) is attached to the phenyl ring bearing group A in a position para to group A; and wherein when E is group (a), A is attached to group (a) meta to B-(CR\(^1\)R\(^{2}\))\(_a\)-NR\(^3\)R\(^4\) and para to (R\(^5\))\(_b\), wherein B is oxygen or CH\(_2\), R\(^1\) and R\(^2\) are hydrogen, R\(^5\) is methoxy, R\(^3\) and R\(^4\) are independently isopropyl or tert-butyl, or R\(^3\) and R\(^4\) taken together with the nitrogen to which they are attached are 1-(2,2,6,6-tetramethylpiperidinyl), 1-(4-acetamido-2,2,6,6-tetramethyl piperidinyl), 1-(4-hydroxy-2,2,6,6-tetramethyl piperidinyl) or 1-(4-hydroxy-2,2,4,6,6-(pentamethyl)piperidinyl), R\(^6\) is
hydrogen, a is 2 when B is oxygen, and b is 1; and wherein when E is group (b), A is attached to group (b) para to J, J is oxygen, R¹³ is hydrogen, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² are hydrogen, R³⁰ is isopropyl, g is 2 and h is 1; and wherein when E is group (g), A is attached to group (g) meta to R⁷¹ and para to R⁷² wherein R⁷¹ is piperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, or pyrrolidin-3-yl substituted on nitrogen with isopropyl, 3-pentyl, cyclopropyl, cyclopentyl, tetrahydro-2H-pyran-4-yl, or cyclopent-3-enyl, R⁷¹ is hydrogen or 4-cyano, R⁷² is methoxy, y is 1, and R⁷³ is hydrogen.

8. The compound of formula (I) according to claim 1, wherein A is CONR⁴⁶, wherein R⁴⁶ is hydrogen; Ar is (i) or (ii), wherein the terminal phenyl in (i) and (ii) is attached to the phenyl ring bearing group A in a position para to group A; E is group (g); R²" is hydrogen, cyanomethyl, or cyanoethyl attached to the 3'-position; wherein A is attached to group (g) meta to R⁷¹ and para to R⁷², R⁷¹ is piperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, or pyrrolidin-3-yl substituted on nitrogen with isopropyl, 3-pentyl, cyclopropyl, cyclopentyl, tetrahydro-2H-pyran-4-yl, or cyclopent-3-enyl, R⁷¹ is hydrogen or 4-cyano, R⁷² is methoxy, y is 1, and R⁷³ is hydrogen.

9. The compound of formula (I) according to claim 1, selected from:
   N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-
   (ethoxyacetyl)-1,1'-biphenyl-4-carboxamide;
   N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-
   (hydroxyacetyl)-1,1'-biphenyl-4-carboxamide;
   N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-
   (methoxyacetyl)-1,1'-biphenyl-4-carboxamide;
   N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'(2-methoxy-2-
   oxoethoxy)-1,1'-biphenyl-4-carboxamide;
   N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'
   biphenyl-4-carboxamide;
   3'(2-Cyanoethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-
   piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide;
   3'(2-Cyanoethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-
   piperidinyl)ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide;
   N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'(cyanoethyl)-
   1,1'-biphenyl-4-carboxamide;
   N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'
   (cyanomethyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-[(cyanooethyl)-1,1'-biphenyl-4-carboxamide;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-
(cyanomethyl)-1,1'-biphenyl-4-carboxamide;
3'-[(2-Cyanoethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
3'-[(2-Cyanomethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
N-[3-[1-(tetrahydro-2H-pyran-4-yl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-
biphenyl-4-carboxamide;
3'-[(2-Carboxyethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide; and
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-
(carboxyethyl)-1,1'-biphenyl-4-carboxamide;
3'-Chloro-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-
ethoxycarbonyl-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-
sulfamoyl-1,1'-biphenyl-4-carboxamide;
3'-[(2-Cyanoethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-
methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-ureido-
1,1'-biphenyl-4-carboxamide;
3'-((Cyanoethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-
methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-
isopropoxy-1,1'-biphenyl-4-carboxamide;
3'-Cyano-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-
dimethyl-1,1'-biphenyl-4-carboxamide;
3'-Acetamido-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-
methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
3'-Acetyl-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
3'- (2-Carboxyethyl)-N-[3-4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'- (1H-tetrazol-5-yl)-1,1'-biphenyl-4-carboxamide;
N-[3-4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'- (5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide;
N-[3-4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'- (methanesulfonamido)-1,1'-biphenyl-4-carboxamide;
N-[3-4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'- dichloro-1,1'-biphenyl-4-carboxamide;
N-[3-4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'- bis(methoxycarbonyl)-1,1'-biphenyl-4-carboxamide; and
3'-Carboxamido-N-[3-4-cyano-1-(1-methylethyl)-4-piperidinyl]-4- methoxyphenyl]-1,1'-biphenyl-4-carboxamide.

10. A method of treating a CCR5-mediated disease in mammals, comprising administering to a mammal in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:

\[ \text{Ar} - A - E \]

Formula (I)

wherein \( \text{Ar} \) is a group selected from (i), (ii) or (iii);

wherein:

the basic nitrogen in moiety \( E \) may be optionally quaternized with \( C_{1-6} \)-alkyl or is optionally present as the N-oxide;

\( R^1' \) and \( R^2' \) are each independently one or more of hydrogen, \( C_{1-6} \)-alkyl, \( C_{2-6} \)-alkenyl, \( C_{2-6} \)-alkynyl, \( C_3-7 \)-cycloalkyl, \( C_3-6 \)-cycloalkenyl, aryl, \( (CH_2)_aNR_7^7R_8^8 \), \( (CH_2)_aNR_7^7CO_2R_9^9 \), \( (CH_2)_aNR_7^7SO_2R_10^10 \), \( (CH_2)_aCONR_11^12R_13^13 \), hydroxyC_{1-6}alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), \( (CH_2)_bOC(O)R_14^14 \), \( CR_15^15=NOR_16^16 \), \( CNR_15^15=NOR_16^16 \), \( COR_17^17 \), \( CONR_12^12R_13^13 \).
CONR^{12}(CH_{2})_{a}OC_{1-4}alkyl, CONR^{12}(CH_{2})_{a}CO_{2}R^{18}, CONHNR^{19}R^{20}, CONR^{12}SO_{2}R^{21}, CO_{2}R^{22}, cyano, trifluoromethyl, NR^{7}R^{8}, NR^{7}COR^{9}, NR^{23}CO(CH_{2})_{d}NR^{23}R^{24}, NR^{23}CONR^{23}R^{24}, NR^{23}CO_{2}R^{10}, NR^{7}SO_{2}R^{11}, N=CNR^{23}NR^{23}R^{24}, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, OC(O)NR^{25}R^{26}, SR^{27}, SOR^{28}, SO_{2}R^{28}, SO_{2}NR^{25}R^{26} or halogen;

R^{3'} and R^{4'} are each independently one or more of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, CONR^{29}R^{30}, CO_{2}R^{31}, cyano, aryl, trifluoromethyl, NR^{29}R^{30}, nitro, hydroxy, C_{1-6}alkoxy, acyloxy, or halogen;

R^{2'} is also R^{2''} wherein R^{2''} is hydrogen, (CH_{2})_{a}CN, (CH_{2})_{a}CO_{2}H, CR^{15'}=CR^{16'}CO_{2}R^{18'}, COCR^{15'}R^{16'}OR^{18'}, Oaryl, Oaralkyl, O(CH_{2})_{a}CO_{2}R^{18'}, and Saryl;

R^{5'} is one or more of hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or halogen;

R^{6'} is one or more of hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl (optionally substituted by a hydroxy or an oxo group), hydroxyC_{1-6}alkyl, hydroxyC_{3-6}alkenyl, hydroxyC_{3-6}alkenyl, (CH_{2})_{a}OR^{32}, (CH_{2})_{d}COR^{33'}, (CH_{2})_{d}CR^{34}=NR^{35'}, CONR^{36}R^{37}, CO_{2}R^{38}, hydroxy, O(CH_{2})_{e}R^{39}, NR^{36}R^{37}, SR^{40}, SO_{2}NR^{41}R^{42} or halogen; or, R^{5'} and R^{6'} form a fused benzo ring optionally substituted with C_{1-6}alkyl, C_{1-6}alkoxy or halogen;

R^{7'} and R^{8'} are independently hydrogen or C_{1-6}alkyl, or together with the nitrogen to which they are attached, R^{7'} and R^{8'} form a 5- to 6-membered heterocyclic ring, which ring may optionally be substituted by an oxo group and, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

R^{9'} is hydrogen, C_{1-6}alkyl or C_{1-4}alkoxyalkyl;

R^{10'} is C_{1-6}alkyl;

R^{11'} is C_{1-6}alkyl or phenyl;

R^{12'} and R^{13'} are independently hydrogen or C_{1-6}alkyl, or together with the nitrogen to which they are attached, R^{12'} and R^{13'} form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

R^{14'} is C_{1-4}alkyl, optionally substituted by C_{1-6}alkoxy;

R^{15'} and R^{16'} are independently hydrogen or C_{1-6}alkyl;

R^{17'} is hydrogen or C_{1-6}alkyl;

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

R^{19'} and R^{20'} are independently hydrogen or C_{1-6}alkyl;

R^{21'} is hydrogen or C_{1-6}alkyl;
R\textsuperscript{22}' is hydrogen or C\textsubscript{1}-alkyl optionally substituted with one or two substituents selected from C\textsubscript{1}-alkyl, C\textsubscript{1}-alkoxy, hydroxy, or NR\textsuperscript{7}R\textsuperscript{8}';
R\textsuperscript{23}' and R\textsuperscript{24}' are independently hydrogen or C\textsubscript{1}-alkyl;
R\textsuperscript{25}' and R\textsuperscript{26}' are independently hydrogen or C\textsubscript{1}-alkyl, or together with the nitrogen to which they are attached, R\textsuperscript{25}' and R\textsuperscript{26}' form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;
R\textsuperscript{27}' is hydrogen or C\textsubscript{1}-alkyl;
R\textsuperscript{28}' is C\textsubscript{1}-alkyl;
R\textsuperscript{29}', R\textsuperscript{30}' and R\textsuperscript{31}' are independently hydrogen or C\textsubscript{1}-alkyl;
R\textsuperscript{32}' is C\textsubscript{1}-alkyl, hydroxyC\textsubscript{1}-alkyl, or C\textsubscript{1}-alkanoyl;
R\textsuperscript{33}' is hydrogen or C\textsubscript{1}-alkyl;
R\textsuperscript{34}' is hydrogen or C\textsubscript{1}-alkyl;
R\textsuperscript{35}' is hydrogen or C\textsubscript{1}-alkyl;
R\textsuperscript{36}' and R\textsuperscript{37}' are independently hydrogen or C\textsubscript{1}-alkyl or together with the nitrogen to which they are attached, R\textsuperscript{36}' and R\textsuperscript{37}' form a 5- to 6-membered heterocyclic ring, which ring may be optionally substituted by an oxo group and, which, when the ring is 6-membered, may optionally contain one oxygen or sulfur atom or an NH group or a group NR\textsuperscript{43}', wherein R\textsuperscript{43}' is C\textsubscript{1}-alkyl, CONR\textsuperscript{44}', or CO\textsubscript{2}R\textsuperscript{45}', wherein R\textsuperscript{44}' and R\textsuperscript{45}' are independently hydrogen or C\textsubscript{1}-alkyl;
R\textsuperscript{38}' is hydrogen or C\textsubscript{1}-alkyl;
R\textsuperscript{39}' is C\textsubscript{1}-alkoxy, CO\textsubscript{2}H, CO\textsubscript{2}C\textsubscript{1}-alkyl or CONR\textsuperscript{36}R\textsuperscript{37}';
R\textsuperscript{40}' is C\textsubscript{1}-alkyl;
R\textsuperscript{41}' and R\textsuperscript{42}' are independently hydrogen or C\textsubscript{1}-alkyl;
P is a 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;
\textsuperscript{a} is 1, 2, 3 or 4;
\textsuperscript{b} is 0, 1, 2 or 3;
\textsuperscript{c} is 1, 2 or 3;
\textsuperscript{d} is 0, 1, 2, 3, 4, 5, or 6; and
\textsuperscript{e} is 1, 2, 3, 4, 5 or 6;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONR\textsuperscript{46}', NHCO, -NHCH\textsubscript{2}, or CH\textsubscript{2}NH, wherein R\textsuperscript{46}' is hydrogen or C\textsubscript{1}-alkyl,
E is a group (a):
wherein:

- B is oxygen, C=S, S(O), CR²=CR³, or CR²R³, or B is NR⁴;
- R¹ and R² are independently hydrogen or C₆-alkyl; alternatively B(CR¹R²)ₐ
- R₃ and R⁴ are independently hydrogen, C₆-alkyl, C₃-7cycloalkyl, aralkyl, C₅-7cycloalkenyl, a C₅-7heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur,

where optional substituents include C₆-alkyl, aryl, CONR¹R¹, NR¹R¹, hydroxy, COOR¹, NHCOCF₃, NHCO₂R¹, hydroxy, C₆-alkoxy, benzyloxy, OCH₂CO₂C₆-alkyl, OCF₃,

S(O)ₐR¹, SO₂NR²R² or halogen;

- R⁶ is hydrogen, C₆-alkyl, aryl, trifluoromethyl, hydroxy, C₆-alkoxy or halogen, or R⁶ taken together with R³⁰' forms a group D where D is (CR²²R²⁳)ₐ or D is (CR²²R²³)ₐ×G where G is oxygen, sulfur or CR²²=CR²³, CR²²=N=CR²²O, =CR²²S, or =CR²².NR²³;

R⁷, R⁸, R¹⁰, R¹₁, R¹₂, R¹₅, R¹₆, R¹₇, R¹₉, R¹₇, R²¹, R²₂, and R²₃ are independently hydrogen or C₆-alkyl;

- R⁹ is hydrogen, C₆-alkyl, or phenylC₆-alkyl;
- R¹³, R¹₄, R¹₈, and R¹₉ are independently C₆-alkyl;

- a is 1, 2, 3, or 4;

b is 1 or 2;
c and d are independently 0, 1 or 2;
e is 2, 3 or 4;
f is 0, 1, 2 or 3;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONR⁴⁶, NHCO, or CH₂NH, wherein R⁴⁶ is hydrogen or C₆-alkyl,
alternatively, E is a group (b):
R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³¹, and R³² are independently hydrogen or C₁-6-alkyl;
R³⁰ is hydrogen, C₁-6-alkyl, C₃-7-cycloalkyl C₅-7-cycloalkenyl, or a C₅-
7 heterocyclic ring;
R³³ is hydrogen, C₁-6-alkyl, trifluoromethyl, hydroxy or halogen, or R³³ and
R³⁰ together form a group -K- where K is (CR³⁴R³⁵)ᵢ or K is (CR³⁴R³⁵)ᵢ -M and M
is oxygen, sulfur, CR³⁴=CR³⁵, CR³⁴=N, or N=N;
J is oxygen, CR³⁶R³⁷, or NR³⁸, or J is a group S(O)ᵢ;
R³⁴, R³⁵, R³⁶, R³⁷, and R³⁸ are independently hydrogen or C₁-6-alkyl;
g is 1, 2 or 3;
h is 1, 2 or 3;
i is 2, 3, or 4;
j is 0, 1, 2, or 3;
k is 0, 1 or 2;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONR⁴⁶, NHCO, -
NHCH₂, or CH₂NH, wherein R⁴⁶ is hydrogen or C₁-6-alkyl,
alternatively, E is a group (c):

20 wherein:
Q is oxygen, S(O)ᵢ, CR⁴⁴=CR⁴⁵, CR⁴⁴R⁴⁵, or Q is NR⁴⁶;
R³⁹ and R⁴⁰ are independently hydrogen or C₁-6-alkyl;
R⁴¹ is a group of formula (d):

73
or R41 is a group of formula (e):

\[
\begin{array}{c}
\text{(e)} \\
\text{R}^{47} \\
\text{N} \\
\text{CH}_{2} \\
\text{R}^{41}
\end{array}
\]

R42 is hydrogen, C1-6alkyl, aryl, CN, CONR48R49, CO2R50, trifluoromethyl, NHCO2R51, hydroxy, C1-6alkoxy, benzylxoy, OCH2CO2C1-6alkyl, OCF3, S(O)8R52, SO2NR53R54, or halogen;

R43 is hydrogen or R43 together with R30' forms a group R where R is CR55=CR56, CR55=CR56CR55R56, or (CR55R56)t;

R44, R45, R46, R48, R49, R50, R53, R54, R55, and R56 are independently hydrogen or C1-6alkyl;

R47 is hydrogen, C1-6alkyl, C3-7 cycloalkyl C5-7cycloalkenyl, or a C5-

\[\text{7heterocyclic ring; \}}
\]

R51 and R52 are independently C1-6alkyl;

l is 0, 1, 2, or 3;

m is 1 or 2;

n is 0, 1, or 2

o, p, and q are independently integers having the value 1, 2, or 3;

r is 0, 1, 2, or 3;

s is 0, 1, or 2;

t is 2 or 3;

and further wherein, when Ar is (i), (ii) or (iii), and A is CONH, NHCO, or CH2NH,

alternatively, E is a group (f):

\[
\begin{array}{c}
\text{(f)} \\
\text{W} \\
\text{---(CR57R58)---NR69R60} \\
\text{T}
\end{array}
\]

R57 and R58 are independently hydrogen or C1-6alkyl;

R59 and R60 are independently hydrogen, C1-6alkyl, C3-7cycloalkyl, aralkyl, C5-7cycloalkenyl, a C5-7heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur,

where optional substituents include C1-6alkyl, aryl, CONR61R62, NR61R62, hydroxy,
OCOR\textsuperscript{63}, NHCOC\textsubscript{2}F\textsubscript{3}, NH\textsubscript{2}SO\textsubscript{2}R\textsuperscript{64}, NHCO\textsubscript{2}R\textsuperscript{65}, or NHCO\textsubscript{2}O-alkyl wherein the alkyl of NHCO\textsubscript{2}O-alkyl is optionally substituted by OH;

T is -(CR\textsuperscript{66}R\textsuperscript{67})\textsubscript{v}- or -O(CR\textsuperscript{66}R\textsuperscript{67})\textsubscript{w}--;

W is oxygen, S(O)\textsubscript{x}, NR\textsuperscript{68}, or W is CR\textsuperscript{69}=CR\textsuperscript{70} or CR\textsuperscript{69}R\textsuperscript{70};

R\textsuperscript{61}, R\textsuperscript{62}, R\textsuperscript{63}, R\textsuperscript{66}, R\textsuperscript{67}, R\textsuperscript{68}, R\textsuperscript{69}, and R\textsuperscript{70} are independently hydrogen or C\textsubscript{1}-alkyl;

R\textsuperscript{64} and R\textsuperscript{65} are independently C\textsubscript{1}-alkyl;

u is 1 to 4;

v is 2 or 3;

w is 1, 2, or 3;

x is 0, 1 or 2;

and further wherein, when Ar is (i), (ii) or (iii), and A is CONR\textsuperscript{46}, NHCO, or CH\textsubscript{2}NH, wherein R\textsuperscript{46} is hydrogen or C\textsubscript{1}-alkyl,

alternatively, E is a group (g):

\begin{center}
\begin{tikzpicture}
    \node (n1) at (0,0) {R\textsuperscript{71}};
    \node (n2) at (0,1) {R\textsuperscript{73}};
    \node (n3) at (0,2) {R\textsuperscript{75}};
    \node (n4) at (0,3) {R\textsuperscript{76}};
    \node (n5) at (0,4) {R\textsuperscript{77}};
    \node (n6) at (0,5) {R\textsuperscript{78}};
    \draw (n1) -- (n2);
    \draw (n2) -- (n3);
    \draw (n3) -- (n4);
    \draw (n4) -- (n5);
    \draw (n5) -- (n6);
    \draw (n6) -- (n1);
\end{tikzpicture}
\end{center}

R\textsuperscript{71} is a 5- to 7-membered saturated or partially saturated heterocyclic ring containing a basic nitrogen atom and optionally a further 1 or 2 heteroatoms selected from nitrogen, oxygen or sulfur or R\textsuperscript{71} is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur, which ring systems may be optionally substituted with one or more of C\textsubscript{1}-alkyl and optionally substituted on nitrogen with hydrogen, C\textsubscript{1}-alkyl, C\textsubscript{3}-cycloalkyl C\textsubscript{5}-7cycloalkenyl, or a C\textsubscript{5}-7heterocyclic ring;

R\textsuperscript{71} is substituted with one or more of R\textsuperscript{71}'\textsuperscript{1}, wherein R\textsuperscript{71}'\textsuperscript{1} is hydrogen, CR\textsuperscript{1a}R\textsuperscript{2}NR\textsuperscript{3}R\textsuperscript{4}\textsuperscript{1}, CR\textsuperscript{1a}R\textsuperscript{2}OR\textsuperscript{3}\textsuperscript{1}, COR\textsuperscript{5}, CONR\textsuperscript{6}R\textsuperscript{7}, CO\textsubscript{2}R\textsuperscript{8}, cyano, NR\textsuperscript{3}R\textsuperscript{4}, nitro, hydroxy, C\textsubscript{1}-alkoxy, SR\textsuperscript{9}, SOR\textsuperscript{10}, SO\textsubscript{2}R\textsuperscript{10}, SO\textsubscript{2}N\textsubscript{R}\textsuperscript{6}R\textsuperscript{7}, or SO\textsubscript{3}H,

wherein:

R\textsuperscript{1a} and R\textsuperscript{2} are independently hydrogen or C\textsubscript{1}-alkyl;

R\textsuperscript{3} and R\textsuperscript{4} are independently hydrogen or C\textsubscript{1}-alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom; alternatively R\textsuperscript{4} is COR\textsuperscript{11}, CONR\textsuperscript{12}R\textsuperscript{13}, CO\textsubscript{2}R\textsuperscript{14}, SO\textsubscript{2}R\textsuperscript{15}, SO\textsubscript{2}N\textsubscript{R}\textsuperscript{12}R\textsuperscript{13}, or SO\textsubscript{2}OR\textsuperscript{16}, wherein R\textsuperscript{11} is hydrogen, C\textsubscript{1}-alkyl, aryl, or trifluoromethyl; R\textsuperscript{12} and R\textsuperscript{13} are independently hydrogen or C\textsubscript{1}-alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one
oxygen or one sulfur atom; R^{14} is hydrogen or C_{1-6}alkyl; R^{15} is hydrogen, C_{1-6}alkyl, aryl, or trifluoromethyl; and R^{16} is hydrogen or aryl;

R^{5} is C_{1-6}alkyl, aryl, or trifluoromethyl;
R^{6} and R^{7} are independently hydrogen or C_{1-6}alkyl, or taken together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when the ring is 6-membered, may optionally contain one oxygen or one sulfur atom;

R^{8} is hydrogen or C_{1-6}alkyl;
R^{9} is hydrogen, C_{1-6}alkyl, aryl, or trifluoromethyl; and
R^{10} is C_{1-6}alkyl, aryl, or trifluoromethyl;
R^{72} is hydrogen, C_{1-6}alkyl, aryl, CN, CONR^{74}R^{75}, CO_{2}R^{76}, trifluoromethyl, NHCO_{2}R^{77}, hydroxy, C_{1-6}alkoxy, benzyl, OCH_{2}CO_{2}C_{1-6}alkyl, OCF_{3},
S(O)_{2}R^{78}, SO_{2}NR^{79}R^{80}, or halogen;
R^{73} is hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or halogen, or R^{73} and R^{30}' taken together from a group -X- where X is (CR^{81}R^{82})_{aa} or X is (CR^{81}R^{82})_{ab}; Y and Y is oxygen, sulfur or CR^{81} = CR^{82};
R^{74}, R^{75}, R^{76}, R^{79}, R^{80}, R^{81}, and R^{82} are independently hydrogen or C_{1-6}alkyl;
R^{77} and R^{78} are independently C_{1-6}alkyl;
y is 1 or 2;
z is 0, 1, or 2;
ab is 0, 1, 2 or 3;
and further wherein, when Ar is (i), (ii) or (iii), and A is CONR^{46}, NHCO, or CH_{2}NH, wherein R^{46} is hydrogen or C_{1-6}alkyl;
alternatively, E is a group (h):

\[
\begin{array}{c}
Z \\
\text{(CR^{83}R^{84})_{aa}} \\
\text{NR^{85}R^{86}} \\
\end{array}
\]

(R^{87});
R^{83} and R^{84} are independently hydrogen or C_{1-6}alkyl;
R^{85} and R^{86} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, C_{5-7}cycloalkenyl, a C_{5-7}heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, CONR^{88}R^{89}, NR^{90}R^{91}, hydroxy, OCOR^{92}, NHCO_{2}F, NHSO_{2}R^{93}, NHCO_{2}R^{94}, or NHCO_{0-6}alkyl wherein the alkyl of NHCO_{0-6}alkyl is optionally substituted by OH;
$R^{87}$ is hydrogen or C$_1$-alkyl, C$_1$-alkoxy, or halogen, or $R^{87}$ together with $R^{30'}$ forms a group -AA- where AA is (CR$_{95}$R$_{96}$)$_{ad}$ or AA is (CR$_{95}$=CR$_{96}$)$_{ae}$-AB and AB is oxygen, sulfur, CR$_{95}$=CR$_{96}$, CR$_{95}$=N, CR$_{95}$NR$_{96}$ or N=N;

Z is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

$R^{88}$, $R^{89}$, $R^{90}$, $R^{91}$, $R^{92}$, $R^{95}$, and $R^{96}$ are independently hydrogen or C$_1$-alkyl;

$R^{93}$ and $R^{94}$ are independently C$_1$-alkyl;

ac is 0 to 4;

ad is 1, 2 or 3;

ae is 0, 1 or 2;

and further wherein, when Ar is (i), (ii) or (iii), and A is CONR$_{46'}$, NHCO, or CH$_2$NH, wherein $R^{46'}$ is hydrogen or C$_1$-alkyl, alternatively, E is a group (i):

$$
\begin{align*}
\text{(CH$_2$)$_{al}$NR$_{97}$R$_{98}$} \\
\text{(CR$_{99}$R$_{100}$)$_{ah}$}
\end{align*}
$$

$R^{97}$ and $R^{98}$ are independently hydrogen, C$_1$-alkyl, C$_3$-cycloalkyl, aralkyl, C$_5$-cycloalkenyl, a C$_5$-heterocyclic ring, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C$_1$-alkyl, aryl, CONR$_{102}$R$_{103}$, NR$_{104}$R$_{105}$, hydroxy, OCOR$_{106}$, NHCOF$_3$, NHSO$_2$ R$_{107}$, NHCO$_2$R$_{108}$, or NHCOC$_{0-alkyl}$ wherein the alkyl of NHCOOC$_{0-alkyl}$ is optionally substituted by OH;

$R^{99}$ and $R^{100}$ are independently hydrogen or C$_1$-alkyl;

$R^{101}$ is hydrogen or C$_1$-alkyl or $R^{101}$ and $R^{30'}$ together form a group -AD- where AD is (CR$_{109}$R$_{110}$)$_{ai}$ or AD is (CR$_{109}$R$_{110}$)$_{aj}$-AE and AE is oxygen, sulfur or CR$_{109}$=CR$_{110}$;

AC is oxygen, CR$_{111}$R$_{112}$ or NR$_{113}$ or AC is a group S(O)$_{ak}$;

R$_{102}$, R$_{103}$, R$_{104}$, R$_{105}$, R$_{106}$, R$_{109}$, R$_{110}$, R$_{111}$, R$_{112}$, and R$_{113}$ are independently hydrogen or C$_1$-alkyl;

$R^{107}$ and $R^{108}$ are independently C$_1$-alkyl;

af is 0, 1, 2, 3, or 4;

ag is 1, 2, or 3;
ah is 1, 2, 3 or 4;
ai is 2, 3 or 4;
aj is 0, 1, 2, or 3; and
ak is 0, 1 or 2, provided that when \( R^2'' \) is hydrogen and E is a group (a), (f) (h) or (i), then one or both of \( R^3 \) or \( R^4 \); \( R^5 \) or \( R^6 \); or \( R^97 \) or \( R^98 \) is \( C_5 \)-
cycloalkenyl, or a \( C_5 \)-heterocyclic ring; or when \( R^2'' \) is hydrogen and E is a group (b) or (c), then \( R^{30} \) and \( R^{47} \) are \( C_5 \)-cycloalkenyl, or a \( C_5 \)-heterocyclic ring; or when \( R^2'' \) is hydrogen and E is group (g), then either \( R^{71}'' \) is not hydrogen and/or \( R^71 \) is substituted on nitrogen with \( C_5 \)-cycloalkenyl or a \( C_5 \)-heterocyclic ring.

11. The method of claim 10, wherein the compound of formula (I) is selected from:

\[
\text{N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-}
\text{(ethoxyacetyl)-1,1'-biphenyl-4-carboxamide;}
\]

\[
\text{N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'}
\text{(hydroxyacetyl)-1,1'-biphenyl-4-carboxamide;}
\]

\[
\text{N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'}
\text{(methoxyacetyl)-1,1'-biphenyl-4-carboxamide;}
\]

\[
\text{N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'}
\text{(2-methoxy-2-oxoethoxy)-1,1'-biphenyl-4-carboxamide;}
\]

\[
\text{N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'}
\text{-biphenyl-4-carboxamide;}
\]

\[
3'-(2-Cyanoethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl]ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide;}
\]

\[
3'-(2-Cyanomethyl)-N-[4-methoxy-3-[2-(2,2,6,6-tetramethyl-1-piperidinyl]ethoxy]phenyl]-1,1'-biphenyl-4-carboxamide;}
\]

\[
N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'-(cyanoethyl)-
1,1'-biphenyl-4-carboxamide;}
\]

\[
N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3'
\text{(cyanomethyl)-1,1'-biphenyl-4-carboxamide;}
\]

\[
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-(cyanoethyl)-
1,1'-biphenyl-4-carboxamide;}
\]

\[
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-(cyanomethyl)-1,1'-biphenyl-4-carboxamide;}
\]

\[
3'-(2-Cyanoethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
\]
3'- (2-Cyanomethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[1-(tetrahydro-2H-pyran-4-yl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
5 3'- (2-Carboxyethyl)-N-[3-[1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide; and
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-
(carboxyethyl)-1,1'-biphenyl-4-carboxamide;
3'- Chloro-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-
ethoxycarbonyl-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-
sulfamoyl-1,1'-biphenyl-4-carboxamide;
10 3'- (2-Cyanoethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-
methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-ureido-
1,1'-biphenyl-4-carboxamide;
3'- (Cyanomethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-
methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-
isopropoxy-1,1'-biphenyl-4-carboxamide;
3'- Cyano-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
20 N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-
dimethyl-1,1'-biphenyl-4-carboxamide;
3'- Acetamido-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-
methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
3'- Acetyl-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-
1,1'-biphenyl-4-carboxamide;
30 3'- (2-Carboxyethyl)-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-
methoxyphenyl]-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(1H-
tetrazol-5-yl)-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(5-
methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3'-(methanesulfonamido)-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-dichloro-1,1'-biphenyl-4-carboxamide;
N-[3-[4-Cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-3',5'-bis(methoxycarbonyl)-1,1'-biphenyl-4-carboxamide; and
3'-Carboxamido-N-[3-[4-cyano-1-(1-methylethyl)-4-piperidinyl]-4-methoxyphenyl]-1,1'-biphenyl-4-carboxamide.

12. The method of claim 10, wherein the CCR5-mediated disease state is
selected from COPD, asthma and atopic disorders, rheumatoid arthritis, sarcoidosis, or
idiopathic pulmonary fibrosis and other fibrotic diseases, atherosclerosis, psoriasis,
autoimmune diseases such as multiple sclerosis, treating and/or preventing rejection of
transplanted organs, inflammatory bowel disease, or HIV infection.

13. The method according to claim 10, wherein the compound of formula (I)
is as follows: A is CONR\textsuperscript{46'} or NHCO, wherein R\textsuperscript{46'} is hydrogen; Ar is (i) or (ii), and
the terminal phenyl in (i) and (ii) is attached to the phenyl ring bearing group A in a
position para to group A; E is group (a), (b), or (g); and R\textsuperscript{2''} is hydrogen, or
(CH\textsubscript{2})\textsubscript{a}CN, (CH\textsubscript{2})\textsubscript{a}CO\textsubscript{2}H, COCR\textsuperscript{15}R\textsuperscript{16'}OR\textsuperscript{18'}, and O(CH\textsubscript{2})\textsubscript{a}CO\textsubscript{2}R\textsuperscript{18'} attached to
the 3'-position.

14. The method according to claim 10, wherein the compound of formula (I)
is as follows: when E is group (a), A is attached to group (a) meta to B-(CR\textsuperscript{1}R\textsuperscript{2})\textsubscript{a}NR\textsuperscript{3}R\textsuperscript{4} and para to (R\textsuperscript{5})\textsubscript{b}, wherein B is oxygen or CR\textsuperscript{7}R\textsuperscript{8}, R\textsuperscript{1} and R\textsuperscript{2} are hydrogen,
R\textsuperscript{5} is methoxy, methylthio or iodo, R\textsuperscript{3} and R\textsuperscript{4} are independently C\textsubscript{3-6}alkyl, or R\textsuperscript{3} and
R\textsuperscript{4} taken together with the nitrogen to which they are attached form a 5- or 6-
membered heterocyclic ring optionally substituted with one or more of C\textsubscript{1-6}alkyl and
acetamido or hydroxyl, R\textsuperscript{6} is hydrogen, a is 2 or 3 when B is oxygen and a is 2 when B
is CH\textsubscript{2}, and b is 1; or when E is group (b), A is attached to group (b) para to J, J is
oxygen, R\textsuperscript{33} is hydrogen, R\textsuperscript{21}R\textsuperscript{25}, R\textsuperscript{26}, R\textsuperscript{27}, R\textsuperscript{28}, R\textsuperscript{29}, R\textsuperscript{31} and R\textsuperscript{32} are hydrogen,
R\textsuperscript{30} is C\textsubscript{3-6}alkyl, g is 2 and h is 1; or when E is group (g), A is attached to group (g)
meta to R\textsuperscript{71} and para to R\textsuperscript{72}, R\textsuperscript{71} is an optionally substituted 5- or 6-membered
saturated or partially saturated heterocyclic ring containing a nitrogen atom and
substituted on nitrogen with C\textsubscript{3-6}alkyl or C\textsubscript{3-7}cycloalkyl, R\textsuperscript{72} is methoxy, methylthio
or iodo, y is 1, R\textsuperscript{73} is hydrogen, and R\textsuperscript{71''} is hydrogen or cyano.
15. The method according to claim 10, wherein the compound of formula (I) is as follows: A is CONR⁴⁶⁺, wherein R⁴⁶⁺ is hydrogen; Ar is (i), (ii), or (iii); E is group (a), (b), or (g), wherein when Ar is (i) or (ii), the terminal phenyl in (i) and (ii) is attached to the phenyl ring bearing group A in a position para to group A; and wherein when E is group (a), A is attached to group (a) meta to B-(CR¹R²)ₐNR³R⁴ and para to (R⁵)b, wherein B is oxygen or CH₂, R¹ and R² are hydrogen, R⁵ is methoxy, R³ and R⁴ are independently isopropyl or tert-butyl, or R³ and R⁴ taken together with the nitrogen to which they are attached are 1-(2,2,6,6-tetramethylpiperidiny1), 1-(4-acetamido-2,2,6,6-tetramethyl piperidiny1), 1-(4-hydroxy-2,2,6,6-tetramethyl piperidiny1) or 1-(4-hydroxy-2,2,4,6,6-(pentamethyl)piperidiny1), R⁶ is hydrogen, a is 2 when B is oxygen, and b is 1; and wherein when E is group (b), A is attached to group (b) para to J, J is oxygen, R³³ is hydrogen, R²⁴, R₂⁵, R₂⁶, R₂⁷, R₂⁸, R₂⁹, R₃¹ and R₃² are hydrogen, R₃⁰ is isopropyl, g is 2 and h is 1; and wherein when E is group (g), A is attached to group (g) meta to R⁷¹ and para to R⁷² wherein R⁷¹ is piperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, or pyrrolidin-3-yl substituted on nitrogen with isopropyl, cyclopropyl, or cyclopentyl, R⁷¹⁺ is hydrogen or 4-cyano, R⁷² is methoxy, y is 1, and R⁷³ is hydrogen.

16. The method according to claim 10, wherein the compound of formula (I) is as follows: A is CONR⁴⁶⁺, wherein R⁴⁶⁺ is hydrogen; Ar is (i) or (ii), wherein the terminal phenyl in (i) and (ii) is attached to the phenyl ring bearing group A in a position para to group A; E is group (g); R²⁺ is hydrogen, cyanomethyl, or cyanoethyl attached to the 3'-position; wherein A is attached to group (g) meta to R⁷¹ and para to R⁷², R⁷¹ is piperidin-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, or pyrrolidin-3-yl substituted on nitrogen with isopropyl, cyclopropyl, or cyclopentyl, R⁷¹⁺ is hydrogen or 4-cyano, R⁷² is methoxy, y is 1, and R⁷³ is hydrogen.